CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210595Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210595
Priority or Standard	Standard
Submit Date(s)	May 31, 2018
Received Date(s)	May 31, 2018
PDUFA Goal Date	March 31, 2019
Division/Office	Division of Pulmonary, Allergy, and Rheumatology Products
Review Completion Date	March 29, 2019
Established/Proper Name	Aclidinium bromide/formoterol fumarate inhalation powder
(Proposed) Trade Name	Duaklir Pressair
Pharmacologic Class	Long-acting muscarinic/Long-acting B_2-agonist
Code name	
Applicant	AstraZenecaPharmaceuticals LP
Doseage form	Inhalation powder
Applicant proposed Dosing Regimen	One inhalation (400 µg aclidinium bromide/ 12 µg formoterol fumarate) twice daily
Applicant Proposed Indication(s)/Population(s)	- (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD), (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4) maintenance treatment of patients with COPD
Recommended Dosing Regimen	One inhalation (400 µg aclidinium bromide/ 12 µg formoterol fumarate) twice daily

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
IC	Inspiratory capacity
ICH	International Conference on Harmonization
IND	Investigational- New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1. Executive Summary

1.1. Product Introduction

The Applicant, AstraZeneca, submitted a 505(b)(1) New Drug Application (NDA) for Duaklir Pressair. This product is a fixed dose combination (FDC) dry powder for inhalation of aclidinium bromide (AB) and formoterol fumarate (FF) administered via the Pressair inhaler. AB is a long-acting muscarinic antagonist (LAMA), and FF is a long-acting β2-adrenergic receptor agonist (LABA). The proposed dose is one oral inhalation of AB/FF 400/12 µg twice-daily (BID). The proposed indication is for the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4) This product has been approved in 69 countries since 2014. The monocomponent AB (tradename Tudorza Pressair) was approved in the U.S. in 2012 for the maintenance treatment of bronchospasm associated with COPD. In addition, the monocomponent FF, under the tradename Perforomist, has been on US market since 2001.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for AB/FF 400/12 µg for the indication of the (b) (4) maintenance treatment of patients with COPD.

To support this application, the Applicant submitted results from two phase 3 twenty-four week placebo-controlled trials (M/40464/30 and LAC-MD-31) and one phase 3 twenty-four week active-controlled trial (D6571C00001) as the primary evidence of efficacy in terms of bronchodilation. These will be referred to as Trials 30, 31, and 01, respectively. To support the proposed (b) (4) claim, the Applicant referenced data from (b) (4) (b) (4) (b) (4) Trials 30, 31, and 01 demonstrated substantial evidence of efficacy as determined primarily based on statistically significant improvements in the co-primary endpoints, change from baseline in trough FEV1 and 1 hour post-dose FEV1 at Week 24. The increases from baseline in trough FEV1 were statistically significantly greater for AB/FF 400/12 µg than for FF 12 µg for Trials 30, 31, and 01, demonstrating the contribution of AB 400 µg. Similarly, The increases from baseline in 1 hour post-dose FEV1 were statistically significantly greater for AB/FF 400/12 µg than for AB 400 µg in Trials 30, 31, and 01, demonstrating the contribution of FF 12 µg. Additionally, as AB 400 µg is approved for COPD, superiority of AB/FF 400/12 µg to AB 400 µg also demonstrated the efficacy of AB/FF 400/12 µg. In Trials 30 and 31, the trials which included a placebo arm, AB/FF 400/12 µg also demonstrated superiority to placebo. Efficacy of AB/FF 400/12 µg, as well as the contribution of monocomponents was also supported by other secondary spirometric endpoints (e.g., FEV1 AUC_{0-3}, serial spirometry). Numerical improvements in symptoms based on St. George's Respiratory Questionnaire (SGRQ)

responder analysis were also observed. These data represent substantial evidence of efficacy of AB/FF 400/12 µg as a bronchodilator in COPD patients.

With regard to exacerbation, in Trial 02, AB 400 µg demonstrated a statistically significant exacerbation benefit compared to placebo. As the LABA and LAMA in this FDC are pharmaceutically equivalent to their monoproduct counterparts, scientifically, the two drugs are not expected to have a negative interaction in terms of exacerbation reduction. As such, it is likely that AB/FF 400/12 µg retains the exacerbation benefit of the AB 400 µg component and inclusion of such data in section 14 of the label is warranted. However, as discussed below, a separate exacerbation indication will not be included in Section 1.

Given the potential for multiple claims [airflow obstruction, exacerbations, St. George's Respiratory Questionnaire (SGRQ)] in COPD programs, the Division has determined that a more general COPD indication is appropriate for inhaled products (including monotherapies and fixed-dose combinations). To this end, the Division's new approach to COPD indications for inhaled products will no longer include separate indications for the maintenance treatment of airflow obstruction and exacerbation reduction, but will rather be more general. A more general COPD indication is consistent with the approach taken for labeling other recently approved products in the Division, e.g. asthma and rheumatoid arthritis. Details of clinical trials supporting efficacy in COPD with respect to the different efficacy endpoints (e.g., forced expiratory volume in 1 second (FEV_1), exacerbation, SGRQ) will be included in Section 14 of the product label.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

COPD is a debilitating respiratory condition that involves significant morbidity and mortality; it is the third leading cause of death in the US. A large amount of healthcare resources are utilized in managing long-term COPD as well as treating acute exacerbations. It is often associated with active or prior cigarette smoking (typically > 10 pack-years), but a number of other environmental and genetic factors have been found to contribute to its etiology. Multiple LAMA/LABA fixed dose combination inhalers exist, and this product provides another alternative treatment for patients with COPD.

The Applicant has submitted an NDA for Duaklir Pressair (AB/FF 400/12 µg) that is a fixed-dose combination of inhaled aclidinium bromide (AB) and formoterol fumarate (FF) administered via the Pressair inhaler. The proposed indication is for the (b) (4) maintenance treatment of (b) (4) patients with COPD (b) (4). The proposed dose is AB/FF 400/12 µg BID. AB 400 µg monotherapy is already approved as a maintenance treatment of airway obstruction for COPD. To support this application, the Applicant submitted three phase 3 twenty-four week trials [M/40464/30 (Trial 30), LAC-MD-31 (Trial 31) and D6571C00001 (Trial 01)] as the primary evidence of efficacy. The Applicant also references a thirty-six month COPD exacerbation trial [D6560C00002 Trial 02]) comparing AB 400 µg versus placebo to support exacerbation reduction. Regarding safety, the assessment is based on the pooled analyses of the 24-week placebo-controlled replicate trials (30 and 31), one active-controlled 24-week trial (01), and one 28-week safety extension trial [LAC-MD-36 (Trial 36)].

Trials 30, 31, and 01 demonstrated substantial evidence of efficacy as determined primarily based on statistically significant improvements in the co-primary endpoints, change from baseline in trough FEV1 and 1 hour post-dose FEV1 at Week 24. The increases from baseline in trough FEV1 were statistically significantly greater for AB/FF 400/12 µg than for FF 12 µg for Trials 30, 31, and 01, demonstrating the contribution of AB 400 µg. Similarly, the increases from baseline in 1 hour post-dose FEV1 were statistically significantly greater for AB/FF 400/12 µg than for AB 400 µg in Trials 30, 31, and 01, demonstrating the contribution of FF 12 µg. In Trials 30 and 31, the trials which included a placebo arm, AB/FF 400/12 µg also demonstrated superiority to placebo. Efficacy of AB/FF 400/12 µg, as well as the contribution of monocomponents was also supported by other secondary spirometric endpoints (e.g., FEV1 AUC_{0-3}, serial spirometry). Numerical improvements in symptoms based on St. George's Respiratory Questionnaire (SGRQ) responder analysis were also observed. These data represent substantial evidence of efficacy of AB/FF 400/12 µg as a bronchodilator in COPD patients.

With regard to exacerbation, in Trial 02, AB 400 µg demonstrated a statistically significant exacerbation benefit compared to placebo. As the LABA and LAMA in this FDC are pharmaceutically equivalent to their monoproduct counterparts, scientifically, the two drugs are not expected to have a negative interaction in terms of exacerbation reduction. As such, it is likely that AB/FF 400/12 µg retains the exacerbation benefit of

the AB 400 µg component and inclusion of such data in section 14 of the label is warranted. However, as discussed below, a separate exacerbation indication will not be included in Section 1.

Given the potential for multiple claims [airflow obstruction, exacerbations, St. George's Respiratory Questionnaire (SGRQ)] in COPD programs, the Division has determined that a more general COPD indication is appropriate for inhaled products (including monotherapies and fixed-dose combinations). To this end, the Division's new approach to COPD indications for inhaled products will no longer include separate indications for the maintenance treatment of airflow obstruction and exacerbation reduction, but will rather be more general. A more general COPD indication is consistent with the approach taken for labeling other recently approved products in the Division, e.g. asthma and rheumatoid arthritis.

With regard to safety, analyses of safety data from Trials 30, 31, 01, and 36 did not reveal new safety concerns and were consistent with safety findings for other similar products.

This review recommends Approval of Duaklir Pressair for the (b) (4) maintenance treatment of patients with COPD at a dose of AB/FF 400/12 µg BID based on the clinical evidence discussed above. Efficacy was demonstrated over placebo and monocomponents in the bronchodilator trials and no safety concerns were identified that would preclude approval or require a REMS (Risk Evaluation and Mitigation Strategy).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COPD is a debilitating respiratory condition that involves significant morbidity, mortality, and healthcare resource utilization. • COPD primarily affects tobacco users over 40 years of age; it is the third leading cause of death in the US and rates continue to rise. • Common symptoms of COPD include one or more of the following: dyspnea, fatigue, cough, sputum production, chest tightness, wheezing, worsened exercise capacity, depression, anxiety, weight changes. • Diagnosis primarily rests on spirometry; a decreased FEV1/FVC ratio <	COPD is a common debilitating respiratory condition causing significant morbidity and mortality. The diagnostic and symptom assessment instruments used by the Applicant are reasonable to assess COPD.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	0.7 is used for diagnosis of COPD in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. • Treatment primarily involves use of inhaled medications for symptom control of acute exacerbations and chronic long term maintenance; other treatment adjuncts (e.g. tobacco cessation, pulmonary rehabilitation, oxygen use) are important as well.	
Current Treatment Options	• Several classes of inhaled medications exist for the long-term maintenance treatment of COPD: Anticholinergics, LABA, and combination products (with and without ICS).	Multiple inhaled medications including LAMA/LABA fixed dose combination inhalers exist, and this product provides another alternative treatment for patients with COPD.
Benefit	• The Applicant has demonstrated substantial evidence of efficacy for AB/FF 400/12 µg in COPD patients based on statistically significant improvements in trough FEV1 and 1 hour post-dose FEV1 at Week 24, with support from other spirometric endpoints (e.g., AUC_{0-3}), as well as numerical improvements in symptoms based on St. George's Respiratory Questionnaire (SGRQ).	AB/FF 400/12 µg provides clinically relevant treatment benefits in COPD patients. Clinical data demonstrated that AB/FF 400/12 µg was superior to its monocomponents in terms of the primary endpoint with supportive data from secondary endpoints.
Risk and Risk Management	• The safety program for Duaklir Pressair demonstrated no new concerning safety signals beyond that seen with medications in its class. • No REMS is proposed.	No safety findings were identified in the clinical development program that outweigh the potential benefit. Labeling and routine pharmacovigilance alone are recommended.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.3
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

COPD is a debilitating respiratory condition that involves significant morbidity and mortality; it is the third leading cause of death in the US and rates continue to rise. Given its high prevalence and significant disease burden, a large amount of healthcare resources is utilized in managing long-term COPD as well as treating acute exacerbations. It is often associated with active or prior cigarette smoking (typically > 10 pack-years), but a number of other environmental and genetic factors have been found to contribute to the development of COPD.

COPD is defined as a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation. The chronic airflow limitation that characterizes COPD is caused by a mixture of small airways disease (e.g. obstructive bronchiolitis) and parenchymal destruction (emphysema). Chronic inflammation causes structural changes, small airways narrowing, and destruction of lung parenchyma. This results in a loss of small airways which may contribute to airflow limitation and mucociliary dysfunction, leading to the clinical characteristic features of the disease.

Common symptoms of COPD include the following: dyspnea, fatigue, cough, sputum production, chest tightness, wheezing, worsened exercise capacity, depression, anxiety, weight changes. The impact these symptoms have on patient's daily living can be substantial; often, routines are altered to minimize symptoms. Physical exam findings can be minimal but may include: wheezing, prolonged expiration, decreased breath sounds, crackles at the lung bases, distant heart sounds, increased AP chest diameter, diminished diaphragmatic excursion, yellow finger stains, clubbing, accessory muscle use, jugular venous distention. Diagnosis primarily rests on spirometry; a decreased FEV1/FVC ratio < 0.7 is used for diagnosis of COPD in the GOLD guidelines. Other diagnostic test features can include a decreased FEV1, lower peak expiratory flow rates, increased lung volumes (residual volume, total lung capacity, functional residual capacity), decreased diffusing capacity, oxygen desaturation, and hypercapnia. Radiography typically has a lower sensitivity but can also reveal changes such as vascular tapering, radiolucency, flattened diaphragms, bullous disease, apical radiolucency, and prominent hilar vascularity.

Despite a variable natural history, attempts at prognosticating have long been based on spirometry (particularly the FEV1). Additional prognostic indicators have been identified such as airway responsiveness, coexisting cardiac disease, amount of tobacco use, BMI/nutritional status, exercise capacity, VO2, and presence of emphysema on radiography, to name a few. Using several of these indicators, prognostic measuring tools have been constructed (e.g. the BODE index) but their use is limited at present. The GOLD guidelines use symptom measurement scales (MMRC and CAT), prior exacerbation and hospitalization history, and FEV1 to assess risk and therapeutic strategy.

In conclusion, COPD is a serious disease with significant societal and individual impact due to its prevalence, rising incidence, and morbidity and mortality. It involves respiratory debility from pulmonary symptoms and is mainly diagnosed via spirometry (GOLD guidelines). Its symptoms can overlap with multiple other disease processes that sometimes frequently occur together given the older comorbid population that COPD occurs in. Treatment options are discussed in Section 2.2.

2.2. Analysis of Current Treatment Options

There are multiple current treatment options for COPD, the majority of which are shown in Table 1.

Table 1: Current COPD treatment options

Class		Generic Name	Brand Name	Approval
Beta$_2$-adrenergic agonists	Short-acting (SABA)*	Albuterol sulfate	Accuneb ProAir HFA Proventil HFA Ventolin HFA	1981
		Levalbuterol tartrate	Xopenex HFA	1999
	Long-acting (LABA)	Salmeterol xinafoate	Serevent Diskus	1997
		Formoterol fumarate	Foradil Aerolizer**	2001
		Arformoterol tartrate	Brovana	2006
		Formoterol Solution	Perforomist	2001
		Indacaterol maleate	Arcapta Neohaler	2011
		Olodaterol hydrochloride	Striverdi Respimat	2014
Anticholinergic	Long-acting (LAMA)	Tiotropium bromide	Spiriva Handihaler Spiriva Respimat	2004
		Revefenacin	Yupelri	2018
		Aclidinium bromide	Tudorza Pressair	2012
		Umeclidinium bromide	Incruse Ellipta	2014
		Glycopyrrolate	Seebri Neohaler	2015
			Lonhala Magnair	2017
	Short-acting	Ipratropium bromide	Atrovent HFA	2004
Combination	SABA/anticholinergic	Albuterol/Ipratropium	DuoNeb Combivent Combivent Respimat	1996
	Corticosteroid (ICS)/LABA	Fluticasone/Salmeterol	Advair Diskus Advair HFA	2000
		Budesonide/Formoterol	Symbicort	2006
		Fluticasone/Vilanterol	Breo Ellipta	2013
	Anticholinergic/LABA	Umeclidinium/Vilanterol	Anoro Ellipta	2013
		Tiotropium/Olodaterol	Stiolto Respimat	2015
		Glycopyrrolate/Indacaterol	Utibron Neohaler	2015
		Glycopyrrolate/Formoterol	Bevespi Aerosphere	2016
	LAMA/LABA/ICS	Fluticasone/Umeclidinium/ Vilanterol	Trelegy	2017
Xanthines		Theophylline	Multiple	1992
Phosphodiesterase inhibitors	PDE4 Inhibitors	Roflumilast	Daliresp	2011

*General bronchodilator claim, not specifically indicated for COPD
**no longer marketed

Source: Reviewer composition, Drugs@FDA (December 2018)

There are treatment options for both long-term maintenance treatment of airflow obstruction as well as options to reduce exacerbations. Some inhaled medications have indications for both long-term maintenance treatment and exacerbation reduction (e.g. tiotropium, Fluticasone/Vilanterol). Acute exacerbations are treated with corticosteroids, increased frequency of short-acting bronchodilators, and/or antibiotics.

Although pharmacologic therapy is the mainstay of management for COPD, non-pharmacologic treatments play an important role as well: tobacco cessation, pulmonary rehabilitation and education, oxygen therapy, vaccination maintenance, risk factor reduction, nutritional optimization, lung volume reduction surgery (LVRS), and palliative measures.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

AB/FF 400/12 µg (Duaklir Pressair) is not marketed or approved in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

AB/FF 400/12 µg (Duaklir Pressair) was studied under IND 72252, opened in 2006. Relevant key regulatory interactions are summarized below:

Pre-IND Meeting August 8, 2013

- AB fine particle dose (FPD) in AB/FF was over 10% higher than in AB.
- FF 12 ug demonstrated less bronchodilatory effect than FORADIL 12 ug.

Pre-IND Meeting July 10, 2014

- The factorial design trial (D6571C00001) comparing AB/FF to monotherapy was acceptable, provided that CMC issues such as FPD in each arm were resolved.
- 1h post-dose FEV1 and trough FEV1 as co-primary endpoints in trial D6571C0001 were acceptable.
- Trial replication of FF contribution to AB/FF was not needed.
- Trial D6571C00002 with multiple doses of FF and FORADIL in a bronchodilator-sensitive COPD population was recommended to support FF dose selection.

Pre-IND Meeting November 28, 2017

- The proposed efficacy data package would support filing and review of the future NDA. Spirometric parameters as well as clinically relevant endpoints (e.g., SGRQ, COPD exacerbation) would be considered in determining efficacy.
- FF 12 ug demonstrated less effect than FORADIL 12 ug.

Tudorza (aclidinium) Supplemental NDA (202450) submission May 9, 2018

- The Applicant proposed to include the indication of [redacted] (b) (4) in the label of Tudorza Pressair. The Applicant has proposed to use this same data to support an [redacted] (b) (4) indication for AB/FF. This submission is currently under review.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Given that Tudorza Pressair containing AB and Foradil and Perforomist containing FF were approved in US market years ago (although Foradil was withdrawn for business reasons), the

efficacy/safety profiles of each monocomponent are well-understood, and that the contribution of each study site to each of the trials was small, no inspections were deemed necessary.

4.2. Product Quality

The application is recommended for Approval from the CMC/quality perspective.

AB/FF inhalation powder (400 µg/12 µg) with proposed proprietary name Duaklir Pressair, is a fixed-dose combination product containing aclidinium bromide, a long-acting muscarinic antagonist (LAMA), and formoterol fumarate, a long-acting β_2-agonist (LABA). The drug product is a breath-actuated pre-metered multi-dose inhalation powder (or dry powder inhaler).

Information for the two drug substances are provided in drug master files (DMFs) and are incorporated by reference. Both DMFs have been recently reviewed and were found to be adequate. As a result, there are no approvability issues for the drug substance portion of this application and there are no deficiencies that need to be reported to the Applicant with respect to the drug substance portion of this application. The data are adequate to support the use of aclidinium bromide and formoterol fumarate in the manufacture of AB/FF inhalation powder drug product.

Data have been provided to support that each actuation from Duaklir Pressair meters 12 mg powder from cartridge, containing 400 µg of aclidinium bromide and 12 µg of formoterol fumarate (as a dihydrate), and delivers 396 µg of aclidinium bromide and 11.8 µg of formoterol fumarate (as a dihydrate). The Applicant has performed several product development studies to demonstrate chemical and physical stability, and robustness of Duaklir Pressair. The Applicant has provided 36 months of long-term and 6 months of accelerated stability data for three primary stability batches of the 60 actuation configuration, and for a supportive stability batch of the 30 actuation configuration, all manufactured at their Ireland facility. These primary stability batches were also used in the clinical trials. Additionally, the Applicant has provided 3 months of both long-term and accelerated stability data for three stability batches manufactured at their proposed alternative manufacturing site in Sweden. The overall stability data submitted by the Applicant adequately support their proposed shelf-life of 36 months, and (b) (4) days for the in-use period (after opening protective packaging). The Applicant has adequately demonstrated comparability between the drug product batches manufactured at their Ireland facility and Swedish facility. The Applicant has also adequately demonstrated in vitro comparability of Duaklir Pressair 400 µg/12 µg with the respective mono-therapy products, aclidinium bromide 400 µg inhalation powder and formoterol fumarate 12 µg inhalation powder, for the batches used in the clinical trial D6571C00001. During the review cycle, one information request (IR) was sent to the Applicant for data to support their proposed label claims for metered powder mass, metered dose of each active pharmaceutical ingredient (API), and delivered dose of each API, and devices used in their Phase 3 clinical program. The Applicant adequately provided the requested information in the IR response dated September 20, 2018. The Phase 3 studies were conducted with the inhaler intended for commercialization; after Phase 3, only one change to the device, the orange color for the dosage key and the

mouthpiece cap, was introduced. The CMC drug product information submitted in the original submission and in the IR response dated September 20, 2018, were adequate, and there are no approvability issues.

The manufacturing steps for the drug product includes (b) (4) (b) (4)

The pivotal clinical batches and the primary registration stability batches were manufactured at (b) (4), which will be the alternate commercial manufacturing site for the drug product. The primary commercial manufacturing site for the product will be AstraZeneca in Sweden (FEI # 3003342394). A pre-approval inspection (PAI) was performed at each of the facilities by the drug and device investigators to cover the profile classes of Aerosol Dispensed Medication (ADM) and Orally Inhaled Delivery (OID). The PAI at the AstraZeneca site resulted in a one-item FDA 483 reflecting the firm's deficiency in reviewing analytical source data such as electronic files, audit trails, and logbooks and was classified VAI (voluntary action indicated). The PAI at the (b) (4) was classified NAI (no action indicated). All facilities, including drug substance and drug product manufacture and testing facilities, are considered acceptable based on the PAIs or firm's history.

4.3. Devices and Companion Diagnostic Issues

This product is administrated via the Pressair device. Tudorza Pressair uses the same device and has been approved in the US market since 2012. No additional device and companion diagnostic issues are identified.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Nonclinical safety of aclidinium bromide was assessed under NDA 202450 (referenced by the Applicant). Nonclinical safety of formoterol fumarate was assessed under NDA 021929 (referenced by the Applicant). The Applicant conducted two repeat dose- 4- and 13-week inhalation toxicology studies in dogs with the combination of aclidinium bromide (LAS34273) and formoterol fumarate dihydrate to support clinical development of this combination product.

5.2. Toxicology

In the 4-week inhalation toxicology study, dogs received LAS34273/formoterol at nominal doses of 33/2, 100/6, and 500/30 µg/kg/day (pulmonary deposited doses were 7/0.5, 21/1.5, and 105/7.5 µg/kg/day, respectively). LAS34273 alone or formoterol alone group was not included in the study and would have allowed for further assessment of potential additive or synergistic toxic effects. Multifocal ventricular tachycardia with ventricular premature complexes were observed after the first and/or second dose for 2 dogs from the mid dose combination group and 7 dogs from the high dose combination group. Besides, there were some arrhythmogenic findings for dogs in the high dose combination group. Heart rates were dose-dependently increased in treated males and females during week 1 and week 3/4; and increased heart rates were more pronounced during week 1 as compared to week 3/4. The target organ of toxicity was the heart based on findings in the high dose combination group of minimal to slight fibrosis in the papillary muscle and moderate arterial media proliferation in the intramural arteries of the papillary muscle. This is a well-known β-adrenergic toxicity.

There were additional findings in the tracheal carina, kidneys, spleen, and testes for dogs in the high dose combination group that were potentially related to treatment with LAS34273 + formoterol; however, only the findings in the testes were evident in the 13-week toxicology study given that the high dose of the combination had been lowered (see below). The incidence of tubular degeneration in the testes was increased for males in the high dose combination group. Therefore, the NOAEL was established at the low dose combination group (LAS34273/formoterol- 33/2 µg/kg/day) based upon occurrences of ventricular tachycardia and ventricular premature complexes for the mid and high dose combination groups as well as histopathological findings in the heart, tracheal carina, kidneys, and testes for the high dose combination group.

In the 13-week inhalation toxicology study, dogs received LAS34273/formoterol at nominal doses of 33/2, 100/6, and 300/18 µg/kg/day (pulmonary deposited doses were 7.1/0.5, 21/1.5, and 62.5/4.4 µg/kg/day, respectively). LAS34273 alone and formoterol alone groups were included in the study at nominal doses identical to the high dose combination group. A 3- to 5-day dose escalation was used to reach target doses for the mid and high dose combination

groups and formoterol only group. This dose escalation may have potentially reduced the observed β-adrenergic cardiac toxicity for these treatment groups. However, the impact of dose escalation was judged to be minimal because the NOAEL was established at the low dose combination, for which dose escalation was not used.

Ventricular tachycardia and/or ventricular premature complex were observed for 3 dogs in the high dose combination group on day 5/6 (after the nominal target dose had been achieved) and for one dog in the LAS34273 only group during week 13. It is possible that the dose escalation procedure used in the present study may have prevented detection of arrhythmogenic activity for the mid dose combination group that was observed in the 4-week study, where dose escalation was not used. Ventricular tachycardia and/or ventricular premature complex were not observed for either the LAS34273 only or formoterol only groups at day 5/6, which was suggestive of potential additive or synergistic activity for the high dose combination group and the mid dose combination group based upon the results of the 4-week toxicology study. However, there was no evidence of an additive or synergistic effect for the low dose combination group based upon the results of present study and the 4-week toxicology study. Notably, in a separate cardiovascular safety pharmacology study with intravenous LAS34273 or formoterol given separately or together, findings of ventricular tachycardia and/or ventricular premature complexes with the combination were attributed to formoterol. Besides arrhythmogenic activity, increased heart rates were observed in males and females across all dose groups during weeks 1 and 13 with no evidence of an additive or synergistic effect of LAS34273 and formoterol.

Histopathological findings were observed in the liver, testes, thymus, and paranasal sinuses. Bile duct proliferation in the liver was observed for 2/4 females in each of the mid and high dose combination groups. Tubular degeneration in the testes was observed for 1/4 male dogs in each of the mid and high dose combination groups, the LAS34273 only group, and the formoterol only group indicating there was no potentiation. Thymic congestion was observed for 1/4 male dogs in the high dose combination group. A papilloma was observed in the paranasal sinuses for one female in the high dose LAS34273/formoterol group. A relationship of these findings to treatment could not be ruled out; therefore, the NOAEL was established at the low dose combination group (LAS34273/formoterol- 33/2 µg/kg/day) based upon occurrences of ventricular tachycardia and/or ventricular premature complexes for the mid and high dose combination groups as well as histopathological findings of bile duct proliferation and testicular tubular degeneration for the mid and high dose combination groups. Moreover, findings of ventricular tachycardia, premature ventricular complexes, and bile duct proliferation in the mid and high dose combination groups might be suggestive of additive or synergistic effects of LAS34273 and formoterol as these findings were not observed in LAS34273 alone or formoterol alone group. However, there was no evidence of toxicity or additive/synergistic effects for the low dose combination identified as the NOAEL.

6. Clinical Pharmacology

6.1. Executive Summary

On May 31, 2018, AstraZeneca (Applicant) submitted a 505(b)(1) new drug application seeking approval of aclidinium bromide (AB) and formoterol fumarate (FF) dry powder inhaler (proposed name Duaklir Pressair) for (b) (4) maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). The drug product is a breath-actuated multi-dose dry powder inhaler. The proposed dosing regimen is one inhalation twice daily (BID).

The clinical development program included two pharmacokinetic (PK) studies: one in healthy subjects (Study M/40464/02), and one in patients with moderate-to-severe COPD (Study LAC-PK-01). The Applicant also conducted one dose-ranging study in patients with mild-to-moderate asthma (Study LAC-MD-21) and two dose-ranging studies in patients with moderate-to-severe COPD (Studies D6571C00002 and LAC-MD-27). In addition, the Applicant conducted three Phase 3 studies in patients with stable COPD (Studies M/40464/30, LAC-MD-31 and D6571C00001). The following are the major findings from the current review:

1. Following single-dose administration of 400 µg/12 µg AB/FF combination product via the Pressair device in healthy subjects, the mean peak plasma concentration (C_{max}) and the total systemic exposure (AUC_{inf}) of aclidinium and formoterol were 270 pg/mL and and 406 pg.hr/mL, and 11 pg/mL and 42.9 pg.hr/mL, respectively. There were no clinically relevant differences in the pharmacokinetics of either aclidinium and formoterol when administered alone or in combination (Study M/40464/02).
2. Following repeat dosing (BID) of 400 µg/12 µg AB/FF via the Pressair device in patients with moderate-to-severe COPD for 5 days, the steady-state C_{max} and AUC_{tau} of aclidinium were 128 pg/mL and 404 pg.hr/mL, respectively, and that for formoterol were 16.7 pg/mL and 85.2 pg.hr/mL, respectively (Study LAC-PK-01).
3. The dosing for FF has been adequately explored in two Phase 2 studies. In Study LAC-MD-21, FF doses of 6 and 12 µg via the Pressair device were investigated. Both the FF doses delivered via the Pressair device showed statistically significant improvement in the primary efficacy endpoint (i.e., FEV1 $AUC_{0\text{-}6h}$ on Day 14 post-dose) compared to placebo with a trend of dose-response. In addition, the FEV1 $AUC_{0\text{-}6h}$ for the 12 µg FF dose was generally comparable to the active control, Foradil® Aerolizer® 12 µg. In Study D6571C00002, FF doses of 6, 12 and 24 µg via the Pressair device were investigated in patients with moderate-to-severe COPD with reversible airway limitation. All three FF doses showed statistically significant improvement in the primary efficacy endpoint (i.e., FEV1 $AUC_{0\text{-}12h}$ on Day 7 post-dose) compared to placebo with a trend of dose-response. FEV1 $AUC_{0\text{-}12h}$ for both 6 and 12 µg FF dose were comparable to the active control, Perforomist 20 µg; however, the 24 µg FF dose was superior to Perforomist 20 µg. Hence, both 6 and 12 µg doses of FF, in combination with aclidinium bromide, were investigated in Phase 3 studies. Dose of AB was optimized under the Tudorza Pressair (NDA 202450) clinical development program.

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 210595 and finds the application approvable.

6.2. Summary of Clinical Pharmacology Assessment

Pharmacokinetics:
The pharmacokinetics of AB and FF in healthy subjects, and drug interaction between AB and FF were investigated in Study M/40464/02. The PK of AB and FF was also investigated in patients with COPD in Study LAC-PK-01.

In Study M/40464/02, healthy subjects received a single dose of AB/FF 400 µg/12 µg, AB 400 µg and FF 12 µg in a crossover fashion, all via the Pressair device. The PK parameters from this study are summarized in Table 2. In general, the C_{max} and AUC_{inf} of aclidinium were 26% and 17% higher, respectively, when administered as AB/FF combination product versus AB monoproduct. Similarly, the C_{max} and AUC_{inf} of formoterol were 18% and 4% higher, respectively, when administered as AB/FF combination product versus FF monoproduct.

Table 2. Arithmetic mean PK parameters for aclidinium and formoterol after single dose administration in healthy subjects (Study M/40464/02)

Parameter (unit)	Mean PK of aclidinium (CV%)		Mean PK of formoterol (CV%)	
	AB/FF 400 µg/12 µg	AB 400 µg	AB/FF 400 µg/12 µg	FF 12 µg
C_{max} (pg/mL)	270 (73.5)	215 (66.7)	11 (31.8)	9.3 (42)
AUC_t (pg.hr/mL)	229 (60.9)	222 (58.8)	36 (36.5)	32.4 (43.3)
AUC_{inf} (pg.hr/mL)	406 (52.1)	346 (60.6)	42.9 (25.4)	41.2 (35.9)

Source: NDA 210595, Module5.3, Clinical study report (Study M/40464/02)

In Study LAC-PK-01, patients with moderate-to-severe COPD received AB/FF 400 µg/12 µg BID via Pressair device or Foradil Aerolizer 12 µg BID for 4 days, and then one inhalation in the morning on Day 5. At steady state, C_{max} and AUC_{tau} of aclidinium were 128 pg/mL and 404 pg.hr/mL, respectively, and that of formoterol were 16.7 pg/mL and 85.2 pg.hr/mL, respectively.

Dose selection:

The dose-ranging studies for of AB were conducted under the Tudorza Pressair clinical development program (NDA 202450); refer to the clinical review by Dr. Jennifer Pippins and the clinical pharmacology review by Dr. Ping Ji for details. The Applicant conducted two dose-ranging studies (Studies LAC-MD-21 and D6571C00002) to determine the optimal dose of FF delivered via the Pressair device.

In Study LAC-MD-21, patients with mild-to-moderate asthma received 6 and 12 µg doses of FF delivered via the Pressair device. Both the FF doses showed statistically significant improvement in the primary efficacy endpoint (i.e., FEV1 AUC_{0-6h} on Day 14 post-dose) compared to placebo with a trend of dose-response (Figure 1).

In Study D6571C00002, patients with moderate-to-severe COPD with reversible airway limitation received 6, 12 and 24 µg doses of FF delivered via the Pressair device. All three FF doses showed statistically significant improvement in the primary efficacy endpoint (i.e., FEV1 $AUC_{0\text{-}12h}$ on Day 7 post-dose) compared to placebo with a trend of dose-response (Figure 2).

In addition, the optimal dose of FF in combination with AB was also evaluated in a Phase 2b study (LAC-MD-27), in which patients with moderate-to-severe COPD received AB/FF at doses of 400 µg/6 µg and 400 µg/12 µg, AB 400 µg and FF 12 µg, all via the Pressair device. Both 400 µg/12 µg and 400 µg/6 µg doses showed statistically significant improvement in the primacy efficacy endpoint (i.e., FEV1 $AUC_{0\text{-}12h}$ on Day 14) compared to placebo. However, the study failed to show dose separation between the 400 µg/6 µg and 400 µg/12 µg doses (change in FEV1 $AUC_{0\text{-}12h}$ on Day 14 compared to placebo were 0.200 L and 0.202 L, respectively). Consequently, both the 400 µg/6 µg and 400 µg/12 µg doses of AB/FF were further studied in the Phase 3 confirmatory trials.

6.3. Clinical Pharmacology Background

6.3.1. Background

Aclidinium bromide is a long-acting muscarinic antagonist (LAMA) that is approved in the United States as a 400 µg BID maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema (Tudorza Pressair, NDA 202450). Formoterol is a long-acting β2 agonist (LABA) that is also approved in United States, alone or in combination with inhaled corticosteroids, for treatment of asthma, prevention of exercise-induced bronchospasm and maintenance treatment of bronchoconstriction in patients with COPD.

6.3.2. What is the relevant regulatory background pertinent to this application?

The Applicant carried out the development program for AB/FF powder for inhalation product under IND 72252. During the end-of-Phase 2 meeting in June 2011, the Agency raised concern on Applicant's proposed Phase 3 doses (400 µg/6 and 400 µg/12 µg AB/FF) since FF dose selection studies were conducted in patients with COPD. The Agency recommended that the optimal FF dose be established in a bronchodilator-responsive population (i.e., asthma) since asthma patients are more sensitive to the severe adverse events that have been linked to LABA.[1] Hence, the Applicant conducted a Phase 2 dose-ranging study in asthma patients (LAC-MD-21). However, the Agency did not agree with the Applicant's assessment of FF 12 µg dose being adequate since the study demonstrated lower efficacy of FF 12 µg compared to Foradil Aerolizer 12 µg.[2] The Agency suggested conducting another dose-ranging trial with multiple doses of FF and multiple doses of Foradil Aerolizer in a bronchodilator-sensitive population (e.g., bronchodilator-sensitive COPD population) to support FF dose selection.[3] Consequently, the Applicant conducted another FF dose-ranging study in COPD patients with reversible airway limitation, and used Perforomist as an active comparator in the study (Study D6571C00002). The

[1] DARRTS: IND 72252, Meeting minute dated 07/12/2011
[2] DARRTS: IND 72252, Meeting minute dated 08/30/2013
[3] DARRTS: IND 72252, Meeting minute dated 08/07/2014

Applicant also reported results from two Phase 3 studies conducted in patients with stable COPD (LAC-MD-31 and M/40464/30). The Agency raised concern regarding the validity of the factorial comparisons assessed in the Phase 3 studies citing that the aclidinium fine particle dose (FPD) delivered from the AB/FF combination product was substantially higher than the FPD delivered from the aclidinium monotherapy comparator.[2] To address the Agency's concern on the difference in FPD, the Applicant conducted another Phase 3 study in patients with COPD (Study D6571C00001).[4]

6.3.3. What are the clinical pharmacology studies submitted to support this NDA?

The clinical pharmacology studies submitted in support of this NDA are summarized below:

Table 3: Listing of clinical pharmacology studies in support of this NDA

	Study ID	Objectives	Population	Study Design	Treatment and Device
PK study	M/40464/02	PK	HS (n=30)	SC, R, OL, 3-way, CO	AB/FF via Pressair: 400 µg/12 µg single dose AB via Pressair: 400 µg single dose FF via Pressair: 12 µg single dose
	LAC-PK-01	PK	COPD (n=24)	SC, R, OL, 2-way, CO	AB/FF via Pressair: 400 µg/12 BID for 4 days and single dose on Day 5 Foradil Aerolizer: 12 µg BID for 4 days and single dose on Day 5
Phase 2 study	LAC-MD-21	Dose-ranging	Asthma (n=174)	R, DB, DD CO	FF via Pressair: 6 µg BID for 14 days FF via Pressair: 12 µg BID for 14 days Foradil Aerolizer: 12 µg BID for 14 days Foradil Aerolizer: 24 µg BID for 14 days
	D6571C00002	Dose-ranging	COPD (n=132)	R, DB, CO (Perforomist was OL)	FF via Pressair: 6 µg BID for 7 days FF via Pressair: 12 µg BID for 7 days FF via Pressair: 24 µg BID for 7 days Perforomist: 20 µg BID for 7 days Perforomist: 40 µg single dose Placebo via Pressair
	LAC-MD-27	Dose-ranging	COPD (n=128)	R, DB, CO	AB/FF via Pressair: 400 µg/12 µg BID for 14 days AB/FF via Pressair: 400 µg/6 µg BID for 14 days AB via Pressair: 400 µg BID for 14 days FF via Pressair: 12 µg BID for 14 days Placebo via Pressair

6.4. Comprehensive Clinical Pharmacology Review

6.4.1. What are the proposed mechanism of action and therapeutic indications?

Aclidinium bromide is a long-acting antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in

[4] DARRTS: IND 72252, Written response dated 11/21/2017

vitro as well as in vivo studies, prevention of acetylcholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of aclidinium bromide is predominantly a site-specific effect.[5]

Formoterol fumarate is a long-acting selective beta$_2$-adrenergic agonist (beta$_2$-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at beta$_2$-receptors than at beta$_1$ receptors. The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.[6]

Duaklir Pressair is being proposed for the (b) (4), maintenance treatment of (b) (4) patients with COPD (b) (4) .

6.4.2. What are the proposed dosages and routes of administration?

AB/FF 400/12 is to be administered by oral inhalation only. The proposed dose is 400 µg/12 µg AB/FF twice daily (once in the morning and once in the evening).

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

Relative bioavailability studies:
The clinical pharmacology package submitted for this NDA consisted of two relative bioavailability studies: M/40464/02 was aimed to assess the relative bioavailability of AB/FF combination product compared to the corresponding mono-products in healthy subjects. Study LAC-PK-01 was aimed to evaluate the PK, safety and tolerability of AB/FF 400 µg/12 µg via the Pressair device and FF 12 µg via Foradil Aerolizer in patients with moderate-to-severe COPD. The design features of the two studies are summarized below.

Study M/40464/02 was a Phase 1, randomized, open-label, 3-way crossover study conducted in 30 healthy subjects who received the following three treatments:

- AB/FF via Pressair: 400 µg/12 µg single dose

[5] Prescribing information of Tudorza Pressair.
[6] Prescribing information of Symbicort.

- AB via Pressair: 400 µg single dose
- FF via Pressair: 12 µg single dose

Subjects received all three treatments; one per period. The duration of each period was 24 hours with a washout period of at least 7 days and no more than 14 days between the periods. Blood samples were collected pre-dose and at 5, 15 and 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hr post-dose.

Study LAC-PK-01 was a Phase 2a, single-center, randomized, open-label, 2-way crossover, multiple-dose study conducted in 24 patients with moderate-to-severe COPD who received the following two treatments:

- AB/FF via Pressair: 400 µg/12 µg BID for 4 days, then one inhalation (morning) on Day 5
- Foradil Aerolizer: 12 µg BID for 4 days, then one inhalation (morning) on Day 5

Patients received the treatments in a randomized order; treatments were separated by a 7-day washout period. Blood samples were collected on Day 1 (pre-dose, 5, 15 and 30 min, 1, 1.5, 2, 3, 4, 6, 8 and 12 hr post-AM dose and at 5, 15 min post-PM dose), Days 2–4 (pre-dose, 5 and 15 min both post-AM and PM dose) and Day 5 (pre-dose, 5, 15 and 30 min, 1, 1.5, 2, 3, 4, 6, 8 and 12 hr post-AM dose).

<u>Dose-ranging studies:</u>
The dose-ranging studies for AB were conducted under the Tudorza Pressair clinical development program (refer to the clinical review by Dr. Jennifer Pippins and clinical pharmacology review by Dr. Ping Ji for details). To support dose selection of FF, the Applicant conducted two dose-ranging studies (LAC-MD-21 and D6571C00002) to determine the optimal dose of FF delivered via the Pressair device. In addition, a Phase 2b study (LAC-MD-27) was conducted to evaluate the optimal dose of FF to be administered in combination with AB. The design features of the dose-ranging studies are briefly discussed below.

Study LAC-MD-21 was a Phase 2, randomized, placebo-controlled, double-blind, double-dummy, 5 period, cross-over study conducted in 174 patients with mild-to-moderate asthma who received the following treatments:

- FF via Pressair: 6 µg BID
- FF via Pressair: 12 µg BID
- FF via Foradil Aerolizer: 12 µg BID (Active control)
- FF via Foradil Aerolizer: 24 µg BID (Active control)
- Placebo via Pressair

Patients were randomized and received each treatment for 14 days. A 9 to 13 days washout period was required between all periods. The primary efficacy endpoint was change from baseline in normalized FEV1 AUC_{0-6} after the morning dose at Day 14. Pharmacokinetic assessments were not performed in this study.

Study D66571C00002 was a randomized, double-blind, placebo-controlled, cross-over study conducted in 132 patients with moderate-to-severe COPD with reversible airway limitation who received the following treatments:

- FF via Pressair: 6 µg BID

- FF via Pressair: 12 µg BID
- FF via Pressair: 24 µg BID
- FF via Perforomist: 20 µg BID (Active control)
- FF via Perforomist: 40 µg single dose (Active control)
- Placebo via Pressair

Patients were randomized to one of the treatment sequences each consisting of five treatment periods separated by a washout period of 7 days. The treatment duration in each period was 7(±1) days except for the Perforomist 40 treatment where a single dose was administered. The primary efficacy endpoint was change from baseline in normalized FEV1 AUC over the 12 h period immediately after morning study drug administration ($AUC_{0\text{-}12h}$ at Day 7). Pharmacokinetic assessments were not performed in this study.

LAC-MD-27 was a multicenter, randomized, double-blind, placebo-controlled, 4-period, cross-over, dose-ranging study in 128 patients with stable, moderate-to-severe COPD who received the following treatments:

- AB/FF via Pressair: 400 µg/12 µg BID
- AB/FF via Pressair: 400 µg/6 µg BID
- AB via Pressair: 400 µg BID
- FF via Pressair: 12 µg BID
- Placebo via Pressair

Patients who met the eligibility criteria were randomized to double-blind treatment periods of 14(±1) days, followed by a washout period of 7 to 10 days. The primary efficacy endpoint was change from baseline in normalized FEV1 area under the curve over the 12 hours ($AUC_{0\text{-}12}$) after the morning dose at Day 14. Pharmacokinetic assessments were not performed in this study.

6.4.4. What are the characteristics of the dose/exposure-response relationship for the effectiveness?

The systemic exposure of inhaled aclidinium or formoterol are not directly related to clinical response (FEV1). The dose-response relationship for AB was evaluated under the clinical development program for Tudorza Pressair. For FF, the dose-response has been explored in two Phase 2 studies. In Study LAC-MD-21, following BID administration for 14 days in patients with mild-to-moderate asthma, both 6 and 12 µg doses of FF delivered via the Pressair device showed statistically significant improvement in the primary efficacy endpoint (i.e., FEV1 $AUC_{0\text{-}6h}$ on Day 14 post-dose) compared to placebo; LS mean change from baseline were 0.217 L ($p<0.0001$) and 0.224 L ($P<0.0001$) for FF dose of 6 µg and 12 µg, respectively. In addition, the FEV1 $AUC_{0\text{-}6h}$ for the 12 µg FF dose was comparable to the active control, Foradil Aerolizer 12 µg (0.224 L and 0.252 L, respectively).

Figure 1: Change from baseline in (A) FEV1 (L) at each specific timepoint on Day 14; (B) normalized FEV1 AUC_{0-6h} (L) at Day 14 (Study LAC-MD-21)

Source: NDA 210595, Module 2.7. Summary of Clinical Efficacy; Module 5.3. Clinical study report (LAC-MD-21)

In Study D6571C00002, following BID administration for 7 days in patients with moderate-to-severe COPD, all three doses (6, 12 and 24 µg) of FF delivered via the Pressair device showed statistically significant improvement in the primary efficacy endpoint (i.e., FEV1 AUC_{0-12h} on Day 7 post-dose) compared to placebo; LS mean change from baseline were 0.108 L (p<0.001), 0.117 L (p<0.001) and 0.162 L (p<0.001) for FF dose of 6, 12 and 24 µg, respectively. In addition, FEV1 AUC_{0-12h} for both 6 and 12 µg FF dose were comparable to the active control, Perforomist 20 µg (0.108 L, 0.117 L and 0.122 L, respectively).

Figure 2: LS mean change from baseline FEV1(L) at each specific timepoint on Day 7 (Study D6571C00002)

Source: NDA 210595, Module 2.7. Summary of Clinical Efficacy

The Applicant also conducted study LAC-MD-27 to investigate the efficacy and safety of two fixed combinations of AB/FF (400 µg/12 µg and 400 µg/6 µg) compared to placebo and constituent monotherapies (AB 400 µg and FF 12 µg). Both AB/FF 400 µg/12 µg and 400 µg/6 µg doses

showed statistically significant improvement versus placebo; the adjusted mean change from baseline in normalized FEV_1 AUC_{0-12h} at Day 14 was 0.200 L for AB/FF 400 µg/12 µg, 0.202 L for AB/FF 400 µg/6 µg, 0.157 L for AB 400 µg, and 0.127 L for FF 12 µg (p<0.0001 for all comparisons with placebo). Compared with AB 400 µg, AB/FF 400 µg/6 µg showed statistically significant improvement in change from baseline in FEV1 AUC_{0-12h} at Day 14 by 0.045 L (p = 0.0437), but the improvement of 0.043 L (p = 0.0540) for AB/FF 400 µg/12 µg compared with AB 400 µg did not reach statistical significance. The study also failed to demonstrate dose separation in the primary efficacy endpoint (FEV1 AUC_{0-12h}) between AB/FF 400 µg/6 and 400 µg/12 µg (Figure 3). Additionally, both AB/FF 400 µg/6 µg and AB/FF 400 µg/12 µg showed statistically significant improvement versus FF 12 µg; the change from baseline in morning pre-dose FEV_1 at Day 14 compared to FF 12 µg was 0.053 L (p=0.038) for AB/FF 400 µg/12 µg, and 0.057 L (p=0.022) for AB/FF 400 µg/6 µg. Consequently, both the 400 µg/12 µg and 400 µg/6 µg doses of AB/FF were studied in the confirmatory Phase 3 studies in which AB/FF 400 µg/12 µg was associated with numerically higher increases from baseline to Week 24 primary efficacy endpoint (i.e., 1-hr post-dose FEV1 at Week 24) compared to AB/FF 400 µg/6 µg (refer to the Section 8 for additional detail).

Figure 3: Change from baseline in FEV1 by time point at Day 14 (Study LAC-MD-27)
Source: NDA 210595, Module 5.3. Clinical study report (Study LAC-MD-27)

6.4.5. What are the characteristics of the dose/exposure-response relationships for safety?

For locally-acting inhalation drug products, systemic exposure is related to systemic safety of the drug product. As indicated previously, the systemic exposure of aclidinium and formoterol from the AB/FF 400 µg/12 µg product was comparable to the monotherapies, and the systemic exposure of formoterol for AB/FF 400 µg/12 µg was also comparable to the active control (Foradil Aerolizer). To support the long-term safety of AB/FF 400 µg/12 µg, the Applicant conducted a

28-week extension study of LAC-MD-31; hence, the safety was assessed for a total duration of 52 weeks (Study LAC-MD-36).

In the Phase 3 studies, there was no apparent dose-ordering between treatment groups (AB/FF 400 µg/6 µg and AB/FF 400 µg/12 µg BID) in the overall incidence of subjects experiencing adverse events. Similarly, there was no apparent dose-ordering in the incidence of any treatment emergent adverse events leading to discontinuation, any treatment-emergent SAE or any treatment-emergent death. Refer to Section 8 for additional details.

6.4.6. What are the PK parameters of aclidinium and formoterol in healthy subjects?

Single oral inhalation dose of AB/FF 400 µg/12 µg via the Pressair device was administered to healthy subjects in Study M/40464/02; subjects were also administered the corresponding monoproducts, i.e., AB 400 µg and FF 12 µg via the Pressair device. The mean PK profiles of aclidinium and formoterol are shown in Figure 4 and Figure 5, respectively. In healthy subjects, C_{max} and AUC_{inf} of aclidinium following single-dose administration of AB/FF 400 µg/12 µg were 270 pg/mL and 406 pg.hr/mL, respectively, and the C_{max} and AUC_{inf} of formoterol were 11 pg/mL and 42.9 pg.hr/mL, respectively (Table 2 in section 6.1). The pre-dose concentrations of aclidinium and formoterol between the study periods were not quantifiable, suggesting that the washout period of 7–14 days was adequate and pre-dose concentrations did not contribute to the PK results.

Figure 4: Plasma concentration-time profile for aclidinium in healthy subjects; (inset) plasma concentration-time profile for 2 hr to demonstrate variability around C_{max} (Study M/40464/02)

Source: Reviewer analysis based on data from Study M/40464/02; data presented as arithmetic mean (±SD).

Figure 5: Plasma concentration-time profile for formoterol in healthy subjects (Study M/40464/02)

Source: Reviewer analysis based on data from Study M/40464/02; data presented as arithmetic mean (±SD).

The C_{max} and AUC_{inf} of aclidinium were 26% and 17% higher, respectively, when administered as AB/FF combination product versus AB monoproduct. Similarly, the C_{max} and AUC_{inf} of formoterol were 18% and 4% higher, respectively, when administered as AB/FF combination product versus FF monoproduct. The slightly higher C_{max} of aclidinium with AB/FF combination product as compared to AB monotherapy is not expected to have any clinically meaningful impact on safety of AB (refer to Section 8 for details on long-term safety of AB/FF combination product). Overall, no significant PK interaction was observed between aclidinium and formoterol in healthy subjects.

6.4.7. What are the PK parameters of aclidinium and formoterol in patients with COPD following multiple administration?

The PK of aclidinium and formoterol was investigated in patients with moderate-to-severe COPD where AB/FF 400 µg/12 µg via the Pressair device was administered BID for 4 days followed by a final dose in the morning of Day 5 in Study LAC-PK-01. In this study, formoterol monotherapy 12 µg BID via Foradil Aerolizer was also administered for the same duration. The mean PK profiles of aclidinium and formoterol are shown in Figure 6. In patients with COPD, the steady-state C_{max} and AUC_{tau} of aclidinium following BID administration of AB/FF 400 µg/12 µg were 128 pg/mL and 404 pg.hr/mL, respectively. The steady state C_{max} and AUC_{tau} of aclidinium were 128 pg/mL

and 404 pg.hr/mL, respectively, and that for formoterol were 16.7 pg/mL and 85.2 pg.hr/mL, respectively.

Figure 6: Mean (+SD) steady state plasma concentration-time profile of aclidinium and formoterol following AB/FF 400 µg/12 µg BID administration in COPD patients (Study LAC-PK-01)

Source: NDA 210595, Module 5.3. Clinical study report (Study LAC-PK-01)

6.4.8. How is the proposed to-be-marketed formulation linked to the clinical formulation?

The to-be-marketed formulation and device were used in the Phase 1 PK studies, Phase 2 and Phase 3 studies. In the Phase 2b study (LAC-MD-21), the inhaler version used was the same as the to-be-marketed inhaler except for the difference in the counter ring (30 actuations instead of 60 actuations).

6.5. Bioanalytical section

6.5.1. What are the analytical methods used to measure aclidinium in plasma?

For aclidinium, the bioanalytical method was developed for simultaneous determination of aclidinium and its metabolites in stabilized human plasma. Briefly, the method consisted of mixing the human plasma samples with the internal standard(s), extracting with Oasis HLB 96 well plate, and eluting with acetonitrile into a 96-well plate containing 10% formic acid. The samples were dried down under nitrogen and reconstituted with 0.1 M formic acid. The components in the reconstituted sample were separated by XDB Eclipse C18 column (50x4.6 mm, 1.8 µm particle size) and detected by electrospray ionization mass spectrometry. The method was validated for aclidinium and its metabolites. The validation summary is provided in Table 4.

Table 4. Validation summary of bioanalytical method for aclidinium

Matrix (anticoagulant)	Stabilized human plasma (Lithium heparin)
Sample volume	200 µL

Analytical method/detection	Solid phase extraction/LC-MS/MS
Internal standard	[$^2H_5$]LAS 34273
Validated range	5 to 750 pg/mL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Quantitation method	Peak area ratio
Sensitivity	5 pg/mL (lower limit of quantitation)
Intra-day accuracy (%deviation)	0.0 to 10.4%
Intra-day precision (%CV)	1.3 to 12.4%
Inter-day accuracy (%deviation)	1.9 to 6.9%
Inter-day precision (%CV)	3.6 to 9.4%
Freeze-thaw matric stability	Six cycles at -70°C
Long-term stability	409 days at -70°C
Short-term matrix stability	24 hr at 4°C
Study	M/40464/02 and LAC-PK-01

Source: Module 5.3. PRD-RPT-BDM-00546

The QC sample results met the acceptance criteria, i.e., at least 67% of the QC results were within ±15% of the respective nominal values, and at least 50% of QCs at each level were within ±15% of their nominal concentrations. The PK samples were stored and analyzed within the validated storage stability period and conditions.

6.5.2. What are the analytical methods used to measure formoterol in plasma?

A validated LC/MS/MS method was used for analysis for formoterol in human plasma. Plasma was fortified with the internal standard and 2% ammonium hydroxide. Extraction solvent was added, and tubes were vortexed and centrifuged. The aqueous layer was frozen, the organic layer was decanted to a clean tube containing keeper solution. The organic solution was evaporated, and the remaining residue was reconstituted with reconstitution solution. The final extract was analyzed via LC/MS/MS detection. The validation summary is provided in **Table 5**

Table 5. Validation summary of bioanalytical method for formoterol

Matrix (anticoagulant)	Stabilized human plasma (Lithium heparin)
Sample volume	500 µL
Analytical method/detection	Liquid extraction/HPLC MS/MS
Internal standard	Formoterol-d_6
Validated range	0.5 to 250 pg/mL
Calibration model	Linear regression
Weighting factor	$1/\text{concentration}^2$
Quantitation method	Peak area ratio
Sensitivity	0.5 pg/mL (lower limit of quantitation)

Intra-day accuracy (%deviation)	-0.5 to 14.8%
Intra-day precision (%CV)	2.0 to 17.2% (LLOQ)
Inter-day accuracy (%deviation)	0.3 to 11.6%
Inter-day precision (%CV)	4.3 to 11.7%
Freeze-thaw stability	Four cycles at -20°C
Long-term stability	247 days at -70°C 457 days at -20°C
Ambient matrix stability	23.75 h at RT
Study	M/40464/02 and LAC-PK-01

Source: Module 5.3. Analytical method report – PPD P860 AEFF4

The accuracy and precision of at least 67% of all QC samples were within ±15% of their nominal concentrations and at least 50% of QCs at each level were within ±15% of their nominal values. The PK samples were stored and analyzed within the validated storage stability period and conditions.

6.5.3. What are the results for the re-analysis of the incurred samples?

Pharmacokinetic samples for aclidinium and formoterol were re-analyzed as part of incurred sample reproducibility assessment. Approximately 10% of aclidinium and formoterol samples were re-assessed which met the acceptance criteria of 67% of incurred sample results being within 20% of the original result.

Reference ID: 4410528

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6. Reviewed trials

Trial #	Clinical sites	Date of conduct	Design	Population	Treatments	Endpoints
Efficacy/safety trials						
M/40464/30 & LAC-MD-31	M/40464/30: Europe, South Africa, South Korea LAC-MD-31: US, Canada, Australia, New Zealand	M/40464/30: 10/26/2011-01/04/2013 LAC-MD-31 09/23/2011-02/06/2013	24-wk R, DB, PG, PC	COPD, post-bronchodilator FEV1 30-80% of predicted	AB/FF 400/12 µg (n=385, 338) AB/FF 400/6 µg (n=381, 338) AB 400 µg (n=385, 340) FF 12 µg (n=384, 339) Placebo (n=194, 337)	1º 1h post-dose FEV1 Trough FEV1 2º SGRQ score COPD exacerbation Safety analysis
D6571C00001	US, Europe, Israel, and Russia	07/05/2016-06/08/2017	24-wk R, DB, PG, AC	COPD, post-bronchodilator FEV1 <80% of predicted	AB/FF 400/12 µg (n=317) AB 400 µg (n=478) FF 12 µg (n=320) Tiotropium 18 µg (n=479)	1º 1h post-dose FEV1 Trough FEV1 2º SGRQ score FEV1 $AUC_{0-3/3h}$ COPD exacerbation Safety analysis
D6560C00002	US and Canada	10/16/2013-09/16/2017	36-month R, DB, PG	COPD, post-bronchodilator FEV1 <80% of predicted	AB 400 µg (n=1791) Placebo (n=1798)	Moderate and severe COPD exacerbation rate, Safety analysis
Additional safety trials						
LAC-MD-36	US and Canada	04/06/2012-06/04/2013	28-wk R, DB, PG, PC, extension trial of LAC-MD-31	COPD, post-bronchodilator FEV1 30-80% of predicted	AB/FF 400/12 µg (n=338) AB/FF 400/6 µg (n=338) AB 400 µg (n=340) FF 12 µg (n=339) Placebo (n=337)	Safety analysis

R: Randomized, DB: Double blinded, PG: Parallel-group, AC: Active-controlled, 1º: Primary, 2º: Secondary, AB: aclidinium bromide, FF: formoterol fumarate, AB/FF: aclidinium bromide/formoterol fumarate

7.2. Review Strategy

This review focuses on the three phase 3 twenty-four week trials (M/40464/30, LAC-MD-31 and D6571C00001) as the primary evidence of efficacy. Review of the thirty-six month COPD exacerbation trial (D6560C00002) comparing AB versus placebo is also included. The efficacy results from these trials are reviewed in section 8.1 Review of Efficacy. Regarding the safety review, the safety analyses were based on the pooled analyses of the replicate 24-week placebo-controlled trials (M/40464/30 and LAC-MD-31) as well as the individual analyses of the active-controlled 24-week trial (D6571C00001) and the 28-week safety extension trial of LAC-MD-31 (LAC-MD-36). The safety data are reviewed in section 8.2 Review of Safety. Hereafter the trials M/40464/30, LAC-MD-31, D6571C00001, D6560C00002 and LAC-MD-36 are referred as trials 30, 31, 01, 02 and 36, respectively. Note that the numbers in tables of this review were confirmed by primary reviewers.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

As primary support for efficacy, the Applicant submitted data from replicate placebo-controlled 24-week trials M/40464/30 and LAC-MD-31 and one active-controlled 24-week trial D6571C00001. These trials will be reviewed in this section and will be referred to trials 30, 31, and 01, respectively. In addition, the 36-month exacerbation trial D6560C00002 in support of the reduction of COPD exacerbation is reviewed. This will be referred to as trial 02.

8.1.1. Trials 30, 31, 01, and 02

<u>Trial 30</u>

Title: "Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo when administered to patients with stable chronic obstructive pulmonary disease"

- Study date: 10/26/2011-01/04/2013
- Study report date: 08/19/2013
- Study sites: Europe, South Africa, and Asia (22 countries)

Trial Design

This was a 24-week treatment period, prospective, randomized, parallel group, double-blind, placebo- and active-controlled, multinational clinical trial conducted in patients with stable moderate-to-severe COPD. Prior to Informed Consent Form (ICF) signing, investigators evaluated the patients' eligibility for entry in the trial. A 2-3 week run-in period started with the signing of the ICF, followed by the screening assessments, and ended at the randomization

visit (Visit 1). Patients who were using any of the concomitant medication prohibited for the duration of this trial were to enter a washout period (1 day to 1 month long, depending on the specific medication to be washed-out) prior to the run-in period. The run-in period was followed by a 24-week double-blind treatment period (Visit 1 to Visit 6). Eligible patients were randomized in a 2:2:2:2:1 ratio (AB/FF 400/12 µg, 400/6 µg, AB 400 µg, FF 12 µg and placebo BID, respectively). Patients completed a follow-up contact (Visit 7) two weeks after the last study medication administration.

Rescue medication (salbutamol pressured metered-dose inhaler 100 µg/puff) was allowed as needed for the duration of the trial for all enrolled patients. In addition, several background medications for the treatment of COPD (e.g., inhaled corticosteroids [ICS], oral or parenteral corticosteroids, oxygen therapy, and oral sustained-release theophyllines) were allowed.

The trial was to assess FEV1 and other lung functions, as well as symptomatic benefits, COPD exacerbation and use of rescue medication. Adverse events (AEs) and commonly used tolerability assessments (e.g., ECG, vital signs and clinical laboratory tests) were performed to monitor the study medication safety profile throughout the trial. Two different subsets of patients, each approximately 20% of the total trial population, participated in the 24-hour Holter (317 patients) and 12-hour spirometry (366 patients) substudies involving additional visits and/or assessments. The trial schedule and assessments are summarized in **Table 7**.

Table 7. Trial 30 Assessment Schedule

Period	Run In	Treatment						Follow-up
Visit	screening	1	2	3	4	5	6	7
Week	(-3 to -2)	0	1	4	12	18	24	26
Day	(-21 to -14)	1	8	29	85	127	169	184
MAIN STUDY								
Informed Consent[1]	X							
Medical and COPD History	X							
Height and Weight	X							
Physical exam	X						X	
Bronchodilator test[2]	X							
Inclusion/exclusion criteria	X	X						
Randomisation		X						
IVRS phone call[3]	X	X		X	X		X	
Laboratory test (including pregnancy test and theophylline levels, if applicable)[4]	X				X		X	
BDI/TDI, SGRQ and European Quality of Life Scale 5-dimension questionnaire		X		X	X		X	
ECG and Blood Pressure[5]	X	X	X	X	X		X	
Predose PFT[6]		X	X	X	X	X	X	
Postdose PFT		X[7]	X[8]	X[8]	X[8]		X[8]	
Health Resources Utilisation				X	X	X	X	
COPD exacerbations		X	X	X	X	X	X	X
Electronic Patient	X	X	X	X	X	X	X	
Diary[9]								
Paper Patient Diary[10]	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Co-medication	X	X	X	X	X	X	X	X
SPIROMETRY SUBSTUDY: ADDITIONAL ASSESSMENTS								
12-hour PFT[11]		X			X		X	
HOLTER SUBSTUDY: ADDITIONAL ASSESSMENTS								
24-hour Holter[12]	X				X		X	

[1] Patients requiring the washout of prohibited COPD medication before screening were to sign the informed consent before starting the washout period (one day to one month before, depending on the length of washout period required).

[2] Bronchodilator test consisted of one pulmonary function test (PFT) (one set of forced manoeuvres only for FEV_1 and FVC measurement), followed by the inhalation on 400 µg of salbutamol through a spacer device, and followed 10 to 15 minutes later by another PFT (one set of forced manoeuvres only).

[3] The IVRS was accessed at screening and Visit 6 to inform the system about the patient's status (new patient and treatment completed, respectively). IVRS was accessed at Visits 1, 3 and 4 to obtain the study medication kit number assigned to the respective patient.

[4] Laboratory tests were performed in fasting conditions. On Visit 4 and 6, blood samples were taken before the morning study medication administration. Pregnancy test was only performed when applicable (Section 9.8). Theophylline levels were only performed for patients on theophylline treatment.

[5] ECG and blood pressure (vital signs) measurements were performed once at screening to determine patient eligibility. Afterwards, ECG and blood pressure (vital signs) were performed before the morning study medication administration and 2 hours after the morning study medication administration at the above indicated visits.

[6] Premorning dose PFT: two sets were performed during the hour before the scheduled morning study medication administration, allowing approximately 30 min between them; each set consisted of slow and forced manoeuvre tests (for IC, FEV_1 and FVC calculation).

[7] Postmorning dose PFTs on Day 1: one set of forced manoeuvres only was performed at 5 and 30 min, 1, 2 and 3 hours and one set of slow manoeuvres was performed at 3 hours only, at the above indicated visits.

[8] Postmorning dose PFTs (other than Day 1): one set of forced manoeuvres was performed at 30 min, 1, 2 and 3 hours and one set of slow manoeuvres was performed at 3 hours only, at the above indicated visits.

[9] Electronic Patient Diary: patients recorded the study medication as well as relief medication inhaled every morning and evening; Exacerbations of Chronic Pulmonary Disease Tool (EXACT) questionnaire was completed every evening; and Night time and Early morning COPD symptoms questionnaire every morning.

[10] Paper Patient Diary: patients recorded any adverse event and/or concomitant medication taken.

[11] **Additional assessments ONLY for patients in the 12-hour spirometry substudy** at the above indicated visits: one set of forced manoeuvres was performed at 4, 6, 8, 10 and 12 hours after the morning study medication administration, and one set of slow manoeuvres was measured at 12 hours after the morning study medication administration.

[12] **Additional assessments ONLY for patients in the 24-hour Holter substudy** at the visits indicated above: screening Holter recording started after all the screening assessments were completed. Patients came back to the study centre on the following day to stop the recording and for removal of the electrodes; Visit 4 and Visit 6 Holter recording started in the morning of the day preceding the scheduled visit (that is, Day 84 and 168 respectively) 5 minutes before the morning study medication administration and was stopped before starting the Visit 4 and Visit 6 assessments.

Objectives/Rationale

- To assess the long-term bronchodilation of AB/FF FDCs (Fixed-Dose Combinations) compared to individual components and placebo, when administered bid via inhalation to COPD patients.
- To assess the benefits of AB/FF FDCs in COPD symptoms, disease-related health status and COPD exacerbations compared to individual components and placebo, when administered bid via inhalation to COPD patients.
- To evaluate the long-term safety and tolerability of AB/FF FDCs compared to individual components and placebo when administered bid via inhalation to COPD patients.

Trial population

The trial consisted of 1729 randomized COPD patients. They were randomized using an interactive voice randomization system (IVRS) on Day 1 Visit 1.

Key Inclusion Criteria

1. Adult male, or non-pregnant, non-lactating female patients aged 40 years or older. Females of childbearing potential were allowed to enter the trial if they had a negative serum pregnancy test at screening, and were using one highly effective method of birth control.
2. Current or ex-cigarette smoker, with a smoking history of at least 10 pack-years.
3. Patients with a clinical diagnosis of stable COPD according to the Global Initiative for Obstructive Lung Disease (GOLD 2010) Guidelines at screening.
4. Patients whose FEV1/FVC at screening measured between 10 to 15 minutes post inhalation of salbutamol is <70%.
5. Patients with a diagnosis of moderate to severe COPD according to the GOLD Guidelines classification (stages II and III) at screening: FEV1 measured between 10 to 15 minutes post inhalation of 400 µg of salbutamol is 30% ≤ FEV1 <80% of the predicted normal value.
6. Patients able to perform repeatable pulmonary function testing.

Key Exclusion Criteria

1. History or current diagnosis of asthma, any respiratory tract infection or COPD exacerbation in the 6 weeks before screening, hospitalized for COPD exacerbation within 3 months prior to screening.
2. Clinically significant respiratory conditions defined as known active tuberculosis, history of interstitial lung or massive pulmonary thromboembolic disease, pulmonary resection or lung volume reduction surgery within 12 months prior to screening, history of lung transplantation, history of bronchiectasis secondary to respiratory diseases other than COPD, known a1-antitrypsin deficiency or patients who in the investigator's opinion might have needed thoracotomy or other lung surgery during the trial.
3. Patients who in the investigator's opinion might have needed to start a pulmonary rehabilitation program during the trial and/or patients who started/finished it within 3 months prior to screening.
4. Use of long-term oxygen therapy (≥15 hours/day). Local amendment specific for Germany (17 October 2011): use of long-term oxygen therapy ≥1 hour/day.

5. Clinically significant cardiovascular conditions defined as:
   - Myocardial infarction within the 6 months prior to screening.
   - Thoracic surgery within 12 months prior to screening.
   - Unstable angina or unstable arrhythmia which had required changes in the pharmacological therapy or other intervention within 12 months prior to screening, or newly diagnosed arrhythmia within the previous 3 months prior to screening.
   - Hospitalization within 12 months prior to screening for heart failure functional classes III (marked limitation of activity and only comfortable at rest) and IV (need of complete rest, confinement to bed or chair, discomfort at any physical activity and presence of symptoms at rest) as per the New York Heart Association.
6. Patients (with or without pharmacological therapy) with resting systolic blood pressure (SBP) ≥200 mmHg, a resting diastolic blood pressure (DBP) ≥120 mmHg, or a resting heart rate ≥105 beats per minute (bpm) at screening and at Visit 1 prior to randomization. Local amendment specific for Germany (17 October 2011): resting SBP ≥160 mmHg, a resting DBP ≥100 mmHg.
7. Patients with QTc (calculated according to Bazett formulae [QTc = QT/RR1/2]) >470 ms as indicated in the centralized reading report assessed at screening Visit.
8. Patients with clinically relevant abnormalities in the clinical laboratory tests, ECG parameters (other than QT interval corrected using Bazett's formula [QTcB]) or in the physical examination at screening, if the abnormality defined a disease state listed as exclusion criteria, except for those related to COPD.
9. Patients with a history of hypersensitivity reactions to inhaled anticholinergics, sympathomimetic amines, or inhaled medication or any component thereof (including report of paradoxical bronchospasm); patients with known narrow-angle glaucoma, symptomatic bladder neck obstruction or acute urinary retention; patients with symptomatic non-stable prostate hypertrophy.
10. Patients with known uncontrolled history of infection with human immunodeficiency virus and/or active hepatitis; patients with current diagnosis of cancer other than basal or squamous cell skin cancer; patients with life expectancy of less than 1 year.
11. Patients with a history (within 2 years prior to screening) of drug and/or alcohol abuse that might have prevented trial compliance based on the investigator judgment.
12. Patients previously randomized in a study involving AB/FF FDC or AB monotherapy .
13. Patients treated with any investigational drug within 30 days (or 6 half-lives, whichever is longer) prior to screening.
14. Patients who intended to use any concomitant medication not permitted by this protocol or who had not undergone the required washout period for a particular prohibited medication.
15. Patients unable to give consent, or patients of consenting age but under guardianship, or vulnerable patients.
16. In addition to the above, at Visit 1 prior to randomization, the following criteria applied: Patients who developed a respiratory tract infection or COPD exacerbation during the run-in period; patients with clinically relevant abnormalities in the clinical laboratory tests and/or ECG parameters performed at screening, if the abnormality defined a disease state listed in screening complete exclusion criteria list, except for those related to COPD.

Key withdrawal criteria

1. Non-fulfillment of inclusion/exclusion criteria
2. COPD exacerbation or AE: If at the Investigator or patient's discretion, the event justified premature withdrawal due to its severity or nature, regardless of the causal relationship to the study medication.
3. Lack of efficacy: Only if the Investigator considered the response to the treatment unsatisfactory.
4. Patient's personal request
5. Lost to follow-up: Patient non-attendance. In that case, the Investigator was to make every effort to ascertain the whereabouts, reason for lack of attendance, the health of the patient and to assure patient's attendance as soon as possible.
6. Protocol non-compliance

The trial design and patient population are typical for a COPD trial. It is worth noting that patients with very severe COPD were not included in this trial.

Treatments

The trial consisted of 5 treatment groups; they were as follows:

- AB/FF 400/12 µg
- AB/FF 400/6 µg
- AB 400 µg
- FF 12 µg
- Placebo

All treatments were administered BID using the Pressair inhaler. Every patient was provided with sufficient salbutamol for inhalation (pMDI 100µg/puff) to be used as rescue medication on an "as needed" basis during the trial.

Concomitant/Restricted Medications:

In addition to the trial rescue medication, the following COPD medication were permitted during the trial, provided their administration was stable for at least 4 weeks before screening and any change in daily dose, dosing schedule, formulation or treatment was unlikely during the course of the trial (the exception being the treatment of a COPD exacerbation):

- Oral sustained release methyl-xanthines (e.g., theophylline).
- Oxygen therapy administered on an as needed basis and for less than 15 hours a day.
- Oral or parenteral corticosteroids used at maximal stable doses equivalent to 10 mg of prednisone per day or 20 mg every other day.
- Inhaled corticosteroids (ICS).
- Patients switched from combinations of LABAs and corticosteroids to the same ICS as monotherapy (same dose and dose regimen), who were following a stable regimen of the combination for at least 4 weeks, did not need an additional stabilization period prior to screening provided the β2-agonist's component washout was fulfilled.

The use of the following treatments were prohibited for the duration of the trial:

- Anticholinergic drugs:

  - Oral, intra-nasal or parenteral agents: Patients on these medications could have participated in the trial, provided treatment was stopped at least 72 hours before screening.
  - Short-acting inhaled anticholinergic agents: Patients on these medications could have participated in the trial, provided treatment was stopped at least 12 hours before screening.
  - Long-acting inhaled anticholinergic agents: Patients on these medications could have participated in the trial, provided treatment was stopped at least 7 days before screening.
- β2-agonist drugs:
  - Short-acting inhaled agents: Patients on these medications could have participated in the trial, provided treatment was stopped at least 6 hours before screening, the exception being salbutamol pMDI (100 µg/puff) which was allowed during the trial as rescue medication provided the 6 hours washout was maintained prior to any scheduled visit.
  - Oral agents: Patients on these medications could have participated in the trial, provided treatment was stopped at least 48 hours before screening.
  - Twice-daily long-acting inhaled agents: Patients on these medications could have participated in the trial, provided treatment was stopped at least 48 hours before screening.
  - Once-daily long-acting inhaled agents: Patients on these medications could have participated in the trial, provided treatment was stopped at least 7 days before screening.
- Combination of inhaled drugs:
  - Inhaled fixed dose combinations of a short-acting β2-agonist (SABA) and an anticholinergic agent (e.g., Combivent): Patients on these medications could have participated in the trial, provided treatment was stopped at least 12 hours before screening.
  - Inhaled fixed dose combinations of LABAs and corticosteroids (e.g., Symbicort, Advair): Patients on these medications could have participated in the trial provided:
    1. Treatment was switched to the same ICS as monotherapy, at the same dose and dose regimen during the trial, at least 48 hours before screening.
    2. Treatment was switched to a different ICS as monotherapy, at an equivalent therapeutic dose to the one used for the fixed inhaled combination, at least 14 days before screening or longer until the patient was considered stabilized. The patient was considered stabilized if, according to the Investigator's criteria, during the second week of observation there were no changes in symptoms beyond the day to day variation or, symptoms experienced remained at similar level of those existing before medication change.
- Corticosteroid drugs:
  - Continuous oral or parenteral corticosteroids used at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day. Patients on these medications could have participated in the trial, provided the entire treatment was fully stopped or tapered down to the equivalent of 10 mg of prednisone per day or 20 mg every other day, at least 4 weeks before screening.
- Others:
  - Cromolyn sodium, nedocromil: Patients on these medications could have participated in the trial, provided treatment was stopped at least 5 days before screening.

- Leukotriene modifiers: Patients on these medications could have participated in the trial, provided treatment was stopped at least 48 hours before screening.
- Methyl-xanthines (other than oral sustained release): Patients on these medications could have participated in the trial, provided treatment was stopped at least 72 hours before screening.
- Phosphodiesterase 4 inhibitors: Patients on these medications could have participated in the trial, provided treatment was stopped at least 4 weeks before screening.
- β1-blocking agents: Patients on non-selective agents could have participated in the trial provided treatment was stopped at least 2 weeks prior to screening. However, selective β1-blocking agents were permitted provided they had been stable for at least 2 weeks prior to screening. Patients could have been switched to selective β1-blocking agents, as long as they were at a stable dose for at least 2 weeks prior to screening.

Study Endpoints

Primary Endpoints

- Change from baseline in 1-hour morning post-dose FEV1 of each FDC dose compared to AB monotherapy at Week 24.
- Change from baseline in morning pre-dose (trough) FEV1 of each FDC dose compared to FF monotherapy at Week 24.

Secondary Endpoints

- Improvement of Transition Dyspnea Index (TDI) focal score for each FDC dose compared with placebo at Week 24.
- Change from baseline in SGRQ total score for each FDC dose compared with placebo at Week 24.
- Reduction in the rate of moderate or severe COPD exacerbations per patient per year based on pooled data from the trials 30 and 31, for each FDC dose compared with placebo, and AB monotherapy compared with placebo.
- Change from baseline in SGRQ total score of AB monotherapy compared with placebo at Week 24.

Additional Endpoints

This trial had multiple additional endpoints which included the following:

- Change from baseline in morning pre-dose FEV1, FVC and IC at all visits, except for co-primary variable, at Week 24.
- FEV1, FVC and IC by time point at all visits (including time points from the 12-hour Spirometry substudy).
- Change from baseline in normalized area under the concentration-time curve from time 0 to 3 hours (AUC_{0-3}) FEV1 and FVC at all visits.
- Change from baseline in normalized area under the concentration-time curve from time 0 to 12 hours (AUC_{0-12}) FEV1 and FVC at all visits in the 12-hour Spirometry substudy.

- Change from baseline in dyspnea status as measured by the TDI focal score and three component scores at Weeks 4, 12, and 24 (except for focal score at Week 24).
- Number (%) of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥1 unit) at Weeks 4, 12, and 24.
- Change from baseline in SGRQ total score and three dimension scores at Weeks 4, 12, and 24 (except for total score at Week 24).
- Number (%) of patients achieving a clinically meaningful improvement (≥4 units) compared with baseline in the SGRQ total score at Weeks 4, 12, and 24.
- Rate of COPD exacerbations per patient/year (any, and moderate or severe).
- Time (days) to first COPD exacerbation (any, and moderate or severe).
- Number of patients with at least 1 COPD exacerbation (any, mild, moderate, severe and moderate or severe).
- Time (days) to withdrawal due to COPD exacerbation.
- Duration (days) of the COPD exacerbations (any, and moderate or severe).
- Total number of days of hospitalization for COPD exacerbations (at any unit or emergency room).
- Rescue medication: Change from baseline in the use of rescue medication at all visits and average over 6 months.

Note that COPD exacerbations were analyzed in this trial on the basis of the health care utilization definition (increase of COPD symptoms during at least 2 consecutive days that require a change in COPD treatment). COPD exacerbation was defined according to the intensity categories in the following:

- Mild: Increase of COPD symptoms during at least two consecutive days, self-managed by the patient at home by increasing usual COPD medication (short-acting bronchodilator and/or ICS use).
- Moderate: Increase of COPD symptoms during at least two consecutive days, which does not lead to hospitalization but is treated with antibiotics and/or systemic corticosteroids or an increase in dose of systemic corticosteroids.
- Severe: Increase in COPD symptoms during at least two consecutive days, which leads to hospitalization (overnight stay at hospital or emergency room).

The definition used for exacerbation based on the health care utilization definition is consistent with that used in other COPD trials and acceptable. The primary endpoints are reasonable in light of prior inhaled therapies that have also used 1-hour post-dose FEV_1 or trough FEV1 as principal endpoints. Use of FEV1 is well established as a primary endpoint and has been used as the basis of approval for multiple inhaled COPD products. The 1-hour post-dose FEV1 assesses for the contribution of the LABA component and the trough FEV1 assesses for the contribution of the LAMA component. SGRQ is also used frequently in the evaluation of inhaled medications for COPD. The definition used for exacerbation is the same as used in other COPD exacerbation trials. Overall, these endpoints are appropriate.

Statistical Analysis Plan

All efficacy analyses are performed using intent-to-treat (ITT) population which was defined as all randomized patients who took at least one dose of Investigational Medicinal Product (IMP) and had a baseline and at least one post-baseline FEV_1 assessment, except COPD exacerbation variables were analysed using the ITT-Exacerbation population which was defined as all randomised patients who took at least one dose of IMP.

The change from baseline in morning pre-dose trough FEV_1 and at 1-hour morning post-dose FEV_1 at week 24 were analysed by means of a mixed model for repeated measures (MMRM), adjusted by pre- and post-bronchodilator FEV_1 at screening, age, and baseline FEV_1 as covariates, and treatment group, gender, smoking status, visit, and treatment group-by-visit interaction as fixed effect factors. The within-patient correlation was modeled using the unstructured covariance matrix. Each treatment effect and treatment differences were estimated by the Least Square means (LS Means) on the corresponding treatment group-by-visit interaction at week 24, along with their standard errors (SEs) and 95% confidence intervals (CIs), and the p-value corresponding to the between-treatment group difference.

Secondary endpoint change from baseline in SGRQ total score at week 24 wa analyzed by means of MMRM, adjusted by baseline SGRQ value and age as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors.

A sequentially rejective multiple testing procedure was used to control the family-wise type I error rate at the 5% level. Table 8 lists the sequenced testing null hypotheses. For detail of the strategy, refer to addendum to the statistical analysis plan (SAP) amended on March 21, 2013.

Table 8: Sequence of null hypotheses for multiplicity adjustment

Null Hypotheses	End Point	Treatment Comparison Under the Null
H1	1-hour postdose FEV_1 at Week 24	FDC 400/12 µg = aclidinium 400 µg
H2	Morning predose FEV_1 at Week 24	FDC 400/12 ug = formoterol 12 µg
H3	SGRQ at Week 24	FDC 400/12 µg = placebo

Source: Addendum to the SAP amended on March 21, 2013

Sensitivity analysis using a pattern-mixture model based on non-future depedent 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 pattern for the pattern-mixture model was defined by the patient's last visit with observed value. The observed measurement at a visit was assumed to have a linear relationship with the

patient's prior measurements. The missing value was imputed under the assumption that the distribution of the missing observations differs from that of the observed by a shift parameter value Δ. The dataset with imputed values was analyzed using the same model as the primary analysis for between-treatment group comparisons at week 24. The imputation of missing data values and the analysis was performed 20 times. The final inferences of pattern-mixture model analysis was based on standard multiple imputation by averaging point estimates and combining within- and between- imputation variability. Three values for the shift parameter Δ (0, -0.04 and -0.08 L) were explored. Then the estimates/inference of the sensitivity analysis were compared with those of the original primary analysis.

Protocol Amendments

The first version of the protocol dated 28 April 2011 was amended twice globally (all countries affected) on 05/29/2012 and 10/04/2012. In addition, local (at country level) amendments were also made. Main protocol amendments are summarized as follows:

Global amendment #1
• Removal of spirometry assessments at 5 minutes.

Global amendment #2
• MACE adjudication was to be assessed during the trial.
• Statistical analyses updated according to the CHMP scientific advice.
• COPD exacerbations according to Health Resource Utilization updated.
• An additional analysis population added, ITT-Exacerbations.
• Pooled analysis adjusted for EU and US filing purposes.
• Sensitivity analysis to assess the robustness of the MMRM model was updated.

These amendments did not change the overall design or quality of the trial. These amendments did not affect interpretability of the data.

<u>Trial 31</u>

Title: "A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of two fixed-dose combinations of aclidinium bromide/formoterol fumarate compared with aclidinium bromide, formoterol fumarate and placebo for 24-Weeks treatment in patients with moderate to severe, stable chronic obstructive pulmonary disease (COPD) (Augment COPD)"

- Study date: 10/04/2011-02/06/2013
- Study report date: 08/28/2013
- Study sites: United States, Canada, Australia and New Zealand

Trial Design
The design of trial 31 was largely similar to that of trial 30 except that eligible patients were randomized in a 1:1:1:1:1 ratio (AB/FF 400/12 µg, AB/FF 400/6 µg, AB 400 µg, FF 12 µg and

placebo BID, respectively). Additionally, patients who completed this trial had the option to enroll into an extension trial, LAC-MD-36, for an additional 28 weeks of the double-blind treatment. The trial schedule and assessments are summarized in Table 9.

Table 9: Assessment Schedule, Trial 31

	Informed Consent	*Run-in Period*	*Double-blind Treatment Period*							*Follow-up Period*
Visits	*Visit 0 Registration*[a]	*Visit 1 Screening*	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7*	*Early Termination Visit*	*Visit 8*[b]
Week		**–3 to –2**	**0**	**0.5**	**4**	**12**	**18**	**24**		**26**
Day		**–21 to –14**	**1**	**4**	**29**	**85**	**127**	**169**		**184**
Visit Window				**± 2 Days**	**± 3 Days**	**± 5 Days**	**± 5 Days**	**± 5 Days**		**± 5 Days**
Informed consent	X	X							X[c]	
Medical, smoking and COPD history		X								
Inclusion/exclusion criteria		X	X							
Physical examination[d]		X						X	X	
Vital signs[e]		X	X	X	X	X	X	X	X	
12-lead ECG[f]		X	X	X	X	X		X	X	
Bronchodilator test with PFTs[g]		X								
IWRS access	X	X	X	X	X	X	X	X	X	X
Randomization (IWRS)			X							
Fasting clinical laboratory assessment[h]		X				X		X	X	
Urine pregnancy test			X		X	X	X			
Serum Pregnancy Test		X						X	X	
Dispense investigational product			X	X[i]	X	X	X			
Assess investigational product compliance				X	X	X	X	X	X	
Collect investigational product				X[j]	X[i]	X	X	X	X	
Dispense rescue medication	X	X	X	X	X	X	X			
Assess rescue medication use		X	X	X	X	X	X	X	X	
Collect rescue medication								X	X	
BDI/TDI[k]			X		X	X		X	X	
Health Resource Utilization Questionnaire[l]					X	X	X	X	X	
SGRQ[m]			X		X	X		X	X	
PGIC[n]			X	X	X	X	X	X	X	
Predose PFT[o]			X	X	X	X	X	X	X	
Morning dose of investigational product			X	X	X	X	X	X		
Postdose PFT[p]			X	X	X	X		X		
Patient electronic diary[q]		X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X
COPD exacerbations		X	X	X	X	X	X	X	X	X
Prohibited medications/concomitant medications	X	X	X	X	X	X	X	X	X	X
Holter monitoring[r]		X				X		X		
Spirometry substudy 12-hour PFT[s]			X			X		X		

a For patients who required a wash-out, the patient signed informed consent, be assigned a PID number by the IWRS system, and receive rescue medication at Visit 0 (Registration). Visit 0 (Registration) could have occurred 1 day before Visit 1 (Screening) if the patient did not require a washout.

b Patients who received at least 1 dose of investigational product were followed up to assess moderate or severe COPD exacerbations. Patients participating in the extension study LAC-MD-36 did not require Follow-up Visit 8 (Week 26).

c Additional informed consent to receive follow-up telephone contact according to Section 9.5.5.9 of the protocol, which can be found in Section 16.1.1 of this report, was to be obtained.

d A complete physical examination was performed at Visit 1 (screening) and Visit 7/ET. Genitourinary examinations were not required, but may have been performed at the discretion of the Investigator.

e Vital signs consisted of a pulse rate, sitting systolic and diastolic blood pressure and respiratory rate. Pulse and blood pressure readings were taken after the patient had been sitting for 10 minutes. Body weight was at Visit 1 and Visit 7/ET. Height was recorded at Screening (Visit 1); BMI was calculated in the eCRF automatically.

f ECG was performed predose and 2 hours postdose, except at Visit 1 (Screening), where it was performed only once to determine patient eligibility, and at ET, where it was performed once.

g Bronchodilator test consisted of 1 prebronchodilator PFT set (forced maneuver only, FEV_1 and FVC measurement), followed by the inhalation of 4 puffs of albuterol/salbutamol (SABA) through a spacer device, followed by a postbronchodilator PFT (forced maneuver only, FEV_1 and FVC measurement).

h Hematology, chemistry, and urinalysis laboratory parameters were assessed. For urinalysis, dipstick analysis was performed at the study center; if clinically relevant abnormalities were detected, a urine sample was sent to the central laboratory. Theophylline levels were measured in patients who were taking theophylline.

i United States study centers only: Inhalers #2 and #3 (back-up inhaler) dispensed at Visit 2 were redispensed at Visit 3. Study centers in Canada and the rest of the world redispensed the entire Visit 2 investigational kit at Visit 3.

j United States study centers only were to follow Appendix X of the protocol, which can be found in Appendix 16.1.1 of this report regarding intermediate drug return instructions at Visit 3 and Visit 4.

k BDI/TDI was always completed before the SGRQ. BDI was performed at Visit 2 (predose) only; TDI was subsequently completed at future visits. Both BDI and TDI were recorded in the TrialSlate. The BDI/TDI was completed by an independent interviewer, who was not involved in the study.

l RUQ was administered by the study center and recorded in the TrialSlate.

m SGRQ was completed by the patient in the TrialSlate.

n PGIC was completed after the SGRQ by the patient in the TrialSlate.

o Slow maneuvers (IC) were done before forced maneuvers (FEV_1 and FVC). Slow and forced maneuvers were completed at 1 hour predose and 10 minutes predose, except at ET where only 1 set of maneuvers (forced) was performed if the patient was able to complete pulmonary function testing.

p Forced maneuvers were completed at 30 minutes; 1 hour; and 2 hours 15 minutes postdose. At Visit 2, an additional forced maneuver was completed at 5 minutes postdose. Slow and forced maneuvers were completed at 3 hours postdose; slow maneuvers were done before forced maneuvers.

q Patients recorded the following in the electronic diary twice daily, once in the morning and once in the evening: NiSCI, EMSCI, EXACT, exploratory nighttime and early morning symptoms questions, and questions about investigational product, rescue medication, and concomitant medications.

r Approximately 20% of the study population (at selected sites only) participated in a 24-hour Holter ECG substudy. At the conclusion of Visit 1, after all screening assessments were performed, including wash-out period (if necessary), the Holter monitor was attached to the patient; it was removed on the following day (24 hours later). Holter monitoring began again on the day before Visits 5 and 7 in the morning approximately 5 minutes before dosing with investigational product (between 8:00 AM and 10:00 AM) and continued through the day of Visits 5 and 7 before any study-related procedures.

s Approximately 20% of the study population (at selected sites only) participated in a 12-hour serial PFT substudy in addition to the previously defined spirometry assessments. Forced maneuvers were performed at 4, 6, 8, 10, and 12 hours post-morning dose. IC was to be measured at 12 hours post-morning dose only. Overnight stay was not required.

BDI = Baseline Dyspnea Index; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; eCRF = electronic case report form; EMSCI = Early Morning Symptoms of COPD Instrument; ET = early termination; EXACT = Exacerbations of Chronic Pulmonary Disease Tool; E-RS = Exacerbations of Chronic Pulmonary Disease Tool–Respiratory Symptoms; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; IWRS = interactive web response system; NiSCI=Nighttime Symptoms of COPD Instrument; PFT = pulmonary function test; PGIC = Patient Global Impression of Change; PID = patient identification; RUQ = Resource Utilization Questionnaire; SABA = short-acting β_2 agonist; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index.

Objectives/Rationale

- Assess the maintenance bronchodilator effect of the FDC versus monotherapies
- Assess the effects of the FDC in terms of COPD symptoms and disease-related health status (versus placebo)
- Evaluate the FDCs safety and tolerability (versus monotherapies and placebo)

Trial population

The trial consisted of 1692 randomized COPD patients. They were randomized using an interactive voice randomization system (IVRS) on Day 1 Visit 2.

Key Inclusion/Exclusion/ Patient discontinuation Criteria

These criteria in trial 31 were largely similar to those in trial 30.

Treatments

The trial consisted of 5 treatment groups; they were as follows:

- AB/FF 400/12 µg
- AB/FF 400/6 µg
- AB 400 µg
- FF 12 µg
- Placebo

Concomitant/Restricted Medications:

Drugs that were or not permitted as concomitant medications for either episodic or chronic use are provided in Table 10.

Table 10: Concomitant/Restricted Medications, Trial 31

Drug Class	Restrictions
Long-acting inhaled anticholinergics (eg, tiotropium) and oral, intranasal or parenteral anticholinergics	Not allowed within 72 hours before Visit 1 and throughout the study
Short-acting inhaled anticholinergics (eg, ipratropium, oxitropium)	Not allowed within 12 hours before Visit 1 and throughout the study
Short-acting β2-adrenergic agonists (eg, fenoterol, terbutaline)	Only episodic use of Sponsor-provided albuterol HFA/salbutamol is permitted. Patients on fenoterol, terbutaline or albuterol must discontinue use at least 6 hours before Visit 1 and throughout the study.
Long-acting β2-adrenergic agonists (eg, salmeterol, formoterol, indacaterol)	Not allowed within 48 hours before Visit 1 and throughout the study
Inhaled corticosteroids	Must be stable for at least 4 weeks before Visit 1. Inhaled corticosteroids should be avoided the morning of study visits and begin after visit completion.
Oral or parenteral corticosteroids	Up to 10 mg/d or 20 mg every other day prednisone is allowed, as long as this schedule is stable 4 weeks before Visit 1

Drug Class	Restrictions
Combination therapies (e.g., Combivent, Symbicort, Advair)	Combivent is not allowed within 12 hours before Visit 1 and cannot be used during the study; Advair and Symbicort are not allowed within 48 hours before Visit 1 and cannot be used during the study. Patients on Advair or Symbicort can be switched to the same inhaled corticosteroid dose and allowed rescue short-acting albuterol HFA during the study without an additional stabilization period (must be stable for 4 weeks on inhaled corticosteroids, as above).The patient will be considered stabilized if, according to the investigator's criteria, during the second week of observation there are no changes in symptoms beyond the day to day variation or, symptoms experienced remain at similar level of those existing before medication change.
Methylxanthines (theophylline)	Methylxanthines other than oral sustained-release theophylline are not allowed within 72 hours before Visit 1 and throughout the study. Theophylline use is not allowed within the previous 3 months and throughout the study
H1-antihistamines (loratadine, etc)	Dosage must be stable for at least 4 weeks before Visit 1
Cromones (Cromolyn, Nedocromil)	Not allowed within 6 weeks before Visit 1 and throughout the study
Leukotriene modifiers (e.g., montelukast, zafirlukast, zileuton)	Not allowed within 48 hours before Screening Visit (Visit 1) and throughout the study
Nonselective β-blocking agents (eg, alprenolol, nadolol, propranolol, sotalol, timolol)	Not allowed within 2 weeks of Visit 1. Patients taking nonselective β-blocking agents can be switched to selective β1-blocking agents as long as they are stable for at least 2 weeks at their highest dosage before Visit 1
Selective β1-blocking agents (e.g., atenolol, metoprolol, nebivolol)	Selective agents are permitted for use during the study as long as the patient has been at a stable dosage for at least 2 weeks before Visit 1
Indacaterol	Not allowed within 1 weeks before Screening Visit (Visit 1) and throughout the study
Phosphodiesterase 4 (PDE4) inhibitors (Roflumilast)	Not allowed within 4 weeks before Screening Visit (Visit 1) and throughout the study

Source: LAC-MD-31 Volume 2; Appendix 3; pg 140-142

Study Endpoints

Primary Endpoints

- Change from baseline in 1-hour morning post-dose FEV1 of each FDC dose compared to AB monotherapy at Week 24.
- Change from baseline in morning pre-dose (trough) FEV1 of each FDC dose compared to FF monotherapy at Week 24.

Secondary Endpoints

- Improvement of TDI focal score for each FDC dose compared with placebo at Week 24.
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 (each dose of FDC versus placebo; AB 400 µg versus placebo for US filing only)
- Reduction in the rate of moderate or severe COPD exacerbations per patient per year based on pooled data from the trials 30 and 31, for each FDC dose compared with placebo, and AB monotherapy compared with placebo.

Additional study endpoints in trial 31 were largely similar to those in trial 30. These trial endpoints that are also used in trials of other LAMA/LABA products are acceptable.

Statistical Analysis Plan

The statistical analysis methods of co-primary and key secondary endpoints and methods for

multiplicity control are similar to those in trial 30.

Sensitivity analysis using a pattern-mixture model based on non-future depedent missing value restrictions was performed to assess the robustness of the primary MMRM results to the possible violation of the missing at-random assumption. Please refer trial 30 for details.

Protocol Amendments

Four amendments (Amendment #1, dated 23 Aug 2011; Amendment #2, dated 14 Feb 2012; Amendment #3, dated 07 Jan 2013; and Amendment #4, dated 20 Mar 2013) were made. Relevant changes made in these amendments are summarized as follows:

Amendment #1:
- Provide study-specific instructions on proper rescue medication inhaler use and restrictions before visits according to revised American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria
- Correct the coprimary and secondary efficacy assessments
- Correct the statistical efficacy parameters

Amendment #2:
- Clarify method to assess compliance, redefine inadequate compliance, and provide guidance to the study center as to when the Sponsor should be notified in cases of noncompliance
- Add information regarding the extension trial LAC-MD-36 at the end of Visit 7
- 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 AB and FF

Amendment #3:
- Describe the adjudication of MACE activities
- Add requirement of additional follow-up for COPD exacerbations in patients who prematurely discontinue
- Clarify electronic diary and TrialSlate procedures for patients participating in the extension trial, 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

Amendment #4:
- Add the requirement for a comparison of AB 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

These amendments did not change the overall design or quality of the trial. These amendments did not affect interpretability of the data.

Trial 01

Title: "A 24 -week treatment, multicenter, randomized, double-blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 µg/formoterol fumarate 12 µg fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 µg BID and formoterol fumarate 12 µg BID) and tiotropium (TIO) 18 µg QD when administered to patients with stable chronic obstructive pulmonary disease"

- Study date: 07/05/2016-06/08/2017
- Study report date: 01/05/2018
- Study sites: United States, Europe and Israel (12 countries)

Trial Design

This was a multiple dose, randomized, parallel, double-blind, double dummy, multicenter and multinational Phase 3 trial to determine the efficacy and safety of AB/FF 400/12 µg BID compared to each monotherapy (AB 400 µg BID and FF 12 µg BID) and tiotropium (TIO 18 µg QD) when administered to patients with stable COPD.

After signing the ICF, patients fulfilling inclusion/exclusion criteria at the time of the screening entered into a run-in period of 14±3 days to assess the patient's disease stability. Patients who met entry criteria at Visit 2 were randomized in a ratio 2:3:2:3 to one of the 4 treatment arms (AB/FF 400/12 µg BID, AB 400 µg BID, FF 12 µg BID and TIO 18 ug QD, respectively). Patient received the treatments for 24 weeks and came for scheduled visits at Visit 3 (Week 1), Visit 4 (Week 4), Visit 5 (Week 12), Visit 6 (Week 18), and Visit 7 (Week 24) for assessments of clinical efficacy and safety. A subset of patients (35%), participated in a spirometry substudy, performing additional spirometry timepoints up to 24 hours after the morning dose, at Visits 2 and 7. A follow-up contact was performed 2 weeks after the last dosing. Patients who prematurely discontinued treatment had to attend an End of Treatment (EOT) visit and were encouraged to complete a post-treatment discontinuation follow-up period including scheduled study visits. Patients who withdrew from the trial had to attend an End of Study (EOS).

The trial schedule and assessments are summarized in Table 11.

Table 11: Assessment Schedule, Trial 01

Period	Wash-out period	Screening period	Treatment							Follow-up call
Visit	Visit 0 Registration[1]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	EOT/ EOS visit[1]	
Week	Up to 6	2	0	1	4	12	18	24		26
Day and Visit Window	Up to 42	14±3 d	1	8±2 d	29±3 d	85±3 d	127±3 d	169±3 d		183+3 d
ICF	X									
Medical, smoking, COPD and medication history	X	X								
Physical examination[2]		X[2]						X	X	
Blood pressure and 12-lead ECG [3]		X	X	X	X	X	X	X	X	
Pre and post-bronchodilator test[4]		X								
Dispense wash-out medication	X	X								
Inclusion/exclusion criteria	X	X	X							
Clinical laboratory testing[5]		X						X	X	
Randomisation			X							
SGRQ, CAT[6]		X	X		X	X	X	X	X	
Device preference								X	X	
e-diary completion[7]		Daily since Screening Visit (Visit 1): EXACT in the evening and NiSCI and EMSCI in the morning							X	
Pre-dose PFT[8]			X	X	X	X	X	X	X	
Post-dose PFT			X[9]		X[10]	X[11]	X[10]	X[11]	X[12]	
Training on inhalers			X	As needed						
Dispense relief medication	X	As needed								
Assess study drug compliance				X	X	X	X	X		
Dispense study drug via IWRS			X			X				
Paper diary[13]		X	X	X	X	X	X	X	X	X
Adverse events/COPD exacerbations		X	X	X	X	X	X	X	X	X
Prohibited/ concomitant medications	X	X	X	X	X	X	X	X	X	X[14]
SERIAL SPIROMETRY SUBSTUDY: Additional Assessments										
24-hour PFT[15]			X					X		

CAT=COPD Assessment Test, COPD=chronic obstructive pulmonary disease, d=days; ECG=electrocardiogram; e-diary=electronic diary; EMSCI=Early morning symptoms of COPD instrument; EOS=End of Study; EOT=End of Treatment; EXACT=Exacerbations of Chronic Pulmonary Disease Tool; ICF=informed consent form; IWRS=Interactive Web Response System; NiSCI=Night-time symptoms of COPD instrument; PFT=pulmonary function test; SGRQ=St George's Respiratory Questionnaire.
Note: Time windows for all visits are related to Visit 2.

1 Patients requiring a wash-out of prohibited COPD medications signed the ICF, were assigned a Patient Identification number (enrolment code) by the IWRS system, and received Atrovent® and relief medication (albuterol/salbutamol) at Visit 0. Visit 0 could occur the same day as Visit 1 if the patient did not require a wash-out. In this case, only relief medication was provided to the patient. EOS for patients who discontinued from the treatment and from the study at the same time; patients who discontinued from the treatment post follow-up period attended a reduced EOS visit to collect the diaries.
2 Height and weight only at Screening Visit.
3 Blood pressure (after being seated for 5-10 minutes and before the ECG assessment) and ECG were performed once at Screening Visit to determine patient eligibility and once at EOT/EOS visit. At other visits, ECG and blood pressure were performed pre-morning dose (before the patient exerted any effort, including PFTs) and 2 hours post-morning dose only at Visits 2, 5 and 7.
4 One pre-bronchodilator PFT, followed by one post-bronchodilator PFT 10-15 minutes after the inhalation of 4 puffs of albuterol/salbutamol through a spacer device.
5 Haematology and biochemistry. Serum pregnancy test only in female patients of child bearing potential.
6 At Screening Visit, only the CAT questionnaire was administered to assess the fulfilment of the inclusion criteria. At other visits, both the SGRQ and CAT questionnaires were administered prior to study drug administration. SGRQ was the first questionnaire to be administered.
7 Patient recorded the number of doses taken of relief medication once daily (in the evening); IP intake was recorded in the morning and evening; EXACT questionnaire was completed every evening; and Night-time and early morning COPD symptoms questionnaire were completed every morning. Following EOT visit patients were asked to complete the e-diary only in the evening for the EXACT questionnaire.
8 Two pre-PFTs (approximately 15 to 30 minutes apart) both were to be completed within 60 minutes prior to the morning dose of study drug.
9 At Visit 2: 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours post study drug administration.
10 At Visits 4 and 6: 1 hour post study drug administration.
11 At Visits 5 and 7: 30 minutes, 1 hour, 2 hours, and 3 hours post study drug administration.
12 At EOT/EOS visit: 1 hour post COPD treatment administration.
13 Patient recorded in the paper diary the AEs and new concomitant medication during the study.
14 Only concomitant medication related to AEs had to be recorded at follow-up contact.
15 Additional PFTs at Visit 2 and 7 only for 35% of patients who participated in the 24-hour serial spirometry substudy: +4h, +6h, +9h, +12h (pre-evening dose), +12.5h, +13h, +14h, +22, +23.5h and +24h after the morning dose. Subjects participating in the substudy who chose to discontinue from treatment did not complete the 24h spirometry assessments at the EOT visit.

Objectives/Rationale

- Primary objective: To assess the bronchodilatory effect of AB/FF 400/12 µg compared to each individual component when administered BID via inhalation to COPD patients.
- Secondary objective: To further characterize the effect of AB/FF 400/12 µg on bronchodilation and health related quality of life compared to individual components when administered BID via inhalation to COPD patients.
- Safety objective: To evaluate the safety and tolerability of AB/FF 400/12 µg as compared to individual components in COPD patients.
- Exploratory objectives: To evaluate treatment effects and comparisons in primary and secondary endpoints for the subgroup of patients which were more symptomatic at trial entry based on different definitions.

Trial population
The trial consisted of 1594 randomized COPD patients who were randomized on Day 1 Visit 2.

Key Inclusion Criteria

1. Adult male or non-pregnant, non-lactating female patients aged ≥40 years.
2. Patients with diagnosis of moderate to very severe stable COPD: post-bronchodilator FEV1 <80% of the predicted normal and post-bronchodilator FEV1/forced vital capacity (FVC) <70% at Screening visit.
3. Symptomatic patients with a COPD Assessment Test (CAT) score ≥10 at screening and Randomization visit (Visits 1 and 2).
4. Current or former smokers, with a smoking history of ≥10 pack-years.
5. Patients able to perform acceptable and repeatable pulmonary function testing for FEV1 according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria at Visit 1.
6. Patients eligible and able to participate in the trial and who had signed an ICF prior to initiation of any study-related procedures.

Key Exclusion Criteria

1. Patients with predominant asthma, any respiratory tract infection or COPD exacerbation within 6 weeks prior to screening or during the run-in period.
2. Patients hospitalized for a COPD exacerbation (an emergency room visit for longer than 24 hours was considered a hospitalization) within 3 months prior to Screening Visit.
3. Clinically significant respiratory conditions other than COPD, e.g., known active tuberculosis, history of interstitial lung disease or massive pulmonary thromboembolic disease, pulmonary resection or lung volume reduction surgery, history of lung transplantation, patients who in the investigator's opinion might have needed thoracotomy or other lung surgery during the trial, bronchiectasis secondary to respiratory diseases other than COPD, known α1-antitrypsin deficiency.

4. Patients who in the investigator's opinion may have needed to start a pulmonary rehabilitation program during the trial and/or patients who had started/finished it within 3 months prior to screening.
5. Use of long-term oxygen therapy (≥15 hours/day).
6. Clinically significant cardiovascular conditions, e.g., myocardial infarction within the 6 months prior to screening, thoracic surgery within 6 months prior to screening, unstable angina or unstable arrhythmia which had required changes in the pharmacological therapy or other intervention within 6 months prior to screening, newly diagnosed arrhythmia within the 3 months prior to screening which required the pharmacological therapy or other intervention, hospitalization within 6 months prior to screening for heart failure functional classes III (marked limitation of activity and only comfortable at rest) and IV (need of complete rest, confinement to bed or chair, discomfort at any physical activity and presence of symptoms at rest) as per the New York Heart Association, presence of an implantable cardioverter-defibrillator within the last year prior to Screening Visit.
7. Patients with history of long QT syndrome or whose corrected QT (QTc) (calculated according to Fridericia's Formula $QTc=QT/RR^{1/3}$) >470 ms as indicated in the centralized reading report assessed at Screening.
8. Patients with uncontrolled Type I or Type II diabetes, uncontrolled hypo-or hyperthyroidism, hypokalemia, or hyperadrenergic state, uncontrolled hypertension.
9. Patient with known non-controlled history of infection with human immunodeficiency virus and/or active hepatitis.
10. Patient with a history of hypersensitivity reaction to inhaled medication or any component thereof, including paradoxical bronchospasm.
11. Patients with known narrow-angle glaucoma, symptomatic bladder neck obstruction, acute urinary retention or symptomatic non-stable prostate hypertrophy.
12. History of malignancy of any organ system (including lung cancer), treated or untreated, within the past 5 years other than basal or squamous cell skin cancer.
13. Patients with any other serious or uncontrolled physical or mental dysfunction.
14. Patients with a history (within 2 years prior to screening) of drug and/or alcohol abuse that may have prevented study compliance based on the investigator judgment.
15. Patients treated with any investigational drug within 30 days (or 6 half-lives, whichever was longer) prior to screening.

Key withdrawal criteria

1. Screen failures: patients who do not fulfil the eligibility criteria for the trial.
2. Adverse Event: if a patient experiences an AE, its premature discontinuation will be considered at the discretion of either the investigator or the patient regardless of the causal relationship to the IP.
3. Progressive disease: if at investigator's or patient's discretion the severity of the COPD exacerbation episode jeopardizes the current medical condition of the patient, the patient should be discontinued from the treatment.

4. Lost to follow-up: Non-attendance to visits.
5. Withdrawal by the subject: The patient is permitted to stop his/her participation at any time during the trial without incurring any loss in his/her medical care.

This was an active-controlled 24-week trial. The trial design and patient population are typical for a COPD trial. Compared to the placebo-controlled trials, very severe COPD patients were included in this trial.

Treatments
The trial consisted of 4 treatment groups; they were as follows:

- AB/FF 400/12 µg
- AB 400 µg
- FF 12 µg
- TIO 18 µg

Concomitant/Restricted Medications:
Allowed medications are summarized in Table 12.

Table 12: Concomitant Medications, Trial 01

Medication/Class of drug	Restrictions	Stabilization period
ICS*	Patients who were following a stable regimen of a LABA/ICS combination for at least 4 weeks can be switched to the same ICS (at the same dose and dose regimen) as monotherapy. In this case no stabilization period was needed. If treatment was switched to a different ICS as monotherapy at an equivalent therapeutic dose to the one used for the fixed inhaled combination, a stabilization period of at least 14 days or longer, until patient was considered stabilized, had to occur before screening (Visit 1). The patient was considered stabilized if, according to the investigator's judgment, during the second week of observation there were no changes in symptoms beyond the day to day variation, or symptoms experienced remained at a similar level of those existing before medication change.	4 weeks
Continuous oral or parenteral corticosteroids*	Dose equivalent of 10 mg of prednisone per day or 20 mg every other day or lower than this.	4 weeks
Selective B-blocking agents (e.g., atenolol, metoprolol, nebivolol)	-	2 weeks
Oxygen therapy*	<15 hours a day.	4 weeks

Medication/Class of drug	Restrictions	Stabilization period
Oral sustained-release theophyllines	Theophylline had to be avoided the morning of study visits and begin after visit completion.	4 weeks

* Change in daily dose, dosing schedule, formulation or treatment was unlikely during the course of the trial (the exception being the treatment of a COPD exacerbation).
Source: D6571C00001 Clinical Study Report; Table 5; pg 34-35

Restricted medications are summarized in Table 13.

Table 13: Restricted Medications, Trial 01

Medication/Class of Drug:	Washout before Visit 1
Oral, intra-nasal or parenteral anticholinergic agents such as atropine, glycopyrrolate or biperiden	7 days
BID long-acting inhaled anticholinergics, LAMAs (e.g., AB)	72 hours
QD long-acting inhaled anticholinergics, LAMAs (e.g., umeclidinium, TIO bromide, glycopyrrolate)	7 days
Short-acting inhaled anticholinergics, SAMAs (except for ipratropium which was to be administered during the wash-out and run-in period)	6 hours
Inhaled and short-acting B2-agonists, SABAs (e.g., fenoterol or albuterol, except for albuterol/salbutamol)	6 hours
QD long-acting B2- agonists (LABAs) (e.g., indacaterol, oladaterol) and QD combination of LABAs+ICS (e.g. vilanterol/fluticasone)	7 days
Oral (terbutaline) and BID LABAs (e.g., formoterol, salmeterol) and BID combination of LABAs+ICS (e.g. fluticasone/salmeterol, budesonide/formoterol) *Note: Patients could be switched to the same or a different ICS as monotherapy (see restricted medication section for stabilization period)*	48 hours
Combination of SABAs+SAMA (e.g., ipratropium/salbutamol)	12 hours
Combination of LABA+LAMA (e.g., indacaterol/glycopyrronium, umeclidinium/vilanterol, TIO/olodaterol)	7 days
Methyl-xanthines (e.g., theophylline, theobromine tablets)	72 hours
Leukotriene modifiers (e.g., montellukast)	48 hours
PDE4 inhibitors (e.g., roflumilast)	4 weeks
Continuous oral or parenteral corticosteroids used at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day *Note: could be switched to dose equivalent of I0 mg of prednisone per day or 20 mg every other day as long as they are at stable dose for at least 4 weeks prior to Visit I*	4 weeks

Medication/Class of Drug:	Washout before Visit 1
Non-selective B-blocking agents (e.g., carvedilol, alprenolol, nadolol, propranolol, sotalol, timolol) *Note: could be switched to selective β_1-blocking agents, as long as they are at stable dose for at least 2 weeks prior to Visit 1*	2 weeks

Source: D6571C00001 Clinical Study Report; Table 6; pg 35-36

Study Endpoints

Study endpoints are summarized in Table 14.

Table 14: Objectives and Endpoints, Trial 01

Objective			Main Endpoint
Priority	**Type**	**Description**	
Primary (US)	Efficacy	To assess the bronchodilator effect of AB/FF 400/12 µg compared to each individual component when administered BID via inhalation to COPD patients.	• Change from baseline in 1-hour morning post-dose FEV1 of AB/FF 400/12 µg compared to AB 400 µg at Week 24. • Change from baseline in morning pre-dose(trough) FEV1 of AB/FF 400/12 µg compared to FF 12 µg at Week 24.
Secondary	Efficacy	To further characterize the effect of AB/FF 400/12 µg on bronchodilation and health related quality of life compared to individual components when administered BID via inhalation to COPD patients.	• Change from baseline in normalized $AUC_{0-3/3h}$ FEV1 of AB/FF 400/12 µg at Week 24 compared to AB 400 µg and FF 12 µg. • Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4 units from baseline) with AB/FF 400/12 µg in SGRQ total score at Week 24 compared to AB 400ug and FF 12ug.
Additional	Efficacy	To further support the primary and secondary objectives	• Pulmonary function variables (FEV1, FVC) at each different time points. onset of action, peak and trough FEV1 at each visit and average (ie, $AUC_{0-3/3h}$). FEV1 and FVC at each timepoint and AUC_{0-12h}; AUC_{12-24h}, AUC_{0-24h} in serial spirometry substudy • Health related quality of life outcomes, SGRQ, CAT: change from baseline and responder analysis (percentage of patients reaching the MCID) at each visit. • COPD exacerbations, as defined by HCRU and EXACT:

			• Percentage of patients with at least 1 exacerbation, rate of exacerbations and time to first exacerbation. • Use of rescue medication: change from baseline at each visit and over the treatment period.

AB=aclidinium bromide, AE=adverse event, $AUC_{0-3/3h}$=area under curve 3h post-dose, AUC_{0-12h}=area under curve 12h post-dose, AUC_{12-24h}=area under curve between12-24h post-dose, AUC_{0-24h}=area under curve 24h post-dose, BID=twice daily, CAT=COPD Assessment Test, COPD=chronic obstructive pulmonary disease, CSP=clinical study protocol, ECG=electrocardiogram, EMSCI=early morning symptoms of COPD instrument, E-RSTM:COPD=Evaluating Respiratory Symptoms in COPD, EXACT=exacerbations of Chronic Pulmonary Disease Tool, FEV1=forced expiratory volume in 1 second, FF=formoterol fumarate, FVC=forced vital capacity, HCRU=health care resource utilization, MACE=Major Adverse Cardiac Event, MCID=minimally clinical important difference, NiSCI=night-time symptoms of COPD instrument, PFT=pulmonary function test, QD=once daily, SAE=serious adverse event, SGRQ=St George Respiratory Questionnaire, TIO=tiotropium.
Source: D6571C00001 Clinical Study Report; Table 7; pg 37-38

Consistent with the placebo-controlled trials 30 and 31, the primary endpoints were 1-hour post-dose and trough FEV1, which were commonly used in COPD trials and acceptable.

Statistical Analysis Plan

The analyses of the co-primary endpoints were performed using ITT population which is defined as all randomized patients who take at least one dose of IP and have at least a baseline FEV_1, regardless of their adherence to the randomized treatment.

The co-primary endpoints, change from baseline in 1-hour morning post-dose FEV_1, and change from baseline in morning pre-dose trough FEV_1 at week 24 were analyzed by MMRM, adjusted for pre and post bronchodilator FEV_1 at screening visit, age, and baseline FEV_1 as covariates, and treatment group, sex, smoking-status, visit, and treatment group-by-visit interaction as fixed effect factors, and country as random intercept. An unstructured covariance pattern was used to estimate the variance-covariance of the within-subject repeated measures.

Each treatment effect and treatment differences between all treatments were estimated by the LS Means on the treatment-by-visit interaction at week 24, along with their SE and two-sided 95% CI, and the p-value corresponding to the between-treatment group difference. Statistical comparisons were two sided hypothesis tests, and the significance level is set at 0.05. P-values are reported as two-sided.

Analyses of change from baseline in normalized AUC_{0-3} FEV_1 at week 24 used same MMRM model used for the co-primary endpoints.

The number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units from baseline) compared to monotherapies in the SGRQ total score was analyzed

based on a logistic random-effect model using GLIMMIX that includes a random intercept to account the variability between subjects, and treatment, sex, smoking-status, country, visit, and treatment group-by-visit interaction as fixed factors, and with age and baseline as covariate. Odds ratios between treatments groups were estimated on the treatment-by-visit interaction at week 24, along with their SE, 95% CI, and 2-sided p-values.

A sequentially rejective multiple testing procedure was used to control the family-wise type I error at the 5% level. Table 15 lists the sequence of testing.

Table 15: Sequence of testing for multiplicity adjustment, Trial 01

Testing Order in Hierarchy	Variable (at week 24)	Treatment Comparison
1	Change from baseline in 1-hour post-dose FEV_1	AB/FF 400/12 µg vs. AB 400 µg
2	Change from baseline in morning pre-dose FEV_1	AB/FF 400/12 µg vs. FF 12 µg
3	Change from baseline in nAUC0-3 FEV_1	AB/FF 400/12 µg vs. AB 400 µg
4	Change from baseline in nAUC0-3 FEV_1	AB/FF 400/12 µg vs. FF 12 µg
5	Responder analysis of SGRQ total score (a decrease of at least 4-units from baseline)	AB/FF 400/12 µg vs. AB 400 µg
6	Responder analysis of SGRQ total score (a decrease of at least 4-units from baseline)	AB/FF 400/12 µg vs. FF 12 µg

Note: Both co-primary variables (the first two testing hypothesis) should overcome the statistical hierarchy to meet the primary bronchodilator objective
Source: Statistical Analysis Plan, Edition 1.0, Dated 14 Dec 2016

Sensitivity analysis were conducted on the co-primary endpoints using two approaches, one is copy reference (CR) approach and the other one was analysis based on treatment policy estimand.

With CR approach, missing data is imputed under missing-not-at-random (MNAR) assumption. To compare AB/FF 400/12 µg versus AB 400 µg in the change from baseline in 1h morning post-dose FEV_1 at week 24, it assumes patients from the AB/FF 400/12 µg treatment arm behave as patients from the AB 400 µg after drop-out. So patients who withdraw from AB/FF 400/12 µg arm will be imputed as if they were a member of the AB 400 µg. Twenty (20)datasets were created under this approach, then each imputed dataset wasanalyzed using the same MMRM used in the main analysis. Finally, the results of multiple datasets were combined using the SAS proc MIANALYZE to obtain the estimation of the treatment effect and treatment comparison. The same CR approach was also used to compare AB/FF 400/12 ug versus FF 12 µg in change from baseline in morning pre-dose (trough) FEV_1 at week 24.

The primary analysis of co-primary endpoints estimates on-treatment estimand. Sensitivity analysis targeting treatment policy estimand was conducted on the co-primary endpoints. The sensitivity analysis includedall data regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, unless the patients withdrew consent to study participation. Missing data was modelled using MAR assumptions. The dataset including data collected after discontinuation of IP study treatment was analyzed using the same MMRM used in the main analysis.

Protocol Amendments

Four amendments (Amendment #1, dated 03/01/2016; Amendment #2, dated 03/21/2016; Amendment #3, 03/31/2016; and Amendment #4, dated 06/17/2016) were made.

Amendment #1 :
- Defined primary objective for Market Access and statistical analysis
- Corrected doses for Atrovent and specified brand names for US and non-US countries
- Added clarification on procedures for the End of Treatment (EOT) and End of Study (EOS) visits, including 1h post-dose pulmonary function test (PFT) after COPD prescribed treatment
- Added red blood cells morphology, white blood cells differential and mean corpuscular volume (MCV) in the laboratory assessments

Amendment #2 :
- The collection of investigational product intake was included in the e-diary

Amendment #3 (in US only):
- Extended duration of birth control to 30 days after last investigational product dose for women of childbearing potential

Amendment #4 (in Czech Republic only):
- Included section on 24-hour spirometry sub-study
- Incorporated management of COPD exacerbation
- Clarified that patients treated with ICS as monotherapy for at least 4 weeks could be included in the trial (at the same dose and dose regimen) and clarified that patients treated with LAMA/ICS combination for at least 4 weeks could be switched to the same ICS (at the same dose and dose regimen) as monotherapy. In this case, no stabilization period was needed.

These amendments did not change the overall design or quality of the trial. These amendments did not affect interpretability of the data.

<u>Trial 02</u>

Title: "Double-blind, randomized, placebo-controlled, parallel-group, phase IV study to evaluate the effect of aclidinium bromide on long-term cardiovascular safety and COPD exacerbations in patients with moderate to very Severe COPD (ASCENT COPD)"

- Study date: 10/16/2013-09/06/2017
- Study report date: 03/29/2018
- Study sites: U.S., Canada

Trial Design

This trial was a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the effect of AB 400 mcg on cardiovascular (CV) safety and COPD exacerbations in patients
with moderate to very severe COPD and prior history of CV events or CV risk factors.

The trial consisted of a 2-week washout/run-in period. Patients on a LAMA (i.e., inhaled anticholinergics) had to washout 2 weeks prior to randomization. 3630 patients meeting entry criteria were randomized (1:1) to AB 400 µg twice a day (BID) or placebo BID with a background of standard of care treatment. The treatment duration was 36 months. This trial was submitted in NDA 202450/S-012 for the inclusion of COPD exacerbation reduction into the label indication of Tudorza Pressair (aclidinium bromide) Inhalation Powder. A detailed review of this protocol can be found in unireview of sNDA 202450 supplement 12.

8.1.2. Study Results

Efficacy results from Trials 30, 31, and 01 will be discussed in detail in this section 8.1.2. Results from Trial 02 will be only briefly summarized in section 8.1.4, as the detailed review can be found in the unireview sNDA 202450 supplement 12.

Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in the clinical study report in Trials 30, 31 and 01, within the electronic submission.

Financial Disclosure

See section 19.2.

Patient Disposition

A total of 5015 patients were randomized into the Phase 3 pivotal trials, Trial 30 (1729 patients), 31 (1692 patients) and 01 (1594 patients). Note that as Trials 30 and 31 were essentially identical in design and conduct, data from these trials will be pooled for the analyses of disposition, demographics, and baseline characteristics. Pooled analyses of Trials 30 and 31 indicated that the proportions of patients who prematurely discontinued treatment

were somewhat higher in the placebo arms (25.4%) than in the active treatment arms (13.8% to 16.8%). The most common reasons for discontinuation for all the treatment arms were withdrawal of consent and adverse events. Between groups, reasons for premature treatment discontinuation were similar for the placebo and active treatment groups, except for insufficient therapeutic response that was highest in the placebo groups and lowest in the AB/FF 400/12 µg treatment group. The pooled analysis data are summarized in Table 16.

Table 16: Pooled Patient Disposition, Trials 30 and 31

Population	Number (%) of Patients					
	Placebo	AB/FF 400/12 µg	AB/FF 400/6 µg	AB 400 µg	FF 12 µg	Total
Randomized	531	723	719	725	723	3421
Treatment Completed	396 (74.6)	623 (86.2)	617 (85.8)	603 (83.2)	609 (84.2)	2848 (83.3)
Discontinued	135 (25.4)	100 (13.8)	102 (14.2)	122 (16.8)	114 (15.8)	573 (16.7)
Reason for Treatment Discontinuation						
Adverse Events	28 (5.3)	33 (4.6)	32 (4.5)	27 (3.7)	25 (3.5)	145 (4.2)
Insufficient Therapeutic Response	26 (4.9)	5 (0.7)	8 (1.1)	13 (1.8)	13 (1.8)	65 (1.9)
Protocol Violation	23 (4.3)	16 (2.2)	21 (2.9)	22 (3.0)	27 (3.7)	109 (3.2)
Withdrawal of Consent	36 (6.8)	21 (2.9)	26 (3.6)	40 (5.5)	30 (4.1)	153 (4.5)
Lost to Follow-Up	5 (0.9)	10 (1.4)	5 (0.7)	3 (0.4)	5 (0.7)	28 (0.8)
COPD Exacerbation	10 (1.9)	12 (1.7)	5 (0.7)	14 (1.9)	8 (1.1)	49 (1.4)
Others	7 (1.3)	3 (0.4)	5 (0.7)	3 (0.4)	6 (0.8)	24 (0.7)

Source: Integrated Summary of Efficacy Report; Statistical Report for the Pooled Data Amendment 1 Index; Table 1.1; pg 1077

In Trial 01, the majority of patients (85.1%) completed treatment. The proportions of patients who prematurely discontinued treatment were comparable across treatment arms. The reasons for premature treatment discontinuation were generally similar across treatment arms except that a lower proportion of patients in the AB/FF 400/12 µg arm discontinued treatment due to progressive disease compared to the AB, FF, or TIO treatment arms. The data are summarized in Table 17.

Table 17: Patient Disposition, Trial 01

Population	Number (%) of Patients				
	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	TIO 18 µg	Total
Randomized	317	478	320	479	1594
Treatment Completed	279 (88.0)	405 (84.7)	267 (83.4)	405 (84.6)	1356 (85.1)
Discontinued	38 (12.0)	73 (15.3)	53 (16.6)	74 (15.4)	238 (14.9)
Reason for Treatment Discontinuation					
Adverse Events	11 (3.5)	22 (4.6)	14 (4.4)	14 (2.9)	61 (3.8)
Protocol Deviation	7 (2.2)	5 (1.0)	4 (1.2)	8 (1.7)	24 (1.5)
Withdrawal by Subject	4 (1.3)	14 (2.9)	6 (1.9)	7 (1.5)	31 (1.9)
Progressive Disease	6 (1.9)	15 (3.1)	13 (4.1)	18 (3.8)	52 (3.3)
Lack of Efficacy	7 (2.2)	9 (1.9)	14 (4.4)	20 (4.2)	50 (3.1)
Lost to Follow-up	1 (0.3)	5 (1.0)	2 (0.6)	2 (0.4)	10 (0.6)
Others	2 (0.6)	3 (0.6)	0 (0.0)	5 (1.0)	10 (0.6)

Source: D6571C00001 Clinical Study Report; Table 9; pg 46-47

Protocol Violations/Deviations

In Trial 30, six patients were randomized to the trial but did not meet one of the inclusion criteria, and 39 patients were randomized to the trial but met an exclusion criterion. However, the proportion of patients in each group who had protocol violations were similar. In addition, 12 patients were randomized to the wrong smoking strata which was detected after randomization, and 13 patients received the incorrect study medication kit.

In Trial 31, approximately 10% of patients had protocol violation and the number was similar between groups. The common reasons for protocol violation were that patients did not meet inclusion or exclusion criteria, treatment compliance and other criteria (e.g., receiving unstable oral or parental corticosteroids dose 2 weeks prior to Visits 2 or 7).

In Trial 01, 15.1% of patients had an important protocol deviation. Similarly, regarding the proportion of patients in each group who had protocol violation, no large differences between groups were noted. The common reasons for protocol violation were that patients received incorrect investigational treatment/dose and did not adhere to protocol procedures.

While some protocol violations were observed, as they were similar between treatment arms in Trials 30, 31, and 01, these violations would not likely affect interpretation of results.

Table of Demographic Characteristics

Patient demographic characteristics for pooled data from Trials 30 and 31 are summarized in Table 18. Over 93% of patients were white in each group. A slightly higher proportion of patients had severe or very severe COPD at baseline in placebo compared to other groups. Otherwise, the demographic characteristics were comparable between groups.

Table 18: Pooled Patient Demographic and Baseline Characteristics, Trials 30 and 31

	Placebo	AB/FF 400/12 µg	AB/FF 400/6 µg	AB 400 µg	FF 12 µg	Total
	N=526	N=720	N=714	N=722	N=716	N=3398
Age (years)						
n	526	720	714	722	716	3398
Mean (SD)	63.7 (8.5)	63.4 (8.5)	63.4 (8.5)	63.7 (8.5)	63.5 (8.2)	63.5 (8.4)
Median	64.0	64.0	63.0	64.0	64.0	64.0
Age groups, n (%)						
<65 years	276 (52.5)	393 (54.6)	390 (54.6)	376 (52.1)	379 (52.9)	1814 (53.4)
≥65 - <75 years	194 (36.9)	250 (34.7)	262 (36.7)	273 (37.8)	269 (37.6)	1248 (36.7)
≥75 - <85 years	54 (10.3)	74 (10.3)	56 (7.8)	69 (9.6)	69 (8.9)	317 (9.3)
≥85 years	2 (0.4)	3 (0.4)	6 (0.8)	4 (0.6)	4 (0.6)	19 (0.6)
Gender, n (%)						
Male	313 (59.5)	429 (59.6)	446 (62.5)	444 (61.5)	424 (59.2)	2056 (60.5)
Female	213 (40.5)	291 (40.4)	268 (37.5)	278 (38.5)	292 (40.8)	1342 (39.5)
Race, n (%)						
Asian	7 (1.3)	14 (1.9)	8 (1.1)	15 (2.1)	16 (2.2)	60 (1.8)
Black	11 (2.1)	25 (3.5)	21 (2.9)	22 (3.1)	20 (2.8)	99 (2.9)
Caucasian	500 (95.1)	672 (93.3)	675 (94.5)	677 (93.8)	673 (94.0)	3197 (94.1)
Other	8 (1.5)	9 (1.3)	10 (1.4)	8 (1.1)	7 (1.0)	42 (1.2)
Body mass index (kg/m^2)						
n	526	720	713	722	716	3397
Mean (SD)	27.3 (5.4)	27.3 (5.6)	27.6 (5.6)	27.3 (5.3)	27.6 (5.6)	27.4 (5.5)
Median	26.8	26.8	27.1	26.8	27.2	27.0
Body mass index groups, n (%)						
Under-to-Normal weight	191 (36.3)	271 (37.6)	254 (35.6)	251 (34.8)	260 (36.3)	1227 (36.1)
Pre-obese	174 (33.1)	243 (33.8)	241 (33.8)	272 (37.7)	232 (32.4)	1162 (34.2)
Obese	161 (30.6)	206 (28.6)	218 (30.6)	199 (27.6)	224 (31.3)	1008 (29.7)
Other	0	0	1 (0.1)	0	0	1 (0.0)
COPD Severity, n (%)						
Stage I (Mild)	0	0	1 (0.1)	2 (0.3)	2 (0.3)	5 (0.2)
Stage II (Moderate)	293 (55.9)	418 (58.1)	433 (60.6)	410 (57.1)	434 (60.8)	1988 (58.7)
Stage III (Severe)	227 (43.3)	298 (41.5)	278 (38.9)	304 (42.3)	275 (38.5)	1382 (40.8)
Stage IV (Very Severe)	4 (0.8)	3 (0.4)	2 (0.3)	2 (0.3)	3 (0.4)	14 (0.4)
Missing	2 (0.4)	1 (0.1)	0	4 (0.6)	2 (0.3)	9 (0.3)
Smoking Status, n (%)						
Current smoker	263 (50.0)	354 (49.2)	358 (50.1)	353 (48.9)	350 (48.9)	1678 (49.4)
Ex-smoker	263 (50.0)	366 (50.8)	356 (49.9)	369 (51.1)	366 (51.1)	1720 (50.6)
Pack-years of Cigarette Smoking						
n	526	720	714	722	716	3398
Mean (SD)	49.1 (26.5)	46.6 (25.1)	46.1 (24.5)	44.9 (23.7)	45.8 (22.3)	46.4 (24.4)
Median	44.0	41.0	42.0	40.0	41.1	42.0

Source: Integrated Summary of Safety Report; Table 2.1.4; pg 633-635

The demographic characteristics for Trial 01 were generally similar to Trials 30 and 31. Table 19 summarizes the demographic characteristics data in Trial 01.

Table 19: Patient Demographic and baseline Characteristics, Trial 01

	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	TIO 18 µg	Total
	N=314	N=475	N=319	N=475	N=1583
Age (years)					
n	314	475	319	475	1583
Mean (SD)	64.4 (8.5)	64.4 (8.1)	64.7 (8.3)	64.0 (8.6)	64.3 (8.4)
Min, Max	43.0, 100.0	42.0, 85.0	41.0, 84.0	41.0, 88.0	41.0, 100.0
Age group, n (%)					
≤65 years	166 (52.9)	270 (56.8)	168 (52.7)	263 (55.4)	867 (54.8)
>65 - ≤75 years	119 (37.9)	164 (34.5)	120 (37.6)	170 (35.8)	573 (36.2)
>75 - <85 years	27 (8.6)	41 (8.6)	31 (9.7)	39 (8.2)	138 (8.7)
>85 years	2 (0.6)	0 (0.0)	0 (0.0)	3 (0.6)	5 (0.3)
Gender, n (%)					
Female	121 (38.5)	171 (36.0)	129 (40.4)	199 (41.9)	620 (39.2)
Male	193 (61.5)	304 (64.0)	190 (59.6)	276 (58.1)	963 (60.8)
Race, n (%)					
White	297 (94.6)	444 (93.5)	303 (95.0)	457 (96.2)	1501 (94.8)
Black	17 (5.4)	28 (5.9)	16 (5.0)	16 (3.4)	77 (4.9)
Asian	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.4)	4 (0.3)
American Indian/Alaska native	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
BMI (kg/m^2)					
n	314	475	319	475	1583
Mean (SD)	27.8 (5.7)	28.1 (6.2)	28.3 (7.0)	27.8 (6.3)	28.0 (6.3)
Min, Max	13.9, 54.8	14.1, 53.6	14.9, 62.7	15.2, 51.9	13.9, 62.7
BMI group, n (%)					
Underweight	9 (2.9)	22 (4.6)	16 (5.0)	15 (3.2)	62 (3.9)
Normal weight	91 (29.0)	135 (28.4)	90 (28.2)	166 (34.9)	482 (30.4)
Overweight	110 (35.0)	165 (34.7)	112 (35.1)	149 (31.4)	536 (33.9)
Obese	104 (33.1)	153 (32.2)	101 (31.7)	145 (30.5)	503 (31.8)
COPD Severity, n (%)					
Stage II (moderate)	165 (52.5)	231 (48.6)	148 (46.4)	258 (54.3)	802 (50.7)
Stage III (severe)	123 (39.2)	191 (40.2)	137 (42.9)	182 (38.3)	633 (40.0)
Stage IV (very severe)	26 (8.3)	53 (11.2)	34 (10.7)	35 (7.4)	148 (9.3)
Smoking Status, n (%)					
Current smoker	164 (52.2)	248 (52.2)	163 (51.1)	250 (52.6)	825 (52.1)
Ex-smoker	150 (47.8)	227 (47.8)	156 (48.9)	225 (47.4)	758 (47.9)
Pack-years of Cigarette Smoking					
N	314	475	319	475	1583
Mean (SD)	46.2 (23.5)	45.4 (23.1)	45.2 (24.9)	46.4 (23.4)	45.8 (23.6)
Min, Max	10.0, 180.0	10.0, 165.0	10.0, 200.0	10.0, 180.0	10.0, 200.0

Source: D6571C00001 Clinical Study Report; Table 12,13,14; pg 50-52

Overall the demographic and baseline characteristics were generally similar between trials and between treatment groups. These were also fairly representative of the COPD population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Across trials and between groups, baseline pulmonary function was similar. Background COPD medication use was also similar across trials and between groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

A patient was considered treatment-compliant if the compliance rate was from 75 to 110%, from 80 to 105%, and over 70% in Trials 30, 31 and 01, respectively. In general, the treatment compliance was high. Approximately 90% of patients were compliant with the treatment in Trials 30, 31 and 01. Treatment compliance was similar across the treatment groups.

Concomitant medication was defined as any medication taken between the date of the first dose of investigational product (IP) and the date of the last dose of IP, inclusive, during the study period. The percentage of patients taking the concomitant medications was similar across the treatment groups in Trials 30, 31 and 01. However, patients taking AB/FF 400/12 ug in Trial 30 used ICS slightly more often than those in other treatment groups; metformin, amoxicillin and ciprofloxacin were used most often in the AB/FF 400/12 µg treatment group compared with other treatment groups in Trial 31.

Efficacy Results – Co-primary Endpoints

The co-primary endpoints for Trials 30, 31, and 01 were change from baseline in 1-hour morning post-dose FEV_1 at Week 24 and change from baseline in morning pre-dose (trough) FEV_1 at Week 24. The first co-primary endpoint was used to compare AB/FF 400/12 µg to AB 400 µg to assess the contribution of FF to the combination product. The second co-primary endpoint was used to compare AB/FF 400/12 µg to FF 12 µg to assess the contribution of AB to the combination product.

Analysis results of co-primary endpoint of change from baseline to Week 24 in FEV_1 at 1 hour post-dose in the individual Phase 3 pivotal trials are presented in Table 20.

Increases from baseline to Wweek 24 are observed in FEV_1 at 1 hour post-dose in AB/FF 400/12 µg group in all three Phase 3 pivotal trials, and were ofcomparable magnitude. The increases were0.269 L (in Trial 30), 0.247 L (in Trial 31), and 0.253 L (in Trial 01).

In each of the Phase 3 pivotal trials, the increases in FEV_1 at 1 hour post-dose at Week 24 were statistically significantly greater with AB/FF 400/12 µg than with AB 400 µg monotherapy ($p<0.0001$ for all comparisons), which is approved as a monotherapy for COPD. The increases of the adjusted mean treatment differences between AB/FF 400/12 µg and AB 400 µg monotherapy were 0.125 L (in Trial 30), 0.108 L (in Trial 31) and 0.084 L (in Trial 01).

Table 20: Change from baseline in 1-hour morning post-dose FEV_1 (L) at Week 24, AB/FF 400/12 µg versus AB 400 µg, ITT population

	Trial 30		Trial 31		Trial 01	
	AB 400 µg	AB/FF 400/12 µg	AB 400 µg	AB/FF 400/12 µg	AB 400 µg	AB/FF 400/12 µg
ITT population	327	347	337	335	398	274
Mean change from baseline 1-hour post dose FEV_1 at Week 24: (L)	0.144	0.269	0.139	0.247	0.169	0.253
Difference from AB 400: L (95% CI)		0.125 (0.090, 0.160)		0.108 (0.073, 0.144)		0.084 (0.051, 0.117)
p-value compared to AB 400		<0.0001		<0.0001		<0.0001

Source: Statistical Reviewer

As LABA are generally expected to contribute to bronchodilation in the earlier portion of the dose interval, these data demonstrate that the FF component contributes to the bronchodilator effect of AB/FF. Additionally, as AB 400 µg is approved for COPD and has previously demonstrated efficacy as a bronchodilator, these data also demonstrate efficacy for AB/FF 400/12 µg.

Analysis results of the co-primary endpoint of change from baseline to Week 24 in morning pre-dose (trough) FEV_1 in the individual Phase 3 pivotal studies are presented in Table 21.

The magnitudes of the increases from baseline to Week 24 in morning pre-dose (trough) FEV_1 observed with AB/FF 400/12 µg are comparable across the three Phase 3 pivotal studies. The increases were 0.083 L (in Trial 30), 0.095 L (in Trial 31), and 0.080 L (in Trial 01).

In each of the Phase 3 pivotal studies, the increases from baseline to Week 24 in morning pre-dose (trough) FEV_1 were statistically significantly greater with AB/FF 400/12 µg than with FF 12 µg monotherapy ($p<0.001$ for all comparisons). The increases of the adjusted mean treatment differences between AB/FF 400/12 µg and FF 12 µg were 0.085 L (in Trial 30), 0.045 L (in Trial 31), and 0.055 L (in Trial 01).

Table 21: Change from baseline in pre-dose FEV_1 at Week 24, AB/FF 400/12 µg versus FF 12 µg, ITT population

	Trial 30		Trial 31		Trial 01	
	FF 12 µg	AB/FF 400/12 µg	FF 12 µg	AB/FF 400/12 µg	FF 12 µg	AB/FF 400/12 µg
ITT population	337	349	332	335	259	274
Mean change from baseline trough FEV_1 at week 24: (L)	-0.002	0.083	0.050	0.095	0.025	0.080
Difference from FF 12: L (95% CI)		0.085 (0.051, 0.119)		0.045 (0.011, 0.079)		0.055 (0.023, 0.088)
p-value compare to FF 12		<0.0001		0.0102		0.0009

Source: Statistical Reviewer

As LAMA are generally expected to contribute to bronchodilation later in the dosing interval, these data demonstrate that the AB component contributes to the bronchodilator effect of AB/FF. However, it is worth noting that the magnitude of that contribution is relatively modest. Data from the dose ranging study as well as other spirometric data (e.g. FEV1 1-hour post dose, FEV1 AUC (0-3), serial spirometric data) from the phase 3 trials suggest that FF 12 µg is an effective bronchodilator in COPD. As such, the superiority of AB/FF 400/12 µg to FF 12 µg also support the efficacy of AB/FF 400/12 µg.

Overall the above discussed pre-specified co-primary endpoint data demonstrate efficacy of AB/FF 400/12 µg as a bronchodilator in COPD and that each monocomponent contributes to the bronchodilatory effect.

In addition to the pre-specified formal hypothesis testing which controlled family-wise error rate and the results presented above, comparisons to the placebo arm and to the other mono-components were also conducted. For information purposes, we present these results below.

In each of the Phase 3 pivotal trials, for endpoint of FEV_1 at 1-hour post-dose at Week 24, comparisons of AB/FF 400/12 µg to FF 12 µg were also conducted. The mean treatment differences between AB/FF 400/12 µg and FF 12 µg monotherapy are 0.139 L (95% CI:0.104, 0.174) in Trial 30, 0.083 L (95% CI: 0.047, 0.118) in Trial 31 and 0.084 L (95% CI: 0.048, 0.121) in Trial 01. These data suggest that the AB monocomponent also contributes to some degree to the 1-hour post dose effect.

In each of the Phase 3 pivotal trials, for endpoint of morning pre-dose (trough) FEV_1 at Week 24, comparisons of AB/FF 400/12 µg to AB 400 µg were also conducted. The mean treatment

differences between AB/FF 400/12 µg and AB 400 µg monotherapy are 0.026 L (95% CI: -0.007, 0.060) in Trial 30, 0.028 L (95% CI: -0.008, 0.064) in Trial 31, and 0.014 L (95% CI: -0.016, 0.043) in Trial 01. These data suggest that FF contributes minimally to bronchodilation at the end of the dosing interval. This is not entirely surprising as LABA typically bronchodilate in the earlier portion of the dosing interval. Moreover, based on monotherapy dose ranging studies, the effect of FF 12 µg appears to wane by the end of the dosing interval (Figure 2).

In Trial 30 and Trial 31, for endpoint of FEV_1 at 1-hour post-dose at Week 24, comparisons of AB/FF 400/12 µg to placebo were also conducted. The mean treatment differences between AB/FF 400/12 µg and placebo are 0.299 L (95% CI: 0.255, 0.343) in Trial 30 and 0.284 L (95% CI: 0.247, 0.320) in Trial 31.

In Trial 30 and Trial 31, for endpoint of morning pre-dose (trough) FEV_1 at Week 24, comparisons of AB/FF 400/12 µg to placebo were also conducted. The mean treatment differences between AB/FF 400/12 µg and placebo are 0.143 L (95% CI: 0.101, 0.185) in Trial 30 and 0.130 L (95% CI: 0.095, 0.165) in Trial 31.

It is worth noting that in the trials that included both the AB/FF doses of 400/12 µg and 400/6 µg (30 and 31), the magnitude of the effect was numerically higher for the higher dose compared to the lower dose with respect to placebo, supporting approval of the higher dose.

Overall these data for the co-primary endpoints of trough FEV1 and 1-hour post-dose FEV1 from Trials 30, 31, and 01 support the efficacy of AB/FF 400/12 µg and that each monocomponent contributes to the bronchodilatory effect.

Data Quality and Integrity

The NDA submission was appropriately indexed and complete to allow for review. There were no issues with submission quality or data integrity.

Efficacy Results – Secondary and other relevant endpoints

SGRQ

Analysis results of secondary endpoint of change from baseline to Week 24 in SGRQ total score in Trial 30 and Trial 31 are presented in Table 22.

In Trial 31, at Week 24, the adjusted mean treatment differences of SGRQ total score between AB/FF 400/12 µg and placebo were statistically significant and clinically meaningful (-4.35 units [p<0.0001]). In contrast, in Trial 30, there was only a small adjusted mean treatment difference between AB/FF 400/12 µg and placebo are observed (-0.65 units [p=0.598]).

Table 22: Change from baseline in SGRQ total score (Units) at Week 24, ITT population (Trials 30 and 31)

	Trial 30		Trial 31	
	PBO	AB/FF 400/12 µg	PBO	AB/FF 400/12 µg
ITT population	154	338	331	335
Mean change from baseline SGRQ total score: (Units)	-6.51	-7.16	-2.21	-6.57
Difference from PBO 12: Units (95% CI)		-0.65 (-3.08, 1.78)		-4.35 (-6.46, -2.24)
p-value		0.5980		<0.0001

Source: Statistical Reviewer

The minimal clinically important difference (MCID) for SGRQ is a decrease of 4 units from baseline. The proportion of patients who achieved a clinically meaningful improvement was assessed in patients treated with AB/FF 400/12 µg and placebo (Trial 30 and Trial 31) or TIO 18 ug (Trial 01)

The responder analysis of SGRQ in Trial 30 did not show a statistically significant improvement of AB/FF 400/12 µg compared to placebo; on the other hand, Trial 31 did demonstrate a clinically meaningful and statistically significant improvement of AB/FF 400/12 µg compared to placebo. In Trial 01, the SGRQ responder analysis was not statistically different when comparing AB/FF 400/12 µg to Tio 18 µg. See Table 23.

Table 23: Number (%) of patients achieving a clinically meaningful improvement (a decrease of at least 4-units) from baseline in SGRQ total score over at Week 24, ITT population

	Trial 30		Trial 31		Trial 01	
	PBO	AB/FF 400/12 µg	PBO	AB/FF 400/12 µg	TIO 18 µg	AB/FF 400/12 µg
ITT population	154	338	331	335	389	270
Responder Rate in %	53.2	55.3	38.7	58.2	50.6	48.1
Odds Ratio (95% CI)		1.12 (compare to placebo) (0.68, 1.84)		2.26 (compare to placebo) (1.41, 3.61)		0.87 (Compare to Tio 18 µg) (0.56, 1.36)
p-value compare to PBO or TIO 18		0.6685		0.0007		0.5426

Source: Statistical Reviewer

Comparisons of SGRQ responder rate were also conducted between AB/FF 400/12 µg and AB 400 µg, and between AB/FF 400/12 and FF 12 µg. For Trial 30, the odds ratio is 1.12 (95% CI: 0.76 1.67) for AB/FF 400/12 µg vs. AB 400 µg; the odds ratio is 1.16 (95% CI: 0.78, 1.73) for AB/FF 400/12 µg vs. FF 12 µg. For Trial 31, the odds ratio is 1.03 (95% CI: 0.66, 1.62) for AB/FF

400/12 µg vs. AB 400 µg; the odds ratio is 1.21 (95% CI: 0.77, 1.90) for AB/FF 400/12 µg vs. FF 12 µg.

While the 95% CI for the SGRQ responder analyses did not exclude 1 for all trials, these data are considered useful for a healthcare provider and will be included in section 14 of the label.

FEV1 AUC (0-3hours)

For Trial 01, as a secondary endpoint, the effect of the AB/FF 400/12 µg on the change from baseline in normalized AUC $_{0\text{-}3/3h}$ FEV_1 at Week 24 was compared with the effect of AB 400 µg and FF 12 µg and the comparison is summarized in Table 24.

For the combination of AB/FF 400/12 µg , the change from baseline in normalized AUC $_{0\text{-}3/3h}$ FEV_1 at Week 24 was increased by 0.075 L compared to AB 400 µg and by 0.087 L compared to FF 12 µg. These differences reached statistical significance (p<0.0001 for both comparisons).

Table 24: Change from baseline normalized AUC $_{0\text{-}3h}$ FEV_1 at Week 24, ITT population, Trial 01

	AB 400 µg	FF 12 µg	AB/FF 400/12 µg
ITT population	396	257	273
Change from baseline normalized AUC $_{0\text{-}3h}$ FEV_1 at week 24: L	0.162	0.149	0.237
AB/FF 400/12 versus AB 400, FF 12 differences for change from baseline at week 24: L (95% CI)	0.075 (0.043, 0.107)	0.087 (0.052, 0.122)	
p-value	<0.0001	<0.0001	

Source: Statistical Reviewer

For Trial 30 and Trial 31, normalized AUC $_{0\text{-}3/3h}$ FEV_1 at Week 24 was not a secondary endpoint. However, for comparison purpose, the results are summarized in Table 25 along with results of Trial 01.

Table 25: Change from baseline normalized AUC $_{0\text{-}3h}$ FEV_1 at Week 24, ITT population

	Trial 30			Trial 31			Trial 01		
	AB 400 µg	FF 12 µg	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	AB/FF 400/12 µg
ITT population	330	336	348	337	332	335	396	257	273
Change from baseline normalized AUC $_{0\text{-}3h}$ FEV_1 at week 24: L	0.138	0.118	0.25	0.134	0.146	0.233	0.162	0.149	0.237
AB/FF 400/12 versus AB 400, FF 12 differences for change from baseline at week 24: L (95% CI)	0.111 (0.077, 0.145)	0.131 (0.097, 0.166)		0.099 (0.065, 0.134)	0.088 (0.053, 0.123)		0.075 (0.043, 0.107)	0.087 (0.052, 0.122)	
p-value (nominally)	<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	<0.0001	

Source: Statistical Reviewer

These data are consistent with the co-primary endpoint of 1-hour post dose FEV_1 and lend further support to the contribution of the LABA monocomponent to the combination as well as efficacy for AB/FF 400/12 µg.

Serial Spirometry Substudy

For each of the phase 3 pivotal trials, serial spirometry 0-12 hours at Day 1 and Week 24 were measured and are shown in Figure 7 to Figure 12.

These figures demonstrate a consistently greater effect of AB/FF 400/12 µg on FEV1 compared to each of the monocomponents and placebo, as measured over the 12 hours post-dose. The effect was evident on Day 1 and persistent at Week 24 across trials.

Figure 7: Change from baseline in serial FEV_1 over 12-hours post-dose on Day 1 (ITT population), Trial 30

Source: Statistical Reviewer

Figure 8: Change from baseline in serial FEV_1 over 12-hours post-dose at Week 24 (ITT population), Trial 30

Source: Statistical Reviewer

Figure 9: Change from baseline in serial FEV_1 over 12-hours post-dose on Day 1 (ITT population), Trial 31

Source: Statistical Reviewer

Figure 10: Change from baseline in serial FEV_1 over 12-hours post-dose at Week 24 (ITT population), Trial 31

Source: Statistical Reviewer

Figure 11: Change from baseline in serial FEV_1 over 12-hours post-dose on Day 1 (ITT population), Trial 01

Source: Statistical Reviewer

Figure 12: Change from baseline in serial FEV_1 over 12-hours post-dose at Week 24 (ITT population), Trial 01

Source: Statistical Reviewer

The serial spirometric data across Trials 30, 31, and 01 are consistent with the primary analysis, demonstrating the contribution of each monocomponent to the combination and efficacy of the combination. These data are also supportive of the dosing interval.

Dose/Dose Response

AB/FF 400/12 µg demonstrated numerically higher improvement across the bronchodilatory endpoints compared to AB/FF 400/6 µg in Trials 30 and 31. While these differences between doses were not statistically significant, these data are supportive of approval of the higher dose. Table 26 presents the results of the mean treatment difference between AB/FF 400/12 µg and placebo, and the mean treatment difference between AB/FF 400/6 µg andplacebo in 1-hour post-dose FEV_1 at Week 24. Table 27 presents the results of mean treatment difference between AB/FF 400/12 µg and placebo, and mean treatment difference between AB/FF 400/6 µg and placebo in pre-dose (trough) FEV_1 at Week 24.

Table 26: Change from baseline in 1-hour morning post-dose FEV_1 at Week 24, AB/FF 400/6 µg and AB/FF 400/12 µg versus placebo in Trials 30 and 31 (ITT population)

	Trial 30			Trial 31		
	Placebo	FF/AB 400/6 µg	FF/AB 400/12 µg	Placebo	FF/AB 400/6 µg	FF/AB 400/12 µg
ITT population	157	339	347	331	333	335
Mean change from baseline 1-hour post dose FEV1 at week 24: (L)	-0.030	0.213	0.269	-0.037	0.226	0.247
Difference from placebo: L (95% CI)		0.244 (0.200, 0.287)	0.299 (0.255, 0.343)		0.263 (0.227, 0.299)	0.284 (0.247, 0.320)
p-value compare to placebo		<0.0001	<0.0001		<0.0001	<0.0001

Source: Statistical Reviwer

Table 27: Change from baseline in morning pre-dose (trough) FEV_1 at Week 24, AB/FF 400/6 µg and AB/FF 400/12 µg versus placebo, Trials 30 and 31 (ITT population)

	Trial 30			Trial 31		
	Placebo	FF/AB 400/6 µg	FF/AB 400/12 µg	Placebo	FF/AB 400/6 µg	FF/AB 400/12 µg
ITT population	159	340	349	331	333	335
Mean change from baseline 1-hour post dose FEV1 at week 24: (L)	-0.061	0.050	0.083	-0.035	0.076	0.095
Difference from placebo: L (95% CI)		0.111 (0.069, 0.153)	0.143 (0.101, 0.185)		0.111 (0.076, 0.146)	0.130 (0.095, 0.165)
p-value compare to placebo		<0.0001	<0.0001		<0.0001	<0.0001

Source: Statistical Reviewer

Durability of Response

The absolute changes of 1-hour post-dose FEV_1 and trough FEV_1 were noted at Week 24 when AB/FF treatment was completed. These changes were also observed at earlier weeks, indicating that the drug response was durable while on drug. See Figure 13 to Figure 18.

Figure 13: Change from baseline at 1-hour post-dose in FEV_1 (L) over 24 weeks, Trial 30, ITT population

Source: Statistical Reviewer

Figure 14: Change from baseline in morning pre-dose (trough) FEV1 (L) over 24 weeks, Trial 30, ITT population

Source: Statistical Reviewer

Trial 30. Trial 30. 1-hour the 24-week period for the bronchodilatory treatment effect

Figure 15. Change from baseline at 1-hour post-dose in FEV_1 (L) over 24 weeks, Trial 31, ITT population

Figure 16: Change from baseline in morning pre-dose (trough) FEV_1 (L) over 24 weeks, Trial 31, ITT population

Source: Statistical Reviewer

Figure 17: Change from baseline at 1-hour post-dose in FEV_1 (L) over 24 weeks, Trial 01, ITT population

Source: Statistical Reviewer

Figure 18: Change from baseline in morning pre-dose (trough) FEV_1 (L) over 24 weeks, Trial 01, ITT population

Source: Statistical Reviewer

Persistence of Effect

In these trials, 1-hour post-dose FEV1 and trough FEV1 were not measured once the treatment was stopped. Therefore, no data were available to investigate the persistence of the treatment effect following cessation of treatment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

See previous discussion of SGRQ.

Additional Analyses Conducted on the Individual Trials

Rescue medication use

Nominally statistically significant reductions in mean overall daily average use of rescue medication with AB/FF 400/12 µg compared to placebo were observed in Trials 30 and 31. The adjusted mean treatment differences for overall daily use of rescue medication for AB/FF 400/12 µg compared to placebo was -0.66 puffs per day (95% CI: -1.03, -0.29; p=0.0004), and -1.11 puffs per day (95% CI: -1.43, -0.79; p<0.0001) in Trial 30 and Trial 31, respectively. Note that these tests were not pre-specified in the testing hierarchy which controls family-wise error rate, thus the results are nominally significant.

Numerical reductions of rescue medication were observed with AB/FF 400/12 µg compared to AB 400 µg and FF 12 µg monotherapy in Trials 30, 31 and 01.

While these results are only nominally statistically significant, as these types of results are useful for the healthcare provider and have historically been included in the labels of other similar products based on similar data, these data warrant mention in the product label.

Onset of action

Nominal statistical significance for AB/FF 400/12 µg was observed compared with placebo on Day 1 at 5 minutes post-dose for the change from baseline in FEV_1. The increase in FEV_1 compared to placebo was 0.108 L (95% CI: 0.089, 0.127) in Trial 30 and 0.128 L (95% CI: 0.111, 0.144) in Trial 31 within 5 minutes after the first dose.

For rescue medication use and onset of action, while these results were only nominally statistically significant, the data are supportive of inclusion in the label as it is useful for health care providers and similar data has been included in other COPD bronchodilator labels.

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoints

Trials 30, 31, and 01 shared the same co-primary endpoints which were 1-hour post-dose change from baseline in FEV1 and trough FEV1. Results demonstrated that AB/FF 400/12 µg

has statistically superior bronchodilation at Week 24 compared toAB 400 µg (1-hour post-dose FEV_1) and FF 12 µg (trough FEV_1) in all three trials. (see Table 20 and Table 21). These data demonstrated that each monocomponent contributed to the bronchodilatory effect of the AB/FF 400/12 µg combination. Additionally as AB 400 µg has previously been approved for COPD, these data also demonstrate the efficacy of AB/FF 400/12 µg. AB/FF 400/12 µg also demonstrated a statistically significant increase for these co-primary endpoints compared to placebo in placebo-controlled Trials 30 and 31 (see Table 26 and Table 27). Additionally, the higher AB/FF dose (400/12µg) had a numerically larger treatment effect compared to the lower dose (400/6 µg) [see Table 26 & Table 27].

Overall, these co-primary endpoint data support the efficacy of AB/FF 400/12 µg in terms of bronchodilation as well as the contribution of each of the monocomponents to the bronchodilator effect.

Secondary and Other Endpoints

SGRQ
In the placebo-controlled Trials 30 and 31, a numerically larger proportion of patients taking AB/FF 400/12 µg demonstrated clinically meaningful improvements in SGRQ score. However, this was only statistically significant for Trial 31 (see Table 23). Similar trends were observed when comparing AB/FF 400/12µg to its monocomponents, though not all differences were statistically significant. Overall, the data suggest that AB/FF 400/12 µg improved SGRQ score, although statistical significance of the improvements of these outcomes were not observed in all the trials. While the 95% CI for the SGRQ responder analyses did not exclude 1 for all trials, these data are considered useful for a healthcare provider and will be included in section 14 of the label.

Exacerbation

In Trial 02, AB 400 µg, a monocomponent of AB/FF 400/12 µg, demonstrated a statistically significant reduction in the rate of on-study moderate to severe COPD exacerbations by 17% compared to placebo (rate ratio [RR] 0.83; 95% CI 0.73 to 0.94; p=0.003). AB 400 µg also demonstrated a statistically significant reduction in the rate of on-study hospitalizations due to COPD exacerbations during the first year of treatment by 28% compared with placebo (RR 0.72; 95% CI 0.55 to 0.95; p=0.02). These data are supportive of an exacerbation reduction effect for the AB 400 µg. Scientifically, as addition of the FF 12 µg monocomponent to AB 400 µg is expected to not affect the exacerbation reduction benefit of AB 400 µg alone, AB/FF 400/12 µg is expected to retain theexacerbation benefit of the AB 400 µg monocomponent. Therefore, information regarding the AB monocomponent with respect to exacerbation reduction will be described in section 14 of the product label for the combination product, AB/FF.

This is supported by *post-hoc* pooled analyses of exacerbation data from Trials 30 and 31. Rate of moderate or severe exacerbations (per patient per year) of AB/FF 400/12 µg treated and AB 400 µg treated subjects in comparison to placebo in pooled Trials of 30 and 31 are

presented in Table 28. While such a pooled analysis was not prespecified, nor were the trials powered for exacerbation, point estimates for rate ratio versus placebo for AB/FF 400/12 µg and AB 400 µg were similar, suggesting that the addition of FF 12 µg did not adversely affect exacerbation rate.

Table 28: Rate of moderate-to-severe exacerbation per patient/year, pooled Trials 30 and 31 (*post-hoc* analysis)

	AB/FF 400/12 µg	FF 12 µg	AB 400 µg	PBO
Rate of Exac. Per patient/year: estimate (95% CI)	0.334 (0.26, 0.42)	0.409 (0.33, 0.51)	0.386 (0.31, 0.48)	0.477 (0.37, 0.61)
Rate Ratio vs PBO: Estimate (95% CI) Nominal p-value	0.700 (0.58, 0.98) 0.0377	0.858 (0.62, 1.19) 0.3573	0.809 (0.58, 1.12) 0.2055	n/a

Source: Reviewer

The above exacerbation analyses from Trials 30 and 31 were *post-hoc* and pooled, and simply provide support for the exacerbation benefit that was formally evaluated in Trial 02. Therefore, data from Trial 02 will be presented in the product label (section 14).

Subpopulations

Subgroup analyses were conducted on the pooled population of all three Phase 3 trials to assess the consistency of effect in the adjusted mean treatment differences between AB/FF and the monocomponents. The subgroup analyses of demographic characteristics included age (<65 years, ≥65years), gender (male or female), race (white or non-white), and geographic region (Europe, US/Canada, and Rest of World).

Figure 19 presents the forest plot of subgroup analysis results on the co-primary endpoint of change from baseline at Week 24 in FEV_1 at 1 hour post-dose in the pooled ITT population of Trials 30, 31, and 01. Figure 20 presents the forest plot of subgroup analysis results on the co-primary endpoint of change from baseline at Week 24 in pre-dose trough FEV_1 in the pooled

ITT population of Trials 30, 31, and 01.

From the plots, we can conclude that the efficacy results are consistent across all subgroups assessed with respect to both co-primary endpoints.

Figure 19: LS mean treatment differences and 95% CI between AB/FF 400/12 µg and AB 400 µg in the change from baseline at Week 24 in FEV_1 at 1 hour post-dose, pooled ITT populations of Trials 30, 31, and 01

Source: Statistical Reviewer

Figure 20: LS mean treatment differences and 95% CI between AB/FF 400/12 µg and FF 12 µg in the change from baseline to Week 24 in pre-dose trough FEV_1 in the pooled ITT populations of Trials 30, 31, and 01

Source: Statistical Reviewer

We also determined shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model. Shrinkage estimates use more information,are more precise, and therefore closer to the true subgroup treatment effects than the sample estimates.

Sample estimated treatment effects vary across subgroups more than the true treatment effects. The total variability in the sample estimates is the sum of the within subgroup variability of sample estimator and the across subgroups variability in underlying/true parameter values. As such, the sample estimates are susceptible to random highs and random lows. The shrinkage estimated treatment effects quantitatively address the random highs and random lows. The variance in the collection of shrinkage estimated treatment effects across subgroups is close to what we believe is the variance in the true treatment effects across subgroups. For a given subgroup, information from other subgroups are also used to estimate its treatment effect. Outcomes from all subject are considered relevant, with an outcome from a subject in the given subgroup more relevance than the outcome of a subject not in the given subgroup.

A shrinkage estimate of a treatment effect/difference for a subgroup is a "weighted" average of sample estimate and overall estimate (the shrinkage estimate "borrows" information from the other subgroups). The sample estimate is "shrunk" towards the overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio, the smaller the weight on the overall estimate (the less the shrinkage).

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups, are presented in **Figure 21** and **Figure 22**.

In the Bayesian hierarchical modeling approach, the conventional subgroup analysis was conducted first, then the estimated sample means, and standard errors were used in the Bayesian hierarchical modeling by assuming the subgroup sample means are random samples of a normal distribution.

Figure 21 compares the conventional subgroup analysis results of the sample estimate (in blue) and Bayesian shrinkage estimate (in red) for the endpoint of change from baseline in pre-dose FEV1 at Week 24. The overall treatment effect is 0.0615 L (95% CI: 0.0418, 0.0813), which is represented by the dotted line and a dark red diamond. Subgroup analysis using Bayesian shrinkage estimate exhibits narrower confidence intervals, and the shrinkage subgroup estimate is closer to the overall mean.

Figure 21: Comparison of subgroup analysis using sample estimates and Bayesian shrinkage estimates: treatment differences and 95% CI between AB/FF 400/12 µg and FF 12 µg in the change from baseline to pre-dose trough FEV1 at Week 24 i in the pooled ITT populations of Trials 30, 31, and 01

Subgroup	diff w/o Shrink	diff w/ Shrink
Age <65 years	0.0609	0.061
>=65 years	0.0618	0.0618
Gender M	0.0722	0.0715
F	0.0446	0.0457
Race White	0.0635	0.0632
Non-white	0.029	0.0351
Region Europe	0.0847	0.0822
US/Canada	0.0357	0.0381
R. of World	0.0485	0.0521
Summary	**0.0615**	

Source: Statistical Reviewer

Figure 22 compares the conventional subgroup analysis results of the sample estimate (in blue) and Bayesian shrinkage estimate (in red) for the endpoint of change from baseline in 1-hour post-dose FEV1 at Week 24. The overall treatment effect is 0.1075L (95% CI: 0.0873, 0.1278), which is represented by the dotted line and a dark red diamond. Subgroup analysis

using Bayesian shrinkage estimate exhibits narrower confidence intervals, and the shrinkage subgroup estimate is closer to the overall mean.

Figure 22: Comparison of subgroup analysis using sample estimates and Bayesian shrinkage estimates: treatment differences and 95% CI between AB/FF 400/12 µg and AB 400 µg in the change from baseline to Week 24 in FEV1 at 1 hour post-dose in the pooled ITT populations of Trials 30, 31, and 01

Subgroup	diff w/o Shrink	diff w/ Shrink
Age <65 years	0.1191	0.1183
>=65 years	0.0949	0.0959
Gender M	0.1259	0.1248
F	0.0777	0.0796
Race White	0.1103	0.1098
Non-white	0.0643	0.0723
Region Europe	0.1135	0.1124
US/Canada	0.1034	0.1035
R. of World	0.0774	0.0892
Summary	**0.1075**	

Source: Statistical Reviewer

8.1.4. Integrated Assessment of Effectiveness

To support this application, the Applicant submitted results from two phase 3, twenty-four week, placebo-controlled trials (30 and 31) and one phase 3, twenty-four week active-controlled trial (01) as the primary evidence of efficacy(bronchodilation). To support the proposed (b) (4) claim, the Applicant referenced (b) (4) Trials 30, 31, and 01 demonstrated substantial evidence of efficacy as determined primarily based on statistically significant improvements in the co-primary endpoints, change from baseline in trough FEV1 and 1 hour post-dose FEV1 at Week 24. The increases from baseline in trough FEV1 were statistically significantly greater for AB/FF 400/12 µg than for FF µg for Trials 30, 31, and 01 demonstrating the contribution of AB 400 µg . Similarly, The increases from baseline in 1 hour post-dose FEV1 were statistically significantly greater for AB/FF 400/12 µg than for AB 400 µg in Trials 30, 31, and 01 demonstrating the contribution of FF 12 µg . Additionally, as AB 400 µg is approved for COPD, superiority of AB/FF 400/12 µg also demonstrated the efficacy of AB/FF 400/12 µg. In Trials 30 and 31, the trials which included a placebo arm, AB/FF 400/12 µg also demonstrated superiority to placebo. Efficacy of AB/FF 400/12 µg, as well as the contribution of monocomponents was also supported by other secondary spirometric endpoints (e.g., FEV1 AUC_{0-3}, serial spirometry). Numerical improvements in symptoms based on St. George's Respiratory Questionnaire (SGRQ) responder analysis were also observed. These data represent substantial evidence of efficacy of AB/FF 400/12 µg for the maintenance treatment of patients with COPD.

With regard to exacerbation, in Trial 02, AB 400 µg demonstrated a statistically significant exacerbation benefit compared to placebo. As the LABA and LAMA in this FDC are pharmaceutically equivalent to their monoproduct counterparts, scientifically, the two drugs are not expected to have a negative interaction in terms of exacerbation reduction. As such, it is likely that AB/FF 400/12 µg, retains the exacerbation benefit of the AB 400 µg component and inclusion of such data in section 14 of the label is warranted. However, as discussed below, a separate exacerbation indication will not be included in labeling.ded in .

Given the potential for multiple claims [airflow obstruction, exacerbations, St. George's Respiratory Questionnaire (SGRQ)] in COPD programs, the Division has determined that a more general COPD indication is appropriate for inhaled products (including monotherapies and fixed-dose combinations). To this end, the Division's new approach to COPD indications for inhaled products will no longer include separate indications for the maintenance treatment of airflow obstruction and exacerbation reduction, but will rather be more general. A more general COPD indication is consistent with the approach taken for labeling in other recently approved products in the Division, e.g. asthma and rheumatoid arthritis.

Details of clinical trials supporting efficacy in COPD with respect to the different efficacy endpoints (e.g., forced expiratory volume in 1 second (FEV_1), exacerbation, SGRQ) will be included in Section 14 of the product label.

8.2. Review of Safety

8.2.1. Safety Review Approach

To support the safety of this product, the Applicant submitted safety data from multiple clinical trials. However, the clinical assessment of safety primarily focuses on the two 24-week placebo-controlled trials (Trials 30 and 31), one 24-week active-controlled trial (Trial 01), and one 28-week placebo-controlled extension trial to Trial 31 (Trial 36). These trials are of sufficient size and length to characterize the safety profile of this product. The data from the replicate placebo-controlled Trials 30 and 31 were pooled for safety analysis. Trial 01 was not included in the pooling as it was an active-controlled trial, and did not include a placebo group To support long-term safety, data from Trial 36 were analyzed.

8.2.2. Review of the Safety Database

Overall Exposure

In the pooled analyses of the 24-week placebo-controlled Trials 30 and 31, the mean treatment exposure across groups ranged from 140.9 to 156 days. Exposure in the placebo group was somewhat less than that of the other treatment groups. However, the median treatment exposure was the same for all treatment groups (169.0 days). Exposure data for the pooled placebo-controlled trials are summarized in Table 29.

Table 29: Treatment Exposure, Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31)

	Placebo	AB/FF 400/12 µg	AB/FF 400/6 µg	AB 400 µg	FF 12 µg
N	526	720	714	721	716
Extent of Exposure (days)					
Mean	140.9	154.5	156.0	152.0	153.4
SD	54.2	42.3	38.5	43.7	43.0
Minimum	1	1	1	1	1
Median	169	169	169	169	169
Maximum	245	215	191	190	199
Extent of Exposure (No (%))					
≥ 1 day	526 (100)	720 (100)	714 (100)	721 (99.9)	716 (100)
≥ 1 week	516 (98.1)	710 (98.6)	712 (99.7)	711 (98.5)	706 (98.6)
≥ 4 weeks	485 (92.2)	688 (95.6)	689 (96.5)	687 (95.2)	683 (95.4)
≥12 weeks	432 (82.1)	648 (90.0)	660 (92.4)	644 (89.2)	649 (90.6)
≥ 24 weeks	322 (61.2)	526 (73.1)	496 (69.5)	501 (69.4)	493 (68.9)

Source: Summary of Clinical Safety Table 52; pg 146

In Trial 36, similar mean and median treatment durations were also observed in the placebo group compared to other treatment groups. Note that Trial 36 was designed as a 28-week extension of the lead-in Trial 31 with patients staying on the same treatment. After completing the lead-in Trial 31, patients in the US and Canada clinical sites were allowed to participate in this extension trial. Of the 1,322 eligible patients, 918 patients entered the extension trial.

Across treatment groups, similar percentages of patients completed >21 weeks of treatment (86.5-90.7%). Exposure data for this trial are summarized in Table 30.

Table 30: Treatment Exposure, 28-Week Placebo-Controlled Extension Trial (Trial 36)

	Placebo	AB/FF 400/12 µg	AB/FF 400/6 µg	AB 400 µg	FF 12 µg
N	146	182	204	194	192
Extent of Exposure (days) after 24-wk lead-in study					
Mean	183.0	182.3	186.2	182.5	183.5
SD	36.8	38.9	35.9	41.9	41.0
Minimum	30.0	4.0	22.0	3.0	14.0
Median	197.0	197.0	197.0	197.0	197.0
Maximum	219.0	212.0	238.0	220.0	246.0
Extent of exposure [N(%)] after 24-wk lead-in study					
at least 1 day	146 (100)	182 (100)	204 (100)	194 (100)	192 (100)
> 1 week	146 (100)	181 (99.5)	204 (100)	193 (99.5)	192 (100)
> 3 weeks	146 (100)	181 (99.5)	204 (100)	193 (99.5)	191 (99.5)
> 7 weeks	144 (98.6)	178 (97.8)	201 (98.5)	189 (97.4)	186 (96.9)
> 14 weeks	136 (93.2)	169 (92.9)	192 (94.1)	177 (91.2)	177 (92.2)
> 21 weeks	128 (87.7)	157 (86.3)	185 (90.7)	172 (88.7)	166 (86.5)
> 28 weeks	81 (55.5)	110 (60.4)	128 (62.7)	126 (64.9)	109 (56.8)

Source: LAC-MD-36 Clinical Study Report (CSR) Volume 1; Table 12.1.1-1; pg 192

In Trial 01, the-active controlled trial, exposure was consistent across treatment groups with a median treatment exposure of 169 days in all groups. The mean treatment exposure was similar across the treatment groups. In addition, a similar proportion of patients completed 24-week treatment across treatment groups, ranging from 69.9% (FF 12 µg) to 76.1% (AB/FF 400/12 µg). Exposure data for this trial are summarized in Table 31.

Table 31: Treatment Exposure, 24-Week Active-Controlled Trial (Trial 01)

	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	Tio 18 µg
N	314	475	319	475
Extent of Exposure (days)				
Mean	159.4	155.9	153.2	154.4
SD	32.9	39.2	41.1	41.2
Minimum	3	1	1	1
Median	169	169	169	169
Maximum	198	189	188	202
≥ 1 day	314 (100)	475 (100)	319 (100)	475 (100)
≥ 1 week	313 (99.7)	469 (98.7)	314 (98.4)	470 (98.9)
≥ 4 weeks	308 (98.1)	456 (96.0)	308 (96.6)	452 (95.2)
≥12 weeks	296 (94.3)	436 (91.8)	291 (91.2)	433 (91.2)
≥ 18 weeks	289 (92.0)	424 (89.3)	276 (86.5)	418 (88.0)
≥ 24 weeks	239 (76.1)	352 (74.1)	223 (69.9)	355 (74.7)

Source: D6571C00001 CSR Table 40; pg 102

Adequacy of the safety database:

The size and the duration of these trials were appropriate. The safety database was adequate to review the safety of AB/FF 400/12 µg.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity and submission quality were identified.

Categorization of Adverse Events

The Applicant defined an adverse event (AE) as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to the investigational product (IP), whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Adverse events were classified in the individual study dataset using different MedDRA Versions including Version 16.0 for trial 36 and Version 19.0 for trial 01. For the pooled analysis of Trials 30 and 31, AEs were recoded using MedDRA Version 20.0.

An AE was considered a Treatment-Emergent Adverse Event (TEAE) if it started at the time of or after the date of the first IP administration and if it occurred within 15 (Trial 01 and pooled Trial 30 and 31) or 30 days (Trial 36) after the last IP intake. In the safety analysis of this review, TEAEs in the safety population (patients who received at least 1 dose of IP) are assessed. The grading of TEAE severity was determined as mild (awareness of symptoms or signs but easily tolerated), moderate (enough discomfort to interfere with usual activity), or severe (incapacity to work or to perform usual activities).

Adverse events of special interest (AESI) were defined as cardiovascular and cerebrovascular events, lower respiratory tract and lung infections (LRTIs) including pneumonia, and class effects (potential anticholinergic events and β2-adrenergic agonist events). MACE (Major Cardiac Adverse Events) were defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. All deaths and potential MACE were reviewed by an independent Cardiovascular Adjudication Committee.

Routine Clinical Tests

Clinical laboratory testing was performed as per tables in the individual trial reviewed in section 8.1.

8.2.4. Safety Results

Deaths

In the pooled 24-week placebo-controlled, Trials 30 and 31, there were a total of 8 deaths. The proportion of patients who had treatment-emergent deaths in the AB/FF 400/12 µg group was the same as the other active treatment groups (2 patients [0.3%] in each treatment group) While deaths in the AB/FF 400/12 µg group were numerically higher compared to placebo groups (0), the difference was small. The most common causes of death by preferred term (PT) were cardiac failure (0.1%), death (0.1%) and chronic obstructive pulmonary disease (0.1%). When comparing PT associated with deaths, events were generally similar between active treatment groups. No clear dose responses were observed. These data are summarized in Table 32.

Table 32: Treatment-Emergent Deaths, Pooled 24-Week Placebo-Controlled Trials

Preferred term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)	Total N=3398 n (%)
Patients with fatal outcomes	0	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	8 (0.2)
Cardiac failure	0	0	1 (0.1)	0	1 (0.1)	2 (0.1)
Myocardial infarction	0	0	0	1 (0.1)	0	1 (0.0)
Gastrointestinal necrosis	0	0	0	1 (0.1)	0	1 (0.0)
Death	0	1 (0.1)	0	0	1 (0.1)	2 (0.1)
Chronic obstructive pulmonary disease	0	1 (0.1)	1 (0.1)	0	0	2 (0.1)

Source: Summary of Clinical Safety; Table 74; pg 175

In the 28-week extension trial, Trial 36, a total of 6 treatment-emergent deaths were reported: 2 patients (1.4%) in the placebo group, 2 patients (1.1%) in the AB/FF 400/12 µg treatment group, 1 patient (0.5%) in the AB/FF 400/6 µg treatment group, and 1 patient (0.5%) in the AB

400 µg treatment group. Similar to the pooled Trials 30 and 31, fatal events were generally similar between treatment groups. These data are summarized in Table 33.

Table 33: Treatment-Emergent Deaths, 28-Week Placebo-Controlled Extension (Trial 36).

Preferred term	Placebo N=146 n (%)	AB/FF 400/12 µg N=182 n (%)	AB/FF 400/6 µg N=204 n (%)	AB 400 µg N=194 n (%)	FF 12 ug N=192 n (%)	Total N=918 n (%)
Any treatment-emergent death	2 (1.4)	2 (1.1)	1 (0.5)	1 (0.5)	0	6 (0.7)
Myocardial infarction	1 (0.7)	0	0	0	0	1 (0.1)
Death	1 (0.7)	1 (0.5)	0	0	0	2 (0.2)
Cardiac arrest	0	1 (0.5)	0	0	0	1 (0.1)
Cardiopulmonary arrest	0	0	1 (0.5)	0	0	1 (0.1)
Respiratory failure	0	0	0	1 (0.5)	0	1 (0.1)

Source: LAC-MD-36 CSR Volume 1; Table 14.5.2.4A; pg 3338

In the 24-week active-controlled trial, Trial 01, there were a total of 8 deaths. The number and percent of deaths in the AB/FF 400/12 µg group were similar to or lower than the other treatment groups. The proportion of patients reporting TEAEs with fatal outcomes was numerically higher in FF 12 µg compared to other treatment groups. These data are summarized in Table 34.

Table 34: Treatment-Emergent Deaths, 24-Week Active-Controlled Trial (Trial 01)

Preferred term	AB/FF 400/12 µg N=314 n (%)	AB 400 µg N=475 n (%)	FF 12 µg N=319 n (%)	TIO 18 µg N=475 n (%)	Total N=1583 n (%)
Any treatment-emergent death	1 (0.3)	1 (0.2)	4 (1.3)	2 (0.4)	8 (0.5)
Arteriosclerosis	1 (0.3)	0	0	0	1 (0.1)
Septic shock	0	1 (0.2)	0	0	1 (0.1)
Death	0	0	1 (0.3)	0	1 (0.1)
Pancreatic carcinoma	0	0	1 (0.3)	0	1 (0.1)
Pulmonary embolism	0	0	1 (0.3)	0	1 (0.1)
Pulmonary mass	0	0	1 (0.3)	0	1 (0.1)
Cor pulmonale chronic	0	0	0	1 (0.2)	1 (0.1)
Myocardial infarction	0	0	0	1 (0.2)	1 (0.1)

Source: D6571C00001 Statistical Report Part 1; Table 11.3.21; pg 1413

Overall, these data did not demonstrate large differences between the AB/FF 400/12 µg group versus other comparator groups and did not raise safety concerns.

Serious Adverse Events

In the pooled 24-week placebo-controlled trials, Trials 30 and 31, there were 188 (5.5%) patients with treatment-emergent SAEs. These SAEs were balanced across groups, ranging from 5.0% to 6.2%. SAEs were most commonly reported in the respiratory, thoracic, and mediastinal SOC (1.9%), followed by the infections and infestations SOC (1.0%) and cardiac disorders SOC (0.9%). The most common SAEs by PT were COPD (1.7%) and pneumonia (0.5%). Exacerbation of COPD was higher in the placebo group (2.5%) than in either AB/FF treatment group (1.1% and 1.7% in 400/12 µg and 400/6 µg group, respectively). Otherwise, non-fatal SAEs were similar when comparing the AB/FF doses to their monotherapy components or placebo. Non-fatal SAEs in the pooled trials are summarized in Table 35.

Table 35: Treatment-Emergent Non-Fatal SAEs That Occurred in Approximately 1% of Total Patients (by SOC), Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31)

System organ class Preferred term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)	Total N=3398 n (%)
Patients with SAEs	28 (5.3)	43 (6.0)	44 (6.2)	37 (5.1)	36 (5.0)	188 (5.5)
Respiratory, thoracic, and mediastinal disorders	13 (2.5)	8 (1.1)	15 (2.1)	17 (2.4)	10 (1.4)	63 (1.9)
Chronic obstructive pulmonary disease	13 (2.5)	8 (1.1)	12 (1.7)	15 (2.1)	10 (1.4)	58 (1.7)
Bronchiectasis	0	0	0	1 (0.1)	0	1 (0.0)
Respiratory acidosis	0	0	0	1 (0.1)	0	1 (0.0)
Pneumonitis	0	1 (0.1)	0	0	0	1 (0.0)
Pulmonary edema	0	0	1 (0.1)	0	0	1 (0.0)
Pulmonary embolism	0	0	1 (0.1)	0	0	1 (0.0)
Acute respiratory failure	1 (0.2)	0	0	0	1 (0.1)	2 (0.1)
Respiratory failure	0	0	0	0	1 (0.1)	1 (0.0)
Pulmonary mass	0	0	1 (0.1)	0	0	1 (0.0)
Infections and infestations	3 (0.6)	9 (1.3)	7 (1.0)	7 (1.0)	8 (1.0)	34 (1.0)
Appendicitis perforated	0	1 (0.1)	0	0	0	1 (0.0)
Diverticulitis	1 (0.2)	1 (0.1)	0	0	0	2 (0.1)
Peritonitis	0	1 (0.1)	1 (0.1)	0	0	2 (0.1)
Gastroenteritis	0	0	1 (0.1)	1 (0.1)	0	2 (0.1)
Urinary tract infection bacterial	0	0	1 (0.1)	0	0	1 (0.0)
Breast abscess	0	0	0	0	1 (0.1)	1 (0.0)
Cholecystitis infective	0	0	1 (0.1)	0	0	1 (0.0)
Liver abscess	0	0	1 (0.1)	0	0	1 (0.0)
Herpes zoster	0	0	0	1 (0.1)	0	1 (0.0)
Pneumonia	2 (0.4)	5 (0.7)	4 (0.6)	1 (0.1)	4 (0.6)	16 (0.5)
Infectious pleural effusion	0	0	0	0	1 (0.1)	1 (0.0)
Lung abscess	1 (0.2)	0	0	0	0	1 (0.0)
Cardiac disorders	7 (1.3)	4 (0.6)	8 (1.1)	5 (0.7)	8 (1.1)	32 (0.9)
Coronary artery disease	1 (0.2)	0	1 (0.1)	0	0	2 (0.1)

System organ class Preferred term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)	Total N=3398 n (%)
Cardiac failure	0	0	1 (0.1)	0	1 (0.1)	2 (0.1)
Cardiac failure chronic	0	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Acute myocardial infarction	1 (0.2)	2 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)	6 (0.2)
Myocardial infarction	0	2 (0.3)	2 (0.3)	1 (0.1)	1 (0.1)	6 (0.2)
Acute coronary syndrome	0	0	1 (0.1)	0	1 (0.1)	2 (0.1)
Angina pectoris	0	0	2 (0.3)	1 (0.1)	0	3 (0.1)
Angina unstable	1 (0.2)	0	0	0	1 (0.1)	2 (0.1)
Right ventricular failure	1 (0.2)	0	0	0	0	1 (0.1)
Atrial fibrillation	3 (0.6)	0	2 (0.3)	1 (0.1)	2 (0.3)	8 (0.2)
Cardio-respiratory arrest	0	0	0	0	1 (0.1)	1 (0.0)
Torsade de pointes	0	0	0	0	1 (0.1)	1 (0.0)
Ventricular fibrillation	0	0	0	0	1 (0.1)	1 (0.0)

Source: Integrated Summary of Safety Report; Table 8.1.4 and 8.2.4; pg 4461-4487

In the 28-week placebo-controlled extension trial, Trial 36, a total of 74 (8.1%) patients had treatment-emergent SAEs, and the percentage of patients who had an SAE was similar across treatment groups (7.5% to 8.8%). The most common SAEs by PT were COPD (1.7%) and pneumonia (0.5%). Non-fatal SAEs in this trial are summarized in Table 36.

Table 36: Treatment-Emergent Non-Fatal SAEs That Occurred in ≥ 2 Patients in Any Treatment Group (by PT), 28-Week Placebo-Controlled Extension Trial (Trial 36)

System organ class Preferred term	Placebo N=146 n (%)	AB/FF 400/12 µg N=182 n (%)	AB/FF 400/6 µg N = 204 n (%)	AB 400 µg N = 194 n (%)	FF 12 µg N = 192 n (%)	Total N = 918 n (%)
Patients With At Least 1 SAE	11 (7.5)	16 (8.8)	16 (7.8)	16 (8.2)	15 (7.8)	74 (8.1)
Respiratory, thoracic and mediastinal disorders	1 (0.7)	5 (2.8)	4 (2.0)	5 (2.6)	4 (2.1)	19 (2.1)
Chronic obstructive pulmonary disease	1 (0.7)	3 (1.7)	3 (1.5)	5 (2.6)	3 (1.6)	15 (1.7)
Pulmonary mass	0	2 (1.1)	0	0	0	2 (0.2)
Acute respiratory failure	0	0	2 (1.0)	1 (0.5)	1 (0.5)	4 (0.4)
Infections and infestations	1 (0.7)	3 (1.6)	5 (2.5)	5 (2.6)	4 (2.1)	18 (2.0)
Pneumonia	0	0	3 (1.5)	2 (1.0)	0	5 (0.5)
Diverticulitis	1 (0.7)	0	0	0	2 (1.0)	3 (0.3)
Nervous system disorders	1 (0.7)	1 (0.5)	4 (2.0)	3 (1.5)	1 (0.5)	10 (1.1)
Syncope	1 (0.7)	0	2 (1.0)	0	1 (0.5)	4 (0.4)
Cerebrovascular accident	0	0	0	2 (1.0)	0	2 (0.2)
Vascular disorders	2 (1.4)	1 (0.5)	2 (1.0)	0	2 (1.0)	7 (0.8)
Hypotension	0	0	2 (1.0)	0	1 (0.5)	3 (0.3)
Cardiac disorders	3 (2.1)	1 (0.5)	4 (2.0)	4 (2.1)	2 (1.0)	14 (1.5)
Myocardial infarction	1 (0.7)	0	0	2 (1.0)	1 (0.5)	4 (0.4)

Source: LAC-MD-36 CSR Volume 1; Table 14.5.2.3.2A; pg 3254-3261 and clinical reviewer

In the 24-week active-controlled trial, Trial 01, SAEs were reported in 123 (7.8%) patients, ranging from 6.9% to 8.6% across the treatment groups. Consistent with data from other trials, the most common SAEs by PT were COPD (2.7%) and pneumonia (0.6%). The proportion of patients with COPD was similar between AB/FF 400/12 µg group and individual components or tiotropium groups. Pneumonia was reported in a numerically higher proportion of patients in the AB/FF 400/12 µg group (4 patients [1.3%]) versus the AB 400 µg (3 patients [0.6%]), FF 12 µg (1 patient [0.3%]) and tiotropium 18 µg group (2 patients [0.4%]). However, the differences in the number of patients who reported pneumonia were small, and not clinically meaningful.

Overall, SAE analyses did not demonstrate large differences when comparing either AB/FF treatment dose to its monocomponents or placebo. The observed SAEs were consistent with

the studied COPD population and not unexpected. The SAE data did not reveal new safety concerns.

Dropouts and/or Discontinuations Due to Adverse Effects

Of the 3398 patients in the pooled 24-week placebo-controlled Trials 30 and 31, 188 (5.5%) patients prematurely discontinued. The proportion of patients with TEAEs leading to treatment discontinuation was slightly higher in the placebo group (35 patients [6.7%]) than in other active treatment groups (33 to 44 patients [4.6% to 6.1%]). The most common PTs associated with discontinuation were COPD (51 patients [1.5%]) and dyspnea (8 patients [0.2%]), which were similar to or slightly higher in the placebo group than in any other group. In addition, when comparing causes of discontinuation by PT, events were generally similar between any treatment arms. On-treatment adverse events leading to discontinuation are summarized in Table 37.

Table 37: Discontinuations Due to Adverse Events That Occurred in ≥ 2 Patients in Any Treatment Group (by PT), Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31)

Preferred term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)	Total N=3398 n (%)
Number of discontinued patients	35 (6.7)	44 (6.1)	37 (5.2)	39 (5.4)	33 (4.6)	188 (5.5)
Chronic obstructive pulmonary disease	10 (1.9)	12 (1.7)	5 (0.7)	14 (1.9)	10 (1.4)	51 (1.5)
Dyspnea	2 (0.4)	2 (0.3)	3 (0.4)	0	1 (0.1)	8 (0.2)
Acute myocardial infarction	1 (0.2)	2 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)	6 (0.2)
Pneumonia	1 (0.2)	2 (0.3)	1 (0.1)	0	1 (0.1)	5 (0.2)
Electrocardiogram QT prolonged	0	2 (0.3)	0	2 (0.3)	0	4 (0.1)
Coronary artery disease	2 (0.4)	0	0	0	0	2 (0.1)
Nausea	0	0	0	2 (0.3)	0	2 (0.1)
Tremor	0	2 (0.3)	0	0	0	2 (0.1)

Source: Integrated Summary of Safety Report; Table 9.2B.4; pg 5443-5466

In the 28-week placebo-controlled extension Trial 36, the percentage of patients who discontinued due to AEs in the AB/FF treatment groups (4.4% and 2.9% for the AB/FF 400/12 µg and AB/FF 400/6 µg treatment groups, respectively) was lower than the percentage of patients in the placebo treatment group (4.8%). Table 38 presents a summary of AEs reported in 2 or more patients in any treatment group associated with premature discontinuation. COPD (1.5%) and cerebrovascular accident (0.2%) werethe only AEs reported in 2 or more patients who discontinued from the trial. The incidence of any AE associated with discontinuation of treatment in 2 or more patients was not higher in AB/FF treatment group than that in any individual treatment or placebo group.

Table 38: Discontinuations Due to Adverse Events That Occurred in ≥ 2 Patients in Any Treatment Group (by PT), 28-Week Placebo-Controlled Extension Trial (Trial 36)

Preferred term	Placebo N=146 n (%)	AB/FF 400/12 µg N=182 n (%)	AB/FF 400/6 µg N=204 n (%)	AB 400 µg N=194 n (%)	FF 12 µg N=192 n (%)	Total N=918 n (%)
Number of discontinued patients	7 (4.8)	8 (4.4)	6 (2.9)	10 (5.2)	8 (4.2)	39 (4.2)
Chronic obstructive pulmonary disease	2 (1.4)	2 (1.1)	2 (1.0)	4 (2.1)	4 (2.1)	14 (1.5)
Cerebrovascular accident	0	0	0	2 (1.0)	0	2 (0.2)

Source: LAC-MD-36 CSR Volume 1; Table 12.3.1.3.1.1–1; pg 220 and clinical reviewer

A similar pattern was also observed in the 24-week active-controlled trial, Trial 01. The proportion of patients with TEAEs leading to discontinuation was low and similar across treatment groups, ranging from 5.4% (AB/FF 400/12 µg) to 8.5% (FF 12 µg) of patients. The most common causes of discontinuation by PT were COPD (3.3%) and dyspnea (0.6%).

Overall, these results discussed above demonstrated that AEs associated with discontinuation of treatment were comparable between the AB/FF 400/12 µg treatment arm and other treatment arms.

Significant Adverse Events

The majority of TEAEs reported in the pooled 24-week placebo-controlled Trials 30 and 31 were mild or moderate in severity. The number of patients with TEAEs of severe intensity was comparable across study groups, ranging from 6.9% in the AB 400 µg group to 8.3% in the AB/FF 400/12 µg group. The most common PTs of severe intensity were COPD (2.9%) and pneumonia (0.5%). Table 39 presents the AEs of severe intensity that occurred ≥2 patients in any study group.

Table 39: Severe TEAEs That Occurred in ≥2 Patients in Any Treatment Group (by PT) Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31)

Preferred term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)	Total N=3398 n (%)
Patients with at least 1 severe TEAE	40 (7.6)	60 (8.3)	51 (7.1)	50 (6.9)	51 (7.1)	252 (7.4)
Chronic obstructive pulmonary disease	19 (3.6)	21 (2.9)	16 (2.2)	22 (3.0)	21 (2.9)	99 (2.9)
Pneumonia	2 (0.4)	5 (0.7)	4 (0.6)	1 (0.1)	4 (0.6)	16 (0.5)
Acute myocardial infarction	1 (0.2)	2 (0.3)	1 (0.1)	0	1 (0.1)	5 (0.1)
Acute respiratory failure	1 (0.2)	1 (0.1)	0	0	2 (0.3)	4 (0.1)
Atrial fibrillation	2 (0.4)	0	0	1 (0.1)	1 (0.1)	4 (0.1)
Gastroenteritis	1 (0.2)	1 (0.1)	2 (0.3)	1 (0.1)	0	5 (0.1)
Myocardial infarction	0	2 (0.3)	2 (0.3)	1 (0.1)	0	5 (0.1)
Cerebrovascular accident	2 (0.4)	0	1 (0.1)	0	0	3 (0.1)
Headache	0	1 (0.1)	0	2 (0.3)	0	3 (0.1)
Vomiting	0	0	1 (0.1)	3 (0.4)	0	4 (0.1)
Cough	2 (0.4)	1 (0.1)	0	0	0	3 (0.1)
Diarrhea	0	0	2 (0.3)	0	0	2 (0.1)
Colitis	0	2 (0.3)	0	0	0	2 (0.1)
Diverticulitis	2 (0.4)	0	0	0	0	2 (0.1)

Source: Integrated Summary of Safety Report Table 5.1.4, pg 3013-3146

Table 40 presents the incidence of severe TEAEs reported in ≥ 2 patients in any individual treatment group in the 28-week placebo-controlled extension trial, Trial 36. As noted in pooled Trials 30 and 31, most TEAEs reported in this trial were mild or moderate of severity, and the most common PTs of severe intensity were COPD (5.3%) and pneumonia (0.7%). There was no evidence observed that the severity of TEAEs was increased by AB/FF treatment dose.

Table 40: 2 Severe TEAEs That Occurred in ≥2 patients in Any Treatment Group (by PT) 8-Week Placebo-Controlled Extension Trial (Trial 36)

Preferred term	Placebo N=146 n (%)	AB/FF 400/12 µg N=182 n (%)	AB/FF 400/6 µg N=204 n (%)	AB 400 µg N=194 n (%)	FF 12 µg N=192 n (%)	Total N=918 n (%)
Patients with at least 1 severe TEAE	18 (12.3)	21 (11.5)	25 (12.3)	23 (11.9)	21 (10.9)	108 (11.8)
Chronic obstructive pulmonary disease	5 (3.4)	10 (5.5)	11 (5.4)	13 (6.7)	10 (5.2)	49 (5.3)
Fall	0	1 (0.5)	2 (1.0)	0	0	3 (0.3)
Pneumonia	0	0	3 (1.5)	2 (1.0)	1 (0.5)	6 (0.7)
Acute myocardial infarction	0	0	2 (1.0)	0	0	2 (0.2)
Cellulitis	0	0	1 (0.5)	0	2 (1.0)	3 (0.3)
Myocardial infarction	1 (0.7)	0	0	2 (1.0)	1 (0.5)	4 (0.4)
Hypertension	2 (1.4)	0	0	0	1 (0.5)	3 (0.3)

Source: LAC-MD-36 CSR Volume 1; Table 12.2.3.2.1–1; pg 207 and clinical reviewer

An analysis of severe TEAEs in Trial 01, the active controlled trial, were consistent with other trials discussed above. Severe TEAEs were reported in 8.0% of patients, and the most common PTs of severe intensity were COPD (2.7%) and pneumonia (0.6). No large imbalances in severe TEAEs were identified when comparing treatment groups.

Treatment Emergent Adverse Events and Adverse Reactions

In pooled Trials 30 and 31, common adverse events by PT that occurred in at least 2% of patients in any treatment group are summarized in Table 41. The proportion of patients with at least 1 TEAE was similar in the placebo (304 patients [57.8%]) and other treatment groups (407 to 430 patients [57.0% to 60.1%]). The most common PTs were COPD exacerbation (14.7%), viral upper respiratory tract infection (6.2%), headache (6.3%), back pain (3.3%) and cough (2.3%). No AEs based on PT demonstrated a clear dose response. In general, the incidence of common adverse events in the AB/FF treatment groups was similar compared to monotherapy or placebo group.

Table 41: TEAE that Occurred in ≥ 2% of Patients in Any Treatment Group (by PT) Pooled 24-Week Placebo-Controlled Trials (Trial 30 and 31).

Preferred term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)	Total N=3398 n (%)
Patients with at least 1 TEAE	304 (57.8)	420 (58.3)	407 (57.0)	419 (58.0)	430 (60.1)	1980 (58.3)
Chronic obstructive pulmonary disease	90 (17.1)	90 (12.5)	91 (12.7)	108 (15.0)	120 (16.8)	499 (14.7)
Viral upper respiratory tract infection	25 (4.8)	47 (6.5)	49 (6.9)	37 (5.1)	51 (7.1)	209 (6.2)
Headache	27 (5.1)	45 (6.3)	40 (5.6)	48 (6.6)	55 (7.7)	215 (6.3)
Back pain	18 (3.4)	27 (3.8)	18 (2.5)	24 (3.3)	25 (3.5)	112 (3.3)
Cough	14 (2.7)	21 (2.9)	17 (2.4)	12 (1.7)	13 (1.8)	77 (2.3)
Urinary tract infection	13 (2.5)	21 (2.9)	14 (2.0)	16 (2.2)	12 (1.7)	76 (2.2)
Oropharyngeal pain	11 (2.1)	17 (2.4)	8 (1.1)	9 (1.2)	8 (1.1)	53 (1.6)
Upper respiratory tract infection	8 (1.5)	17 (2.4)	17 (2.4)	18 (2.5)	19 (2.7)	79 (2.3)
Muscle spasms	6 (1.1)	15 (2.1)	7 (1.0)	5 (0.7)	11 (1.5)	44 (1.3)
Diarrhea	12 (2.3)	14 (1.9)	15 (2.1)	11 (1.5)	12 (1.7)	64 (1.9)
Sinusitis	8 (1.5)	12 (1.7)	18 (2.5)	15 (2.1)	9 (1.3)	62 (1.8)
Dizziness	8 (1.5)	11 (1.5)	7 (1.0)	5 (0.7)	14 (2.0)	45 (1.3)
Arthralgia	6 (1.1)	9 (1.3)	4 (0.6)	9 (1.2)	17 (2.4)	45 (1.3)
Nausea	9 (1.7)	8 (1.1)	19 (2.7)	16 (2.2)	15 (2.1)	67 (2.0)
Hypertension	8 (1.5)	7 (1.0)	13 (1.8)	12 (1.7)	18 (2.5)	58 (1.7)

Source: Summary of Clinical Safety; Table 65; pg 164

In the 28-week placebo-controlled extension trial, Trial 36, the proportion of patients with at least 1 TEAE was higher in the AB/FF treatment groups (71.4% and 68.1% for the AB/FF 400/12 µg and AB/FF 400/6 µg treatment groups, respectively) than in the placebo treatment group (59.6%), but similar to the percentage of patients in the monotherapy treatment groups (72.2% and 70.3% in the AB 400 µg and FF 12 µg treatment groups, respectively). The most common PTs were COPD exacerbation (22.3%), nasopharyngitis (7.2%) and urinary tract infection (6.1%). The incidence of TEAEs in the AB/FF treatment groups was generally similar compared to monotherapy or placebo group. Table 42 presents the incidence of common TEAEs (reported in ≥ 2% of patients in any individual treatment group) by PT.

Table 42: TEAE That Occurred in ≥ 2% of Patients in any Treatment Group (by PT) 28-Week Placebo-Controlled Extension Trial (Trial 36)

Preferred term	Placebo N=146 n (%)	AB/FF 400/12 µg N=182 n (%)	AB/FF 400/6 µg N=204 n (%)	AB 400 µg N=194 n (%)	FF 12 µg N=192 n (%)	Total N=918 n (%)
Number of patients	87 (59.6)	130 (71.4)	139 (68.1)	140 (72.2)	135 (70.3)	631 (68.7)
Chronic obstructive pulmonary disease	23 (15.8)	40 (22.0)	47 (23.0)	46 (23.7)	49 (25.5)	205 (22.3)
Anemia	2 (1.4)	2 (1.1)	5 (2.5)	3 (1.5)	1 (0.5)	13 (1.4)
Atrial fibrillation	3 (2.1)	1 (0.5)	4 (2.0)	0	0	8 (0.9)
Tachycardia	0	1 (0.5)	1 (0.5)	4 (2.1)	0	6 (0.7)
Diarrhea	3 (2.1)	6 (3.3)	5 (2.5)	4 (2.1)	3 (1.6)	21 (2.3)
Nausea	3 (2.1)	5 (2.7)	3 (1.5)	6 (3.1)	1 (0.5)	18 (2.0)
Vomiting	2 (1.4)	5 (2.7)	1 (0.5)	3 (1.5)	1 (0.5)	12 (1.3)
Constipation	0	4 (2.2)	6 (2.9)	4 (2.1)	4 (2.1)	18 (2.0)
Diverticulum	0	3 (1.6)	5 (2.5)	1 (0.5)	0	9 (1.0)
Gastroesophageal reflux	2 (1.4)	3 (1.6)	5 (2.5)	3 (1.5)	2 (1.0)	15 (1.6)
Edema peripheral	3 (2.1)	5 (2.7)	3 (1.5)	0	2 (1.0)	13 (1.4)
Urinary tract infection	8 (5.5)	16 (8.8)	13 (6.4)	8 (4.1)	11 (5.7)	56 (6.1)
Nasopharyngitis	7 (4.8)	14 (7.7)	14 (6.9)	18 (9.3)	13 (6.8)	66 (7.2)
Sinusitis	5 (3.4)	6 (3.3)	6 (2.9)	4 (2.1)	7 (3.6)	28 (3.1)
Upper respiratory tract infection	8 (5.5)	5 (2.7)	8 (3.9)	9 (4.6)	8 (4.2)	38 (4.1)
Influenza	4 (2.7)	3 (1.6)	3 (1.5)	3 (1.5)	6 (3.1)	19 (2.1)
Gastroenteritis viral	3 (2.1)	2 (1.1)	2 (1.0)	3 (1.5)	4 (2.1)	14 (1.5)
Pneumonia	1 (0.7)	1 (0.5)	5 (2.5)	3 (1.5)	1 (0.5)	11 (1.2)
Tooth infection	2 (1.4)	1 (0.5)	1 (0.5)	4 (2.1)	0	8 (0.9)
Bronchitis	2 (1.4)	0	4 (2.0)	1 (0.5)	4 (2.1)	11 (1.2)
Ear infection	1 (0.7)	0	1 (0.5)	1 (0.5)	4 (2.1)	7 (0.8)
Lower respiratory tract infection	3 (2.1)	0	0	1 (0.5)	1 (0.5)	5 (0.5)
Contusion	4 (2.7)	2 (1.1)	1 (0.5)	0	1 (0.5)	8 (0.9)
Fall	1 (0.7)	2 (1.1)	4 (2.0)	1 (0.5)	4 (2.1)	12 (1.3)
Laceration	1 (0.7)	2 (1.1)	3 (1.5)	4 (2.1)	2 (1.0)	12 (1.3)
Muscle strain	4 (2.7)	2 (1.1)	2 (1.0)	2 (1.0)	1 (0.5)	11 (1.2)

Preferred term	Placebo N=146 n (%)	AB/FF 400/12 µg N=182 n (%)	AB/FF 400/6 µg N=204 n (%)	AB 400 µg N=194 n (%)	FF 12 µg N=192 n (%)	Total N=918 n (%)
Weight decreased	1 (0.7)	4 (2.2)	2 (1.0)	1 (0.5)	2 (1.0)	10 (1.1)
Type 2 diabetes mellitus	3 (2.1)	1 (0.5)	0	0	0	4 (0.4)
Back pain	5 (3.4)	4 (2.2)	4 (2.0)	5 (2.6)	9 (4.7)	27 (2.9)
Arthralgia	3 (2.1)	1 (0.5)	5 (2.5)	1 (0.5)	3 (1.6)	13 (1.4)
Pain in extremity	3 (2.1)	0	1 (0.5)	5 (2.6)	2 (1.0)	11 (1.2)
Headache	4 (2.7)	6 (3.3)	2 (1.0)	3 (1.5)	1 (0.5)	16 (1.7)
Dizziness	0	4 (2.2)	7 (3.4)	1 (0.5)	1 (0.5)	13 (1.4)
Depression	3 (2.1)	1 (0.5)	2 (1.0)	2 (1.0)	1 (0.5)	9 (1.0)
Anxiety	0	0	7 (3.4)	2 (1.0)	3 (1.6)	12 (1.3)
Hematuria	1 (0.7)	4 (2.2)	2 (1.0)	0	4 (2.1)	11 (1.2)
Cough	3 (2.1)	5 (2.7)	6 (2.9)	12 (6.2)	5 (2.6)	31 (3.4)
Oropharyngeal pain	2 (1.4)	4 (2.2)	2 (1.0)	4 (2.1)	3 (1.6)	15 (1.6)
Dyspnea	2 (1.4)	3 (1.6)	5 (2.5)	2 (1.0)	0	12 (1.3)
Nasal congestion	2 (1.4)	1 (0.5)	3 (1.5)	5 (2.6)	2 (1.0)	13 (1.4)
Hypertension	6 (4.1)	4 (2.2)	4 (2.0)	4 (2.1)	5 (2.6)	23 (2.5)
Hypotension	1 (0.7)	0	5 (2.5)	0	1 (0.5)	7 (0.8)

Source: LAC-MD-36 CSR Volume 1; Table 12.2.3.1.1–1; pg 201-203 and clinical reviewer

Analysis of TEAEs in Trial 01 yielded generally similar results. TEAEs were reported in 61.1% of patients, ranging from 58.3% (AB/FF 400/12 µg) to 65.8% (FF 12 µg) across the treatment groups. The most frequent TEAEs were COPD, nasopharyngitis, and headache. Common TEAEs (occurred in >2% of patients in any treatment group) reported by a numerically higher proportion of patients in the AB/FF 400/12 µg treatment group compared to monotherapy and tiotropium were back pain (4.8% versus 1.5-2.5%), sinusitis (2.6% versus 1.5-2.1%), pneumonia (2.6% versus 0.9-1.7%) and arthralgia (2.6% versus 0.8-1.7%). Otherwise, the proportion of patients reporting TEAEs was similar between AB/FF 400/12 µg versus monotherapies and tiotropium.

Overall, the common AEs identified were typical for the COPD patient population and similar to those observed in LABA and anticholinergic development programs.

Laboratory Findings

For laboratory evaluations in pooled 24-week placebo controlled trials, Trial 30 and 31, mean changes from baseline to the end-of-study (EOS) value were generally small and similar between groups. No notable mean changes of blood glucose or potassium levels were observed. No large differences of blood uric acid and lactate dehydrogenase (LDH) were noted between AB/FF treatment groups and monotherapy groups.

There was a decrease in blood creatine kinase in the placebo (-4.76 U/L) and AB 400 µg (-3.67 U/L) group compared with an increase in creatine kinase in the AB/FF 400/12 ug (20.09 U/L), 400/6 µg (26.78 U/L) and FF 12 µg (23.15 U/L) group, however, these changes were small in magnitude.

Potentially clinically significant (PCS) lab changes were defined as laboratory values that are outside either the lower or upper limit of the predefined expanded normal range (ENR). The ENR was reviewed by the clinical reviewer and was reasonable. PCS at EOS were relatively infrequent and evenly distributed between treatment arms. Additionally, shift table analysis was performed. With regard to hematological and chemistry parameters in general, shifts occurred in a similar percentage of patients when comparing the AB/FF treatment groups to their monoproduct or placebo group with the exception of creatine kinase (CK). New increases in CK were seen in a higher proportion of patients in treatment groups that contained FF (7.6%, 4.8% and 7.1% in AB/FF 400/12 µg, AB/FF 400/6 µg and FF 12 µg group, respectively) than in the other treatment groups (4.2% and 3.3% in AB 400 µg and placebo group, respectively). Worsening increase of CK was also noted in FF-containing groups (2.3%, 1.2% and 1.3% in AB/FF 400/12 µg, AB/FF 400/6 µg and FF 12 µg group, respectively) compared to AB 400 µg (0.7%) and placebo group (0.6%). However, no large shift of LDH or uric acid was observed across treatment groups.

In the 28-week placebo-controlled extension trial, Trial 36, shifts of CK were also seen. A higher proportion of patients in AB/FF 400/12 µg (13.2%) and FF 12 µg (7.3%) treatment groups had new increase CK than in the other treatment groups (2.8-5.2%), while a similar shift of uric acid and LDH was not observed.

The shift analysis of the 24-week active-controlled Trial 01 demonstrated that the proportion of patients with new increases of CK, and CK MM values were numerically higher in AB/FF 400/12 µg (6.3% and 9.9%) and FF 12 µg (5.0% and 7.8%) group compared to AB 400 µg (1.0% and 3.5%) and tiotropium 18 µg (3.5% and 5.5%) group. The proportion of patients with new increases of ALT and AST in AB/FF 400/12 µg group was lower than that in AB 400 µg group, although higher or comparable when compared to the FF12 µg or Tiotropium 18 µg group.

In summary, all the 3 trials consistently showed a higher proportion of patients with new increases of CK in FF containing groups compared to placebo or AB group. However, no large difference of LDH or uric acid was observed. In addition, the incidence of myalgia was not higher in FF containing groups. As such, it appears that these elevations were largely asymptomatic and of uncertain clinical relevance. Overall, these lab data did not reveal any new safety concerns.

Vital Signs

In all the trials discussed in this safety review, data did not reveal any relevant mean changes from baseline to EOS for either mean systolic or mean diastolic blood pressure in any treatment group. No clinically relevant changes of pulse rate and respiratory rate were

reported.

Electrocardiograms (ECGs)

In the pooled analysis ofTrials 30 and 31, 12-lead ECG data was obtained. Based on mean values, there were no large changes from baseline in heart rate, PR interval, and QRS interval. Mean changes from baseline in QTcF were also similar between groups (changes from baseline across groups ranged from 1.40 to 3.56 msec). ECGs were also assessed for U waves, ST segment, T-wave, rhythm, ECG conduction and morphological abnormalities. The percentage of patients with abnormalities was generally similar between treatment groups. The most common abnormality was flat T waves, which were similar between the AB/FF 400/12 µg (5.2%) and AB 400 µg (4.7%) groups, though higher compared to placebo (2.9%).

Table 43 presents the number of patients who experienced PCS changes in ECG values at EOS in the pooled Trials 30 and 31. While for some of the parameters there were numerical differences between AB/FF 400/12 µg group versus other groups, these differences were small in magnitude, and not clinically meaningful.

Table 43: Number of Patients With PCS Changes in 12-lead ECG Values at EOS Pooled 24-Week Placebo-Controlled Trials

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 (%)
QTcF interval, msec	>480 msec	2/525 (0.4)	7/720 (1.0)	10/713 (1.4)	8/720 (1.1)	12/716 (1.7)
QTcF interval, msec	Increase >30 msec	76/525 (14.5)	122/720 (16.9)	133/713 (18.7)	128/720 (17.8)	128/716 (17.9)
QRS interval, msec	≥100 msec and increase ≥25%	8/525 (1.5)	15/720 (2.1)	19/713 (2.7)	18/720 (2.5)	18/716 (2.5)
PR interval, msec	≥200 msec and increase ≥25%	7/518 (1.4)	9/715 (1.3)	5/702 (0.7)	7/707 (1.0)	13/708 (1.8)
Tachycardia event, bpm	≥110 bpm and increase ≥15%	3/525 (0.6)	8/720 (1.1)	9/713 (1.3)	10/720 (1.4)	9/716 (1.3)
Bradycardia Event, bpm	≤50 bpm and decrease ≥15%	35/525 (6.7)	25/720 (3.5)	40/713 (5.6)	46/720 (6.4)	34/716 (4.8)

Source: Summary of Clinical Safety; Table 107; pg 211

In addition, 24-hour Holter monitoring was conducted in a subset of patients in Trials 30 and 31. The Holter monitoring sub-study included a total of 551 patients in the trials (81 treated with placebo, 114 with AB/FF 400/12 µg, 117 treated with AB/FF 400/6 µg, 118 treated with AB 400 µg, and 121 treated with FF 12 µg). While cardiac findings including supraventricular and atrial arrhythmias, ventricular arrhythmias, conduction abnormalities and bradycardia were observed at EOS, no large imbalances of these findings between AB/FF 400/12 µg group and other treatment groups were noted.

In Trials 36 and 01, ECG findings were similar. The mean changes of heart rate, PR interval, QTcF and QRS interval were small and not clinically meaningful. Overall, no new ECG related safety concerns were identified in the AB/FF treatment group.

QT

Not applicable

Immunogenicity

Not applicable

8.2.5. Analysis of Submission-Specific Safety Issues

Given specific safety concerns with LABA and anticholinergic agents, the sponsor analyzed TEAEs of special interests that included cardiac, cerebrovascular, and respiratory events and potential anticholinergic and β2-agonist AEs. A Cardiovascular Adjudication Committee provided independent review and adjudication to determine cardiovascular events. All SAEs and deaths and some relevant TEAEs were examined by the Adjudication Committee to identify MACE (Major Adverse Cardiovascular Events). MACE were defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Respiratory Safety
Because of the patient population and disease, AEs related to LRTIs (lower respiratory tract infections) including pneumonia were analyzed. In pooled placebo-controlled Trials 30 and 31, the incidence of LRTI was similar between groups, ranging from 1.8% to 2.2%. The incidence of LRTIs that were SAEs was slightly higher for AB/FF 400/12 µg (0.7%) and 400/6 µg (0.6%) than placebo (0.4%) and AB 400 µg (0.1%), but similar to FF 12 µg (0.6%). However, the differences were small in magnitude. Table 44 summarizes the data regarding the incidence of LRTIs.

Table 44: Treatment-Emergent and Serious Treatment-Emergent Adverse Events of LRTI, Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31).

	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Any event of LRTI	10 (1.9)	13 (1.8)	14 (2.0)	16 (2.2)	14 (2.0)
Any pneumonia event	3 (0.6)	8 (1.1)	8 (1.1)	2 (0.3)	8 (1.1)
Any LRTI SAE	2 (0.4)	5 (0.7)	4 (0.6)	1 (0.1)	4 (0.6)
Any pneumonia SAE	2 (0.4)	5 (0.7)	4 (0.6)	1 (0.1)	4 (0.6)

Source: Summary of Clinical Safety; Table 92; pg 193

A similar AE analysis result regarding LRTIs was also noted in Trials 36 and 01. Overall, the

incidence of LRTIs including pneumonia were comparable between AB/FF treatment group and placebo group. These data are not suggestive of a LRTI safety issue.

Cardiovascular Safety

Two analyses were performed to evaluate the cardiovascular safety, which were analysis of MACE and analysis of cardiac events of interest based on standardized MedDRA queries (SMQs). The analysis of the pooled Trials 30 and 31 indicated that the incidence of MACE in the AB/FF treatment groups was low (0.7% in AB/FF 400/12 µg and 0.8% in AB/FF 400/6 µg) and similar to that seen for placebo (0.6%) and monotherapies (0.3% in AB 400 µg and 0.8% in FF 12 µg). Non-fatal myocardial infarction were slightly more numerically common in the AB/FF 400/12 µg treatment group than placebo and AB 400 µg group. However, the magnitude of the differences was numerically small. The MACE data are summarized in Table 45.

Table 45: MACE Analysis, Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31)

Adjudicated MACE	Placebo (N=526) n (%)	AB/FF 400/12 µg (N=720) n (%)	AB/FF 400/6 µg (N=714) n (%)	AB 400 µg (N=722) n (%)	FF 12 µg (N=716) n (%)
Patients with at least one MACE	3 (0.6)	5 (0.7)	6 (0.8)	2 (0.3)	6 (0.8)
Cardiovascular Death	0	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.3)
Death due to acute myocardial infarction	0	0	0	0	0
Sudden cardiac death	0	1 (0.1)	0	1 (0.1)	2 (0.3)
Death due to heart failure or cardiogenic shock	0	0	1 (0.1)	0	0
Death due to stroke	0	0	0	0	0
Death due to other cardiovascular cause	0	0	0	0	0
Non-fatal Myocardial Infarction (MI)	1 (0.2)	4 (0.6)	3 (0.4)	1 (0.1)	3 (0.4)
Spontaneous	1 (0.2)	4 (0.6)	3 (0.4)	1 (0.1)	3 (0.4)
Demand type	0	0	0	0	0
Procedure-related MI	0	0	0	0	0
Silent	0	0	0	0	0
Non-fatal Stroke	2 (0.4)	0	2 (0.3)	0	1 (0.1)
Ischemic	2 (0.4)	0	2 (0.3)	0	1 (0.1)
Hemorrhagic	0	0	0	0	0
Undetermined	0	0	0	0	0

Source: Integrated Summary of Safety Report; Table 10.11.4; pg 8541

In the 28-week extension trial, Trial 36, the incidence of MACE was low. Only a total of 8 patient were reported to have MACE. No large difference of MACE incidence was observed between groups. Overall, these data did not reveal MACE-related safety concerns.

Regarding cardiac events based on SMQs, the following narrow search SMQs were selected to analyze the incidence of cardiac events of interest: myocardial infarction, tachycardia/atrial

fibrillation, angina, congestive heart failure, bradycardia, and conduction defects. In pooled Trials 30 and 31, for each cardiac SMQ category, the incidence for AB/FF 400/12 µg was similar to or lower than that seen for placebo or either of the monotherapies, with the exception of conduction defects. Conduction defects were more common for AB/FF 400/12 µg than for placebo (1.4% versus 0.4%), although the incidence was the same as that seen with FF monotherapy. Atrioventricular block first degree, bundle branch block left, and ECG QT prolonged were reported more frequently with AB/FF 400/12 µg than with placebo but at a similar incidence to AB or FF monotherapy. The cardiac events data are summarized in Table 46.

Table 46: Cardiac Events of Special Interest by Specific SMQ Category, Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31)

SMQ category	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Any cardiac event (by SMQ Category)	15 (2.9)	20 (2.8)	32 (4.5)	25 (3.5)	24 (3.4)
Ischemic heart disease	6 (1.1)	5 (0.7)	8 (1.1)	7 (1.0)	6 (0.8)
Myocardial infarction	2 (0.4)	4 (0.6)	3 (0.4)	2 (0.3)	3 (0.4)
Other ischemic heart disease	5 (1.0)	2 (0.3)	5 (0.7)	5 (0.7)	4 (0.6)
Supraventricular tachyarrhythmia	5 (1.0)	7 (1.0)	15 (2.1)	8 (1.1)	6 (0.8)
Cardiac failure	1 (0.2)	0	3 (0.4)	2 (0.3)	4 (0.6)
Bradyarrhythmia	1 (0.2)	0	0	3 (0.4)	0
Conduction defects	2 (0.4)	10 (1.4)	6 (0.8)	6 (0.8)	10 (1.4)

Source: Summary of Clinical Safety; Table 86; pg 187

In the 28-week extension trial, Trial 36, cardiac related SMQ analyses were also performed. The incidence of cardiac disorders in SMQ category was also very low and comparable between treatment groups. In Trial 01, similar MACE and cardiac event results were obtained. The incidence of cardiac events was low and comparable between AB/FF 400/12 µg and monotherapy or tiotropium group.

Cerebrovascular safety

The narrow search SMQs of hemorrhagic cerebrovascular-conditions and of ischemic cerebrovascular conditions were combined to analyze cerebrovascular events. In the pooled trials 30 and 31, the numbers of patients with cerebrovascular events were very low in all treatment groups, and there were no notable differences between treatments. No AB/FF dose response was observed. The cerebrovascular data are summarized in Table 47.

Table 47: Cerebrovascular Adverse Events by Specific SMQ category, Pooled 24-Week Placebo-Controlled Trials

SMQ Category Preferred Term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Any cerebrovascular event	3 (0.6)	1 (0.1)	4 (0.6)	0	1 (0.1)
Hemorrhagic central nervous system vascular conditions	2 (0.4)	0	1 (0.1)	0	0
Ischemic central nervous system vascular conditions	3 (0.6)	1 (0.1)	4 (0.6)	0	1 (0.1)

Source: Integrated Summary of Safety Report; Table 10.1.4; pg 8077

An analysis of cerebrovascular events in Trials 36 and 01 yielded generally similar results. The number of the events was low and reported at similar incidences across treatment groups.

Anticholinergic and β2-agonist effects

The sponsor also analyzed AEs using multiple SMQ and PTs which were potentially representative of anticholinergic or β2-adrenergic class effects. The analysis of anticholinergic events in pooled Trials 30 and 31 demonstrated that the incidence of cardiac disorders including sinus tachycardia was slightly more common in AB/FF 400/12 and 400/6 µg group than placebo and monotherapy group. In addition, the incidence of dry mouth, urinary tract infection, urinary retention and oropharyngeal pain was higher in AB/FF 400/12 µg group than other groups. For other anticholinergic events, similar incidence was reported in different groups. Table 48 presents the anticholinergic events.

Table 48: Anticholinergic Events, Pooled 24-Week Placebo-Controlled Trials (Trials 30 and 31)

SMQ Category Preferred Term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Patients with at least one TEAE	47 (8.9)	86 (11.9)	70 (9.8)	73 (10.1)	68 (9.5)
Cardiac disorders					
Sinus tachycardia	0	3 (0.4)	4 (0.6)	0	0
Tachycardia	0	3 (0.4)	3 (0.4)	3 (0.4)	1 (0.1)
Ventricular Tachycardia	0	1 (0.1)	0	0	0
Palpitations	1 (0.2)	0	2 (0.3)	1 (0.1)	4 (0.6)
Supraventricular tachycardia	0	0	1 (0.1)	1 (0.1)	0
Eye disorders					
Vision blurred	0	3 (0.4)	0	1 (0.1)	6 (0.8)

SMQ Category Preferred Term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Visual impairment	0	1 (0.1)	0	0	0
Dry eye	0	0	1 (0.1)	0	2 (0.3)
Glaucoma	0	0	0	1 (0.1)	2 (0.3)
Gastrointestinal disorders					
Dry mouth	2 (0.4)	13 (1.8)	5 (0.7)	4 (0.6)	6 (0.8)
Constipation	7 (1.3)	3 (0.4)	5 (0.7)	12 (1.7)	5 (0.7)
Dysphagia	0	1 (0.1)	2 (0.3)	1 (0.1)	1 (0.1)
General disorders and administration site conditions					
Pyrexia	2 (0.4)	2 (0.3)	5 (0.7)	6 (0.8)	8 (1.1)
Infections and infestations					
Urinary tract infection	13 (2.5)	21 (2.9)	14 (2.0)	16 (2.2)	12 (1.7)
Laryngitis	1 (0.2)	3 (0.4)	0	2 (0.3)	2 (0.3)
Pharyngitis	1 (0.2)	2 (0.3)	3 (0.4)	6 (0.8)	8 (1.1)
Cystitis	2 (0.4)	1 (0.1)	3 (0.4)	2 (0.3)	0
Investigations					
Heart rate increased	0	1 (0.1)	0	0	0
Nervous system disorders					
Dizziness	8 (1.5)	11 (1.5)	7 (1.0)	5 (0.7)	14 (2.0)
Presyncope	1 (0.2)	1 (0.1)	0	0	0
Somnolence	1 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	0
Loss of consciousness	0	0	0	0	1 (0.1)
Psychiatric disorders					
Confusional state	0	1 (0.1)	1 (0.1)	0	0
Agitation	0	0	0	1 (0.1)	0
Restlessness	0	0	1 (0.1)	1 (0.1)	0
Renal and urinary disorders					
Urinary retention	0	3 (0.4)	0	0	1 (0.1)
Dysuria	0	1 (0.1)	3 (0.4)	1 (0.1)	0
Urine flow decreased	1 (0.2)	0	0	0	0
Respiratory, thoracic and mediastinal disorders					

SMQ Category Preferred Term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Oropharyngeal pain	11 (2.1)	17 (2.4)	8 (1.1)	9 (1.2)	8 (1.1)
Dysphonia	0	4 (0.6)	5 (0.7)	3 (0.4)	3 (0.4)
Throat irritation	1 (0.2)	2 (0.3)	6 (0.8)	1 (0.1)	1 (0.1)
Vascular disorders					
Hyperemia	0	0	1 (0.1)	0	0

Source: Integrated Summary of Safety Report; Table 10.13A.4; pg 8562-8565

Regarding potential β2-agonist events, the incidence of hyperglycemia/new onset diabetes mellitus and hypertension based on the narrow search SMQs was balanced between groups. There was a slightly higher incidence of tachyarrhythmia (broad SMQ) in AB/FF 400/12 and 400/6 µg group. Incidence of tremor, cough, muscle spasms, urinary tract infection, and urinary retention was slightly higher in AB/FF 400/12 µg group than other groups. Table 49 presents the β2-agonist events.

Table 49: β2-Agonist Events, Pooled 24-Week Placebo-Controlled Trials.

SMQ Category Preferred Term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Any B2 adrenergic event	99 (18.8)	158 (21.9)	137 (19.2)	137 (19.0)	156 (21.8)
Hyperglycemia/new onset diabetes mellitus (narrow SMQ)	2 (0.4)	2 (0.3)	7 (1.0)	6 (0.8)	8 (1.1)
Blood glucose increased	0	2 (0.3)	1 (0.1)	2 (0.3)	1 (0.1)
Hyperglycemia	1 (0.2)	1 (0.1)	3 (0.4)	1 (0.1)	3 (0.4)
Diabetes mellitus	0	0	3 (0.4)	2 (0.3)	3 (0.4)
Glucose tolerance impaired	0	0	0	0	1 (0.1)
Type 2 diabetes mellitus	1 (0.2)	0	1 (0.1)	1 (0.1)	0
Hypertension (narrow SMQ)	8 (1.5)	8 (1.1)	15 (2.1)	13 (1.8)	18 (2.5)
Hypertension	8 (1.5)	7 (1.0)	13 (1.8)	12(1.7)	18 (2.5)
Hypertensive crisis	0	1 (0.1)	0	0	0
Blood pressure increased	0	0	2 (0.3)	1 (0.1)	0
Tachyarrhythmia (broad SMQ)	7 (1.3)	15 (2.1)	22 (3.1)	13 (1.8)	14 (2.0)
Ventricular extrasystoles	1 (0.2)	4 (0.6)	4 (0.6)	2 (0.3)	2 (0.3)
Sinus tachycardia	0	3 (0.4)	4 (0.6)	0	0

SMQ Category Preferred Term	Placebo N=526 n (%)	AB/FF 400/12 µg N=720 n (%)	AB/FF 400/6 µg N=714 n (%)	AB 400 µg N=722 n (%)	FF 12 µg N=716 n (%)
Supraventricular extrasystoles	0	3 (0.4)	7 (1.0)	3 (0.4)	2 (0.3)
Tachycardia	0	3 (0.4)	3 (0.4)	3 (0.4)	1 (0.1)
Atrial fibrillation	5 (1.0)	1 (0.1)	3 (0.4)	3 (0.4)	4 (0.6)
Extrasystoles	0	1 (0.1)	1 (0.1)	0	0
Heart rate increased	0	1 (0.1)	0	0	0
Ventricular tachycardia	0	1 (0.1)	0	0	0
Atrial flutter	0	0	1 (0.1)	1 (0.1)	0
Palpitations	1 (0.2)	0	2 (0.3)	1 (0.1)	4 (0.6)
Supraventricular tachycardia	0	0	1 (0.1)	1 (0.1)	0
Torsade de pointes	0	0	0	0	2 (0.3)
Ventricular fibrillation	0	0	0	0	1 (0.1)
Tremor (exclude congenital) -HLT-	1 (0.2)	7 (1.0)	2 (0.3)	4 (0.6)	6 (0.8)
Tremor	1 (0.2)	7 (1.0)	2 (0.3)	2 (0.3)	6 (0.8)
Essential tremor	0	0	0	1 (0.1)	0
Intention tremor	0	0	0	1 (0.1)	0
Additional PTs	85 (16.2)	135 (18.8)	104 (14.6)	111 (15.4)	126 (17.6)
Headache	27 (5.1)	45 (6.3)	40 (5.6)	48 (6.6)	55 (7.7)
Cough	14 (2.7)	21 (2.9)	17 (2.4)	12 (1.7)	13 (1.8)
Urinary tract infection	13 (2.5)	21 (2.9)	14 (2.0)	16 (2.2)	12 (1.7)
Muscle spasms	6 (1.1)	15 (2.1)	7 (1.0)	5 (0.7)	11 (1.5)
Dizziness	8(1.5)	11 (1.5)	7 (1.0)	5 (0.7)	14 (2.0)
Insomnia	4 (0.8)	8 (1.1)	6 (0.8)	4 (0.6)	13 (1.8)
Anxiety	1 (0.2)	6 (0.8)	6 (0.8)	6 (0.8)	6 (0.8)
Edema peripheral	6 (1.1)	5 (0.7)	5 (0.7)	8 (1.1)	4 (0.6)
Myalgia	6 (1.1)	4 (0.6)	5 (0.7)	4 (0.6)	6 (0.8)
Constipation	7 (1.3)	3 (0.4)	5 (0.7)	12 (1.7)	5 (0.7)
Dysgeusia	1 (0.2)	3 (0.4)	4 (0.6)	3 (0.4)	0
Urinary retention	0	3 (0.4)	0	0	1 (0.1)
Vision blurred	0	3 (0.4)	0	1 (0.1)	6 (0.8)
Electrocardiogram QT prolonged	0	2 (0.3)	2 (0.3)	3 (0.4)	1 (0.1)
Hypokalemia	1 (0.2)	2 (0.3)	0	1 (0.1)	4 (0.6)
Throat irritation	1 (0.2)	2 (0.3)	6 (0.8)	1 (0.1)	1 (0.1)
Nervousness	0	1 (0.1)	0	1 (0.1)	0

Source: Integrated Summary of Safety Report; Table 10.15A.4; pg 8584-8586

The analysis of anticholinergic and β2-agonist effects in Trials 36 and 01 showed similar results.

Overall, the findings for the submission specific safety concerns are consistent with the known

safety profile of LAMA/LABA products.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No COA analyses informing safety were included in this submission.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant performed a variety of subgroup safety analyses based on baseline demographic information in pooled Trials 30 and 31. TEAEs were more common in female patients compared to males. However, in the male and female subgroups, the incidence of patients with any TEAE who were treated with AB/FF 400/12 µg was comparable to the placebo group. Based on age, the incidence of TEAEs were similar in patients across all age groups <85 years. As over 90% patients were Caucasian, very few patients were included in the non-Caucasian analysis. The incidence of TEAEs was similar across treatment groups in Caucasian population. TEAEs in the Asian subgroup were higher in both AB/FF doses compared to other treatment groups. However, due to the very few Asian patients included in the trial, no conclusions regarding the effect of race on product safety can be drawn. There were no meaningful differences regarding the incidence of AEs based on COPD severity, body mass index (BMI) and smoking status. Overall the subgroup analysis of safety did not reveal new safety concerns.

8.2.8. Specific Safety Studies/Clinical Trials

The sponsor submitted a 120-day update. Data from that submission did not reveal any new issues. Trial 36 was a long-term safety study. In brief, Trial 36 was a 28-week placebo-controlled extension safety study that enrolled patients from US and Canadian sites who had completed Trial 31. Patient who enrolled in the extension continued in their treatment from Trial 31. Safety results from this trial were consistent with those from the 24-week placebo controlled studies (Trials 30 and 31). Results from Trial 36 have been discussed in earlier sections of this review.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No specific trials were conducted to assess for carcinogenicity in humans. See nonclinical review for animal studies.

Human Reproduction and Pregnancy

No specific trials were conducted in pregnant women. There is no human data on exposure during pregnancy.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

It is expected that overdose with AB/FF would produce typical class effects for LABA and anticholinergic agents.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

AB/FF 400/12 µg for treatment in COPD patients has been marketed in 69 countries worldwide since 2014. The ex-US post-marketing surveillance data have not revealed new safety signals The most frequently reported AEs from AB/FF ex-US post-marketing reports are reactions associated with inhaled β2-agonists or anticholinergics and clinical manifestations of the underlying disease and its progression.

Expectations on Safety in the Postmarket Setting

The patient population included in the clinical trials is similar to the target population. Given this fact and the ex-US postmarketing experience with this product, no substantial differences are anticipated.

8.2.11. Integrated Assessment of Safety

The safety data submitted with this application were sufficient to assess the safety of AB/FF 400/12 µg in the COPD patient population. This assessment of clinical safety primarily focuses on the two 24-week placebo-controlled trials (30 and 31), one 24-week active-controlled trial (01) and one placebo-controlled trial (36), a 28-week extension. In the pooled data from Trials 30 and 31, the proportion of patients who had treatment-emergent deaths was slightly numerically higher in the AB/FF 400/12 µg group than in placebo group (2 versus 0, death and COPD), but similar to the monotherapy groups (Table 32). The incidence of SAEs in AB/FF 400/12 µg treatment groups was comparable to either placebo or other active treatment groups in all the trials. The most commonly reported SAEs were COPD and pneumonia (Table 35). With regard to common TEAEs, the most common PTs were COPD exacerbation, viral upper respiratory tract infection, and headache. Events were similar across treatment groups (Table 41). Given the previous clinical experience with LAMA/LABA inhalers, specific safety analyses were also performed to assess for cardiac, cerebrovascular, respiratory events and potential anticholinergic and β2-agonist AEs. No large imbalance of these events was observed across treatment groups. Safety analyses from Trial 01 and Trial 36 were consistent with Trials 30 and 31. Overall, these safety analyses across all trials did not reveal new safety concerns and were consistent with the known safety profile of LAMA/LABA porducts for COPD. Overall, the safety results for AB/FF 400/12 µg support the risk-benefit profile in COPD patients.

8.3. Statistical Issues

This review considered following potential statistical issues:

1. Whether the combination rule is satisfied in this FDC drug development program

2. Whether the estimand used by the Applicant in the data analyses is in line with the agency's guidance
3. Whether the efficacy results are robust

Contribution of monocomponent FF 12 µg to the efficacy of the combination is demonstrated by the treatment differences between AB/FF 400/12 µg and AB 400 µg in the co-primary endpoint of change from baseline to Week 24 in FEV_1 at 1 hour post-dose. Contribution of monocomponent AB 400 µg to the efficacy of the combination is demonstrated by the treatment differences between AB/FF 400/12 µg and FF 12 µg in the co-primary endpoint of change from baseline to Week 24 in trough FEV_1 pre-dose. In all three efficacy phase 3 trials (Trials 30, 31 and 01), the contribution of FF 12 µg to the FDC ranged from 0.084 L to 0.125 L after 24 weeks of treatment (1-hour post-dose FEV_1), and the contribution of AB 400 µg to the FDC ranged from 0.045 L to 0.085 L (trough pre-dose FEV_1) after 24 weeks of treatment. All the null hypotheses are rejected at 2 sided 5% significance level, with p-values less than 0.0001. Therefore, we conclude that the program sufficiently demonstrated contribution of each monocomponent to the combination drug product.

In this program, there was a potential statistical issue regarding estimands. In Trials 30 and 31, after subjects discontinued the study treatment, data was not collected by design and the primary efficacy analyses were based on on-treatment data. Therefore, the primary analysis targets an "on-treatment" estimand, which is not preferred from a regulatory perspective.

The rates of missing data in pooled Trials 30 and 31 listed in Table 16 are not comfortably low enough (placebo arm 25.4%, active treatment arms from 13.8% to 16.8%) to obviate a need for sensitivity analyses to check for a data robustness. To estimate de facto or treatment policy estimand which FDA recommends, the Applicant carried out sensitivity analyses using different imputation approaches on the co-primary endpoints. The purpose of the sensitivity analyses is to check whether the de facto estimand is consistent with the primary analysis estimating the "on-treatment" estimand in terms of statistical significance.

For Trials 30 and 31, a sensitivity analysis using a pattern-mixture model based on non-future depedent missing value restrictions was performed to assess the robustness of the primary MMRM results to the possible violation of the missing at-random assumption.

Table 50 and Table 51 present the sensitivity analysis results using a pattern-mixture model for the co-primary endpoints for Trial 31.

Table 52 and Table 53 present the sensitivity analysis results using a pattern-mixture model for the co-primary endpoints for Trial 30.

Under the pattern-mixture model approach, the missing values in all treatment arms are assumed missing not at random. They are imputed by observed value from same treatment arm plus a shift parameter value Δ; here the possible Δ values are 0 L (which assumes the missing value is same as observed value, least conservative), -0.04 L (which assumes the

missing value is worse than the observed value by 0.04 L), and -0.08 L (which assumes missing value is worse than the observed value by 0.08 L, the most conservative approach among these three).

From Table 20, we note that the mean change from baseline in 1-hour post dose FEV_1 at Week 24 for AB 400 µg arm was 0.144 L (in Trial 30) and 0.1389 L (in Trial 31); for AB/FF 400/12 µg arm, it was 0.269 L (in Trial 30) and 0.247 L (in Trial 31). Shift parameter value Δ of -0.08 L is penalizing considerably (~30%) when compared to 0.269 L, the largest mean change from baseline , meaning that missing value is imputed as 30% worse than the observed value. Using this most conservative assumption to impute the missing data, the analysis results remain unchanged in terms of statistical significance; p-values are less than 0.0001 for the comparison of AB/FF 400/12 µg to AB 400 µg (Table 50 for Trial 31 and Table 52 for Trial 30).

Similarily, from Table 21, we note that the mean change from baseline in pre-dose FEV_1 at Week 24 for FF 12 µg arm were -0.002 L (in Trial 30) and 0.050 L (in Trial 31); for AB/FF 400/12 µg arm, they were 0.083 L (in Trial 30) and 0.095 L (in Trial 31). Shift parameter value Δ of -0.08 L (missing value worse than observed value by 0.08L) compared to the largest mean change from baseline of 0.095 L is very large, so it is considered highly unlikely to happen. Using this most conservative assumption to impute the missing data, the analysis results remain unchanged in terms of statistical significance; comparison of AB/FF 400/12 µg to FF 12 µg resulted in p-value of 0.0161 (Table 51 for Trial 31 and Table 53 for Trial 30).

Therefore, we conclude that the sensitivity analyses results support the primary analyses results. We conclude that the primary analyses results were not influenced by the missingness assumptions and the fact that the primary analyses targeted on-treatment estimands.

Table 50: Pattern-Mixture model for the change from baseline in 1-hour morning postdose FEV_1 (L) at Week 24, ITT population (Trial 31)

Shift parameter value Δ	Statistics	AB/FF 400/12 µg (N=335)	AB 400 µg (N=337)
-0.08	LS mean change (SE) LS mean diff (95% CI) p-value vs. AB 400	0.2370 (0.0130) 0.1090 (0.0721, 0.1458) <.0001	0.1281(0.0139)
-0.04	LS mean change (SE) LS mean diff (95% CI) p-value vs. AB 400	0.2429(0.0131) 0.1080 (0.0726, 0.1435) <.0001	0.1349(0.0129)
0	LS mean change (SE) LS mean diff (95% CI) p-value vs. AB 400	0.2454 (0.0129) 0.1066 (0.0699, 0.1433) <.0001	0.1388 (0.0129)

Source: Sponsor's study report of Study 31: Table 14.4.1.3B

Table 51: Pattern-Mixture model for the change from baseline in trough FEV_1 (L) at Week 24, ITT population (Trial 31)

Shift parameter value Δ	Statistics	AB/FF 400/12 µg (N=335)	FF 12 µg (N=332)
-0.08	LS mean change (SE) LS mean diff (95% CI) p-value vs. FF 12	0.0867 (0.0131) 0.0434 (0.0081, 0.0787) 0.0161	0.0433(0.0127)
-0.04	LS mean change (SE) LS mean diff (95% CI) p-value vs. FF 12	0.0904(0.0122) 0.0462 (0.0115, 0.0809) 0.0090	0.0442(0.0127)
0	LS mean change (SE) LS mean diff (95% CI) p-value vs. FF 12	0.0955 (0.0127) 0.0464 (0.0115, 0.0813) 0.0092	0.0491 (0.0132)

Source: Sponsor's study report of Study 31: Table 14.4.1.3A

Table 52: Pattern-Mixture model for the change from baseline in 1-hour morning postdose FEV_1 (L) at Week 24, ITT population (Trial 30)

Shift parameter value Δ	Statistics	AB/FF 400/12 µg (N=335)	AB 400 µg (N=337)
-0.08	LS mean change (SE) LS mean diff (95% CI) p-value vs. AB 400	0.2642 (0.0129) 0.1281 (0.0924, 0.1638) <.0001	0.1204(0.0130)
-0.04	LS mean change (SE) LS mean diff (95% CI) p-value vs. AB 400	0.2670 (0.0128) 0.1287 (0.0932, 0.1642) <.0001	0.1243(0.0129)
0	LS mean change (SE) LS mean diff (95% CI) p-value vs. AB 400	0.2704 (0.0130) 0.1253 (0.0885, 0.1622) <.0001	0.1273 (0.0133)

Source: Sponsor's study report of Study 30: Table 7.

Table 53: Pattern-Mixture model for the change from baseline in trough FEV_1 (L) at Week 24, ITT population (Trial 30)

Shift parameter value Δ	Statistics	AB/FF 400/12 µg (N=335)	FF 12 µg (N=332)
-0.08	LS mean change (SE) LS mean diff (95% CI) p-value vs. FF 12	0.0810 (0.0122) 0.0865 (0.0530, 0.1200) 0.0161	-0.0055(0.0122)
-0.04	LS mean change (SE) LS mean diff (95% CI) p-value vs. FF 12	0.0812(0.0124) 0.0861 (0.0525, 0.1197) <0.0001	-0.0049(0.0124)
0	LS mean change (SE) LS mean diff (95% CI) p-value vs. FF 12	0.0831 (0.0124) 0.0858 (0.0522, 0.1195) <.0001	-0.0028 (0.0122)

Source: Sponsor's study report of Study 30: Table 6.

8.4. Conclusions and Recommendations

The recommended regulatory action is Approval for AB/FF 400/12 µg for the indication of the (b) (4) maintenance treatment of patients with COPD.

In this NDA, the Applicant submitted results from two phase 3, twenty-four week placebo-controlled trials (30 and 31), and one phase 3, twenty-four week active-controlled trial (01) as the primary evidence of efficacy. To support the proposed (b) (4) claim, the Applicant submitted (b) (4) Trials 30 and 31 (the placebo-controlled trials) demonstrated substantial evidence of efficacy with respect to lung function as determined primarily based on statistically significant improvements from baseline in 1 hour post-dose FEV_1 (demonstrating the contribution of FF) and trough FEV_1 (demonstrating the contribution of AB) at Week 24. The increases from baseline to Week 24 in 1 hour post-dose FEV_1 were statistically significantly greater for AB/FF 400/12 µg than for AB 400 µg. Similarly, the increases from baseline to Week 24 in trough FEV_1 were statistically significantly greater for AB/FF 400/12 µg than for FF 12 µg. In addition, AB had a statistically significant reduction of COPD exacerbation compared to placebo in Trial 02. Efficacy was also supported by other secondary spirometric endpoints as well as numerical improvements in symptoms based on SGRQ responder analysis.

This assessment of clinical safety primarily focuses on the two 24-week placebo-controlled trials (30 and 31), one 24-week active-controlled trial (01), and one placebo-controlled trial (36), a 28-week extension to trial 31. No large imbalance of safety signals was observed across treatment groups. These safety analyses did not reveal new safety concerns and were consistent with the known safety profile of LAMA/LABA inhaler.

The overall risk-benefit assessment supports approval of Duaklir Pressair. The clinical recommendation is Approval.

9. Advisory Committee Meeting and Other External Consultations

No Advisory committee meeting and other external consultations were necessary for this NDA.

10. Pediatrics

This product is indicated for the treatment of COPD, an adult-related disease that rarely or never occurs in pediatric patients. Pediatric Research Equity Act (PREA) waiver was requested and granted.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The label proposed by the Applicant was edited for consistency with current labeling guidelines as well as consistency with labels from similar products (i.e., other LAMA/LABA). The Applicant proposed the following indication:

DUAKLIR PRESSAIR is a combination of aclidinium bromide (an anticholinergic) and formoterol fumarate (a LABA) indicated for:

- the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4) . (b) (4)

This indication is fairly typical of how the Division has historically approached indication statements for inhaled COPD products. However, the Division's current approach to indication statements for inhaled COPD products has evolved.

Given the potential for multiple claims [airflow obstruction, exacerbations, St. George's Respiratory Questionnaire (SGRQ)] in COPD programs, the Division has determined that a more general COPD indication is appropriate for inhaled products (including monotherapies and fixed-dose combinations). To this end, the Division's new approach to COPD indications for inhaled products will no longer include separate indications for the maintenance treatment of airflow obstruction and exacerbation reduction, but will rather be more general. A more general COPD indication is consistent with the approach taken for labeling other recently approved products in the Division, e.g. asthma and rheumatoid arthritis.

Details of clinical trials supporting efficacy in COPD with respect to the different efficacy endpoints (e.g., forced expiratory volume in 1 second (FEV_1), exacerbation, SGRQ) will be included in Section 14 of the product label.

Labels for LABA containing products have in the past included a box-warning for asthma related deaths, even if the products were not indicated for asthma. However, this product label will not include such a box warning. This is due to the results of large safety trials that the FDA required the sponsors for Dulera, Symbicort, Advair Diskus, and Foradil to conduct to evaluate the safety of ICS/LABA in asthma. These studies are referred to as the ICS/LABA safety trials. Given that the results of the ICS/LABA safety trials did not show a significantly increased risk of serious asthma-related events for ICS/LABAs compared to ICS alone, the boxed warning for asthma related death from the labeling of ICS/LABA combination therapies was removed (see Division Director Review for NDAs 21077, 21929, 22518, 21254, 204275, and 208799 by Dr. Sally Seymour dated 12/20/2017). The Division acknowledges that this does not change the risk for asthma-related death for LABA monotherapy. However, as Duaklir will be approved for patients with COPD and the off-label use of LABA monotherapy

for asthma is limited, it was felt that a box-warning was not necessary for this product as the risk can adequately be addressed within the Contraindications and Warnings and Precautions sections of the Prescribing information.

12. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are needed for this application.

13. Postmarketing Requirements and Commitment

No PMRs or PMCs are needed for this application.

14. Division Director (Clinical) Comments

The Applicant submitted NDA 210595 to support the approval of a fixed-dose combation product (FDC) of aclidinium bromide (AB) 400 µg with formoterol fumarate (FF) 12 mcg (LAMA/LABA) for the maintenance treatment of patients with COPD. The Applicant has submitted data to support that AB/FF 400/12 µg improves both airflow obstruction and reduces COPD exacerbation.

Support for the improvement in airflow obstruction (lung function) relies primarily on three trials: 1) Trials 30 and 31 – 24-week, placebo-controlled trials with the typical factorial design and 2) Trial 01 – a 24-week, active-controlled (tiotropium) trial which included AB, FF, and AB/FF treatment arms. Trials 30, 31, and 01 demonstrated substantial evidence of efficacy as determined primarily based on statistically significant improvements in the co-primary endpoints, change from baseline in trough FEV_1 (AB/FF vs FF to demonstrate the contribution of AB) and 1 hour post-dose FEV_1 (AB/FF vs. AB to demonstrate the contrinution of FF) at Week 24. Other secondary spirometric endpoints as well as SGRQ were supportive of the primary endpoint.

Support for the reduction in COPD exacerbations relies on the Trial 02 (ASCENT) – a 36-month trial submitted and reviewed under sNDA 202450 (supplement 12). In Trial 02, AB 400 µg demonstrated a statistically significant benefit in on-study exacerbations when compared with placebo. As the LABA and LAMA in this FDC are pharmaceutically equivalent to their monoproduct counterparts, scientifically, the two drugs are not expected to have a negative interaction in terms of exacerbation reduction. As such, AB/FF 400/12 µg should retain the exacerbation benefit of the AB 400 µg component and the data from the ASCENT trial will be included in Section 14 of the Duaklir product label.

Given the potential for multiple claims [airflow obstruction, exacerbations, St. George's Respiratory Questionnaire (SGRQ)] in COPD programs, the Division has determined that a more general COPD indication is appropriate for inhaled products (including monotherapies and fixed-dose combinations). To this end, the Division's new approach to COPD indications for inhaled products will no longer include separate indications for the maintenance treatment of airflow obstruction and exacerbation reduction, but will rather be more general. A more general COPD indication is consistent with the approach taken for labeling other recently approved products in the Division, e.g. asthma and rheumatoid arthritis. Details of clinical trials supporting efficacy in COPD with respect to the different efficacy endpoints (e.g., forced expiratory volume in 1 second (FEV_1), exacerbation, SGRQ) will be included in Section 14 of the product label.

Overall, the data demonsrate substantial evidence of efficacy for Duaklir Pressair for the treatment of patients with COPD. No new safety signals were identified in this clinical program. These classes of drugs have been commonly used in COPD and their safety/efficacy

profiles are well-understood. The recommendations for approval from the various disciplines are noted. The regulatory action for NDA 210595 for Duaklir Pressair is *Approval.*

15. Appendices

15.1. References

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): M/40464/30

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 193 (Principal investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

In Trial M/40464/30 two investigators reported discloseable financial interests, which were significant equity interest in the sponsor of covered study. This were determined to not have significant impact upon the conduct of this clinical trial, given that the study was randomized,

double-blinded, placebo-controlled trial, with objective spirometric related endpoints, and since each investigator was only responsible for enrolling a small number of patients to this multi-center trial.

Covered Clinical Study (Name and/or Number): LAC-MD-31

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 239 (Principal investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 4		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 56		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

In Trial LAC-MD-31, four investigators reported discloseable financial interests, which were significant equity interest in the sponsor of the covered study. These were determined to not have significant impact upon the conduct of this clinical trial, given that the study was randomized, double-blinded, placebo-controlled trial, with objective spirometric related endpoints, and since each investigator was only responsible for enrolling a small number of patients to this multi-center trial.

Covered Clinical Study (Name and/or Number): D6571C00001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 174 (Principal investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

BANU A KARIMI SHAH
03/27/2019 07:27:38 PM
signing with the delegated authority of Dr. Sally Seymour, Acting Division Director, DPARP

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 210595 and NDA 202450/S-012
Supporting document/s:	SDN 1 (0001); SDN 580 (0126)
Applicant's letter date:	May 31, 2018; May 31, 2018
CDER stamp date:	May 31, 2018; May 31, 2018
Product:	Duaklir Pressair (aclidinium bromide/formoterol fumarate) Inhalation Powder; and Tudorza Pressair (aclidinium bromide) Inhalation Powder
Indication:	Chronic Obstructive Pulmonary Disease (COPD)
Applicant:	AstraZeneca Pharmaceuticals LP
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Reviewer:	Anup K. Srivastava, Ph.D.
Supervisor/Team Leader:	Carol M. Galvis, Ph.D.
Division Director:	Sally Seymour, M.D.
Project Manager:	Ngoc-Linh Do and Sadaf Nabavian

Template Version: September 1, 2010

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summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210595 and NDA 202450/S-012.

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1 Executive Summary

1.1 Introduction

This review evaluates the Pregnancy and Lactation Labeling Rule (PLLR) content for DUAKLIR PRESSAIR (aclidinium bromide/formoterol fumarate) and Tudorza Pressair (aclidinium bromide) inhalation powder submitted by AstraZeneca under NDA 210595 on May 31, 2018 and under NDA 202450/S-012 on May 31, 2018, respectively. The proposed delivered dose for Duaklir Pressair (aclidinium/formoterol) is one oral inhalation of 400/12 mcg twice daily (BID), and for Tudorza Pressair (aclidinium) is one oral inhalation of 400 mcg BID. The proposed indication for Duaklir Pressair is the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4). The approved indication for Tudorza Pressair is the (b) (4) maintenance treatment of (b) (4) COPD (b) (4).

Aclidinium bromide is a long-acting muscarinic antagonist (LAMA) approved at a delivered dose of 400 mcg BID maintenance bronchodilator treatment for COPD under NDA 202450 as Tudorza Pressair. Tudorza is also listed as a reference product for the aclidinium bromide component of Duaklir. The labeling for Tudorza is in the PLR (Prescription Labeling Rule) format and is converted into PLLR format in this review. Formoterol fumarate dihydrate is a selective long-acting beta$_2$-adrenergic receptor agonist (LABA) indicated as a bronchodilator therapy for the treatment of COPD. Symbicort (budesonide/formoterol) at a maximum delivered dose of 160/4.5 mcg, two inhalations BID is an approved product under NDA 021929 and is listed as a reference product for the formoterol fumarate component of Duaklir. The labeling for Symbicort is already in PLLR format. The rationale for combined use of a LABA and a LAMA stems from the fact that several studies have shown a greater improvement in reduction of airflow obstruction and decreased use of rescue medication with LAMA/LABA combination as compared with the use of either pharmacologic class alone.

The following nonclinical sections of the revised label were reviewed and are discussed below: Section 8.1 “Pregnancy”, Section 8.2 “Lactation”, and Section 13 “Nonclinical Toxicology”.

1.3 Recommendations

The content of the nonclinical sections in the proposed labeling was evaluated. Besides the sponsor’s proposed changes, minor edits are recommended in accordance with current Agency labeling practice for nonclinical sections (see below *Integrated Summary*).

1.3.3 Final Labeling

8.1 Pregnancy

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Risk Summary

There are no adequate and well-controlled studies of DUAKLIR or its individual components, formoterol fumarate or aclidinium bromide, in pregnant women to inform drug-associated risks.

No adverse developmental effects were seen with inhalation administration of aclidinium bromide to pregnant rats and rabbits during organogenesis at 15 or 20 times, respectively, the maximum recommended human daily inhaled dose (MRHDID). However, reduced pup weights were seen when pregnant rats continued inhalation administration through lactation at 5 times the MRHDID of aclidinium bromide. Adverse developmental effects occurred when rabbits were orally dosed with aclidinium bromide at approximately 1,400 times the MRHDID [*see Data*].

Formoterol fumarate alone, administered by the oral route, was teratogenic in rats and rabbits at 1,200 and 49,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats at 85 times the MRHDID. These adverse effects generally occurred at large multiples of the MRHDID when formoterol fumarate was administered by the oral route to achieve high systemic exposures. No teratogenic, embryocidal, or developmental effects were seen in rats that received inhalation doses up to 280 times the MRHDID [*see Data*].

The estimated background risk of major birth defects and miscarriage of the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Labor or Delivery

There are no well-controlled human studies that have investigated the effects of DUAKLIR during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of DUAKLIR during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Data

Animal Data

Aclidinium bromide

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-17, no evidence of structural alterations was observed at approximately 15 times the maximum recommended human daily inhaled dose (MRHDID) [based on summed AUCs of aclidinium bromide and its metabolites at

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inhaled doses less than or equal to 5.0 mg/kg/day]. However, in a pre- and post-natal development study, decreased pup weights were observed when pregnant rats were exposed from gestation day 6 and continuing during the lactation period at approximately 5 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at inhaled doses greater than or equal to 0.2 mg/kg/day]. Maternal toxicity was also observed at inhaled doses greater than or equal to 0.2 mg/kg/day.

In an embryo-fetal development study in pregnant Himalayan rabbits administered inhaled doses of aclidinium bromide during the period of organogenesis from gestation days 6-19, no evidence of structural alterations was observed at approximately 20 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at inhaled doses less than or equal to 3.6 mg/kg/day]. However, in another embryo-fetal development study in pregnant Himalayan rabbits dosed orally from gestation days 6-19, increased incidences of additional liver lobes (3-5%), as compared to 0% in the control group, were observed at approximately 1,400 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at oral doses greater than or equal to 150 mg/kg/day], and decreased fetal body weights were observed at approximately 2,300 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at oral doses greater than or equal to 300 mg/kg/day]. These fetal findings were observed in the presence of maternal toxicity.

Formoterol fumarate

In a fertility and reproduction study, male rats were orally dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were either dosed up to gestation day 19 or up until weaning of their offspring. Males were dosed up to 25 weeks. Umbilical hernia was observed in rat fetuses at oral doses 1,200 times and greater than the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and higher). Brachygnathia, abnormal shortness of the mandible, was observed in rat fetuses at a dose 6,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 15 mg/kg/day). Pregnancy was prolonged at a dose 6,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 15 mg/kg/day). Fetal and pup deaths occurred at doses approximately 1,200 times the MRHDID and higher (on a mg/m^2 basis at oral doses of 3 mg/kg/day and higher) during gestation.

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, no teratogenic, embryocidal or developmental effects were seen at doses up to 280 times the MRHDID (on a mg/m^2 basis with maternal inhalation doses up to 0.69 mg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, subcapsular cysts on the liver were observed in the fetuses at a dose 49,000 times the MRHDID (on a mg/m^2 basis with a maternal oral dose of 60 mg/kg/day). No teratogenic effects were observed at doses up to 2,800 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

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In a pre- and post-natal development study, pregnant female rats received formoterol at oral doses of 0, 0.21, 0.84, and 3.4 mg/kg/day from gestation day 6 through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 85 times the MRHDID and higher (on a mg/m^2 basis at maternal oral doses of 0.21 mg/kg/day and higher), although there was no evidence of a dose-response relationship. There were no treatment-related effects on the physical, functional, and behavioral development of rat pups.

8.2 Lactation

Risk Summary

There are no available data on the effects of DUAKLIR, aclidinium bromide, or formoterol fumarate on the breastfed child or on milk production or presence in human milk. Both aclidinium bromide and formoterol fumarate are present in rat milk [*see Data*]. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUAKLIR and any potential adverse effects on the breastfed child from DUAKLIR or from the underlying maternal condition.

Data

In a pharmacokinetic study, levels of radioactivity in milk and plasma in rats were measured after a single intravenous dose of 1 mg/kg of radiolabeled aclidinium bromide on approximately post-natal day 14 *[see Use in Specific Populations (8.1)]*. The maximum concentration of radioactivity [^{14}C-aclidinium] in milk was measured at 6 hours post-dose and was found to be 3-12 times higher than in plasma.

In the fertility and reproduction study in rats, plasma levels of formoterol were measured in pups on post-natal day 15 *[see Use in Specific Populations (8.1)]*. It was estimated that the maximum plasma concentration that the pups received from the maternal animal, at the highest dose of 15 mg/kg, after nursing was 4.4% (0.24 nmol/L for a litter vs. 5.5 nmol/L for the mother).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals with the combination of aclidinium bromide and formoterol fumarate, to evaluate the potential for carcinogenesis, mutagenesis, or impairment of fertility, have not been performed. The data described below is from studies conducted on the individual components.

Aclidinium Bromide

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Two-year inhalation studies were conducted in mice and rats to assess the carcinogenic potential of aclidinium bromide. No evidence of tumorigenicity was observed in rats and mice at aclidinium doses up to 0.20 and 2.4 mg/kg/day, respectively [approximately 10 and 80 times the Maximum Recommended Human Daily Inhalation Dose (MRHDID), respectively, based on summed AUCs of aclidinium bromide and its metabolites].

Aclidinium bromide was positive in the *in vitro* bacterial gene mutation assay and the *in vitro* thymidine locus mouse lymphoma assay. However, aclidinium bromide was negative in the *in vivo* mouse micronucleus assay and the *in vivo/in vitro* unscheduled DNA synthesis assay with rat liver.

Aclidinium bromide impaired several fertility and reproductive performance indices (increased number of days to mate, decreased conception rate, decreased number of corpora lutea, increased pre-implantation loss with consequent decreased number of implantations and live embryos) in both male and female rats administered inhaled doses greater than or equal to 0.8 mg/kg/day [approximately 15 times the MRHDID based on summed AUCs of aclidinium bromide and its metabolites]. These adverse fertility effects were observed in the presence of paternal toxicity as evidenced by mortality and decreased body weight gain. However, there were no effects on mating index and sperm number and morphology. In the separate fertility assessments (treated males mated with untreated females; treated females mated with untreated males), no effect was observed in male and female rats at inhaled doses of 1.9 and 0.8 mg/kg/day, respectively [approximately 30 and 15 times the MRHDID, respectively, based on summed AUCs of aclidinium bromide and its metabolites].

Formoterol Fumarate

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate.

In a 24-month carcinogenicity study in CD-1 mice, formoterol fumarate at oral doses of 0.1 mg/kg and above [approximately 20 times the maximum recommended human daily inhalation dose (MRHDID) on a mg/m^2 basis] caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 0.13 mg/kg (approximately 55 times the MRHDID on a mg/m^2 basis). No tumors were seen at 0.022 mg/kg (approximately 9 times the MRHDID on a mg/m^2 basis).

Other beta-agonist drugs have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown.

Formoterol fumarate was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, and rat micronucleus test.

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A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 6,000 times the MRHDID on a mg/m^2 basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 6,000 times the MRHDID on a mg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No such effect was seen at 3 mg/kg (approximately 1,200 times the MRHDID on a mg/m^2 basis). No effect on fertility was detected in female rats at doses up to 15 mg/kg (approximately 6,000 times the MRHDID on a mg/m^2 basis).

11 Integrated Summary and Safety Evaluation

AstraZeneca Pharmaceuticals, LP submitted the labeling for Duaklir Pressair (aclidinium bromide/formoterol fumarate) and for Tudorza Pressair (aclidinium bromide) inhalation powder on May 31, 2018 under NDA 210595 and under NDA 202450/S-012, respectively. The labeling follows the PLLR format that revises the PLR content and format requirements for subsections 8.1 through 8.3 of section 8 USE IN SPECIFIC POPULATIONS of the prescribing information described in 21 CFR 201.57(c)(9)(i) through (c)(9)(iii).

Duaklir Pressair is a LAMA/LABA combination of aclidinium bromide/formoterol fumarate indicated for the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD (b) (4) . The intended therapeutic dose of aclidinium bromide/formoterol fumarate is one oral inhalation of 400/12 mcg BID. Tudorza Pressair consists of aclidinium bromide monotherapy, which is a LAMA and is indicated for the (b) (4) maintenance treatment of (b) (4) COPD (b) (4) . The intended therapeutic dose of aclidinium bromide is one oral inhalation of 400 mcg BID.

The reference listed drugs for the individual components of Duaklir are: Tudorza at 400 mcg BID (NDA 202450) for aclidinium bromide and Symbicort (budesonide/formoterol) at maximum dose of 160/4.5 mcg, two inhalations BID (NDA 021929) for formoterol. The approved PLR label for Tudorza Pressair (aclidinium bromide) inhalation powder was supported by nonclinical data reviewed under NDA 202450 by Pharm Tox reviewer Dr. Grace Lee dated March 13, 2012 and the approved PLLR label for Symbicort (budesonide/formoterol) inhalation powder was supported by nonclinical data reviewed under NDA 021929 by Pharm Tox reviewer Dr. Timothy Robison dated December 21, 2016.

The following nonclinical sections of the revised label were reviewed and are discussed below: Section 8.1 “Pregnancy”, Section 8.2 “Lactation”, and Section 13 “Nonclinical Toxicology”. Besides the sponsor’s proposed changes, minor edits are recommended in accordance with current Agency labeling practice for nonclinical sections.

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The proposed labeling language with reviewer's recommended labeling is shown below. Deleted text is shown as strikethrough ~~text~~ and inserted text is shown in red font.

LABELING EDITS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DUAKLIR or its individual components, formoterol fumarate or aclidinium bromide, in pregnant women to inform drug-associated risks.

No [redacted] (b) (4) -adverse developmental effects were seen with inhalation administration of aclidinium bromide to [redacted] (b) (4) pregnant rats and rabbits during organogenesis [redacted] (b) (4) at 15 or 20 times, respectively, the maximum recommended human daily inhaled dose (MRHDID) [redacted] (b) (4) . However, reduced pup weights were seen when pregnant rats continued inhalation administration [redacted] (b) (4) through lactation at 5 times the MRHDID of aclidinium bromide. Adverse [redacted] (b) (4) developmental effects occurred when rabbits were orally dosed with aclidinium bromide at approximately 1,400 times [redacted] (b) (4) the MRHDID [*see Data*] [redacted] (b) (4) .

Formoterol fumarate alone, administered by the oral route, was teratogenic in rats and rabbits at 1,200 and 49,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats at 85 times the MRHDID. These adverse effects generally occurred at large multiples of the MRHDID when formoterol fumarate was administered by the oral route to achieve high systemic exposures. No teratogenic, embryocidal, or developmental effects were seen in rats that received inhalation doses up to 280 times the MRHDID [*see Data*].

The estimated background risk of major birth defects and miscarriage of the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Labor or Delivery

There are no well-controlled human studies that have investigated the effects of DUAKLIR during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of DUAKLIR during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Data

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Animal Data

Aclidinium bromide

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-17, no evidence of structural alterations was observed at approximately 15 times the maximum recommended human daily inhaled dose (MRHDID) [based on summed AUCs of aclidinium bromide and its metabolites at inhaled doses less than or equal to 5.0 mg/kg/day]. However, in a pre- and post-natal development study, decreased pup weights were observed when pregnant rats were (b) (4) exposed from gestation day 6 and continuing during the lactation period at approximately 5 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at inhaled doses greater than or equal to 0.2 mg/kg/day]. Maternal toxicity was also observed at inhaled doses greater than or equal to 0.2 mg/kg/day.

In an embryo-fetal development study in pregnant Himalayan rabbits administered inhaled doses of aclidinium bromide during the period of organogenesis from gestation days 6-19, no evidence of structural alterations was observed (b) (4) at approximately 20 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at inhaled doses less than or equal to 3.6 mg/kg/day]. However, in another embryo-fetal development study in pregnant Himalayan rabbits dosed orally from gestation days 6-19, increased incidences of additional liver lobes (3-5%), as compared to 0% in the control group, were observed at approximately 1,400 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at oral doses greater than or equal to 150 mg/kg/day], and decreased fetal body weights were observed at approximately 2,300 times the MRHDID [based on summed AUCs of aclidinium bromide and its metabolites at oral doses greater than or equal to 300 mg/kg/day]. These fetal findings were observed in the presence of maternal toxicity.

Formoterol fumarate

In a fertility and reproduction study, male rats were orally dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were either dosed up to gestation day 19 or up until weaning of their offspring. Males were dosed up to 25 weeks. Umbilical hernia was observed in rat fetuses at oral doses 1,200 times and greater than the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and higher). Brachygnathia, abnormal shortness of the mandible, was observed in rat fetuses at a dose 6,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 15 mg/kg/day). Pregnancy was prolonged at a dose 6,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 15 mg/kg/day). Fetal and pup deaths occurred at doses approximately 1,200 times the MRHDID and higher (on a mg/m^2 basis at oral doses of 3 mg/kg/day and higher) during gestation.

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, no teratogenic, embryocidal or developmental

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effects were seen at doses up to 280 times the MRHDID (on a mg/m^2 basis with maternal inhalation doses up to 0.69 mg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, subcapsular cysts on the liver were observed in the fetuses at a dose 49,000 times the MRHDID (on a mg/m^2 basis with a maternal oral dose of 60 mg/kg/day). No teratogenic effects were observed at doses up to 2,800 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to (b) (4) 3.5 mg/kg/day).

In a pre- and post-natal development study, pregnant female rats received formoterol at oral doses of 0, 0.21, 0.84, and 3.4 mg/kg/day from gestation day 6 through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 85 times the MRHDID and higher (on a mg/m^2 basis at maternal oral doses of 0.21 mg/kg/day and higher), although there was no evidence of a dose-response relationship. There were no treatment-related effects on the physical, functional, and behavioral development of rat pups.

8.2 Lactation

Risk Summary

There are no available data on the effects of DUAKLIR, aclidinium bromide, or formoterol fumarate on the breastfed child or on milk production or presence in human milk. Both (b) (4) aclidinium bromide and formoterol fumarate are present in rat milk [*see Data*]. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUAKLIR and any potential adverse effects on the breastfed (b) (4) child from DUAKLIR or from the underlying maternal condition.

Data

In a pharmacokinetic study, levels of radioactivity in milk and plasma in rats were measured after a single intravenous dose of 1 mg/kg of radiolabeled aclidinium bromide on approximately post-natal day 14 *[see Use in Specific Populations (8.1)]*. The maximum concentration of radioactivity [^{14}C-aclidinium] in milk was measured at 6 hours post-dose (b) (4) and was found to be (b) (4) times higher than in plasma (b) (4) (b) (4)

In the fertility and reproduction study in rats, plasma levels of formoterol were measured in pups on post-natal day 15 *[see Use in Specific Populations (8.1)]*. It was estimated that the maximum plasma concentration that the pups received from the maternal animal, at

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the highest dose of 15 mg/kg, after nursing was 4.4% (0.24 nmol/L for a litter vs. 5.5 nmol/L for the mother).

Reviewer's Comments: The proposed text for Section 8.2 Lactation Risk Summary and Data was revised as per most recent labeling practice. Under the Risk Summary, a statement was added that suggested that if the drug is present in animal milk then there is high probability for the drug to be present in human milk as well. Under Data section, the maximum radioactivity of aclidinium in milk was compared with that in plasma following a single intravenous dose of 1 mg/kg aclidinium bromide on post-natal day 14. The maximum concentration of radioactivity in milk relative to plasma was found to be 12.5 times and 2.7 times higher in [glycolyl-U-^{14}C]-aclidinium (Study No. AML/07) and [phenyl-U-^{14}C]-aclidinium (Study No. AML/05), respectively. This suggests that aclidinium was present in animal milk at a higher concentration as compared to the plasma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals with the combination of aclidinium bromide and formoterol fumarate, to evaluate the potential for carcinogenesis, mutagenesis, or impairment of fertility, have not been performed. The data described below is from studies conducted on the individual components.

Aclidinium Bromide

Two-year inhalation studies were conducted in mice and rats to assess the carcinogenic potential of aclidinium bromide. No evidence of tumorigenicity was observed in rats and mice at aclidinium doses up to 0.20 and 2.4 mg/kg/day, respectively [approximately 10 and 80 times the Maximum Recommended Human Daily Inhalation Dose (MRHDID), respectively, based on summed AUCs of aclidinium bromide and its metabolites].

Aclidinium bromide was positive in the *in vitro* bacterial gene mutation assay and the *in vitro* thymidine locus mouse lymphoma assay. However, aclidinium bromide was negative in the *in vivo* mouse micronucleus assay and the *in vivo/in vitro* unscheduled DNA synthesis assay with rat liver.

Aclidinium bromide impaired several fertility and reproductive performance indices (increased number of days to mate, decreased conception rate, decreased number of corpora lutea, increased pre-implantation loss with consequent decreased number of implantations and live embryos) in both male and female rats administered inhaled doses greater than or equal to 0.8 mg/kg/day [approximately 15 times the MRHDID based on summed AUCs of aclidinium bromide and its metabolites]. These adverse fertility effects were observed in the presence of paternal toxicity as evidenced by mortality and decreased body weight gain. However, there were no effects on mating index and sperm number and morphology. In the separate fertility assessments (treated males mated with

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untreated females; treated females mated with untreated males), no effect was observed in male and female rats at inhaled doses of 1.9 and 0.8 mg/kg/day, respectively [approximately 30 and 15 times the MRHDID, respectively, based on summed AUCs of aclidinium bromide and its metabolites].

Formoterol Fumarate

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate.

In a 24-month carcinogenicity study in CD-1 mice, formoterol fumarate at oral doses of 0.1 mg/kg and above [approximately 20 times the maximum recommended human daily inhalation dose (MRHDID) on a mg/m^2 basis] caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 0.13 mg/kg (approximately 55 times the MRHDID on a mg/m^2 basis). No tumors were seen at 0.022 mg/kg (approximately 9 times the MRHDID on a mg/m^2 basis).

Other beta-agonist drugs have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown.

Formoterol fumarate was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, and rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 6,000 times the MRHDID on a mg/m^2 basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 6,000 times the MRHDID on a mg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No such effect was seen at 3 mg/kg (approximately 1,200 times the MRHDID on a mg/m^2 basis). No effect on fertility was detected in female rats at doses up to 15 mg/kg (approximately 6,000 times the MRHDID on a mg/m^2 basis).

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Table 1. Animal to human dose ratio calculations for aclidinium bromide

Drug	Aclidinium bromide				
Summed AUC values of human dose of 400 µg BID = 39.77 ng.hr/mL					
	Route	**Dose (mg/kg/day)**	**Summed AUC at NOAEL (ng.h/mL)**	**AUC exposure ratio**	**Rounded AUC exposure ratio**
Fertility and Reproduction					
Male and Female rat	Inhalation	0.8	575.8	14.8	15
Male rat	Inhalation	1.9	1233.3	31.0	30
Female rat	Inhalation	0.8	596.6	15.0	15
Teratogenicity					
Rat	Inhalation	5.0	534.9[a]	13.45	15
Rabbit	Inhalation	3.6	847.9[a]	21.3	20
Rabbit	Oral	150	56771.7	1427.6	1400
Rabbit	Oral	300	91874.7	2310.4	2300
Pre- and Post-natal development					
Rat	Inhalation	0.2	192.3[b]	4.84	5
Carcinogenicity					
Mouse	Inhalation	2.4	3237.0	81.4	80
Rat	Inhalation	0.2	375.8	9.45	10

-NOAEL from the inhalation studies were expressed as an achieved dose
-Summed AUC is addition of the parent compound (LAS 34273) and two metabolites (LAS 34823 and LAS 34850).
-The AUC values of human dose of 400 µg BID, which are the overall mean values extrapolated from those obtained in young and elderly COPD patients (n = 24) on day 3 of treatment with an inhaled daily dose of 400 µg QD (clinical study No. M/34273/09).
[a] In the inhalational teratology studies in rats and rabbits, only AUC_{0-7} values, not AUC_{0-24} values, were obtained. The report stated that the AUC_{0-7} is AUC from zero to the last

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quantifiable value, which was obtained after completing two daily administrations. Thus, summed AUC values from these studies were AUC_{0-7} values.
[b] TK data were not collected in the pre- and postnatal development (PPND) study. Since the carcinogenicity rat study was conducted more recently than other toxicity studies with TK evaluation (the carcinogenicity study was initiated in June, 2004 and the PPND study was initiated in April, 2006), the AUC data (week 26 from female rats at 0.2 mg/kg/day) from the carcinogenicity study was used for exposure ratio calculation.

Table 2. Animal to human dose ratio calculations for formoterol fumarate

Drug	Formoterol fumarate							
		mcg/dose	#daily doses	mcg/day	kg	mcg/kg	factor	mcg/m^2
Adult (>12 yrs.)		12	2	24	60	0.4	25	14.8
	Route	mcg/kg/d	conv. factor	mcg/m^2	Dose ratio	Rounded dose ratio		
Fertility and Reproduction								
Rat	Oral	3000	6	18000	1216.22	1200		
Rat	Oral	15000	6	90000	6081.08	6000		
Teratogenicity								
Rat	Inhalation	690	6	4140	279.73	280		
Rabbit	Oral	3500	12	42000	2837.84	2800		
Rabbit	Oral	60000	12	720000	48648.65	49000		
Pre- and Post-natal development								
Rat	Oral	210	6	1260	85.14	85		
Carcinogenicity								
Mouse	Oral	100	3	300	20.27	20		
Rat	Inhalation	22	6	132	8.92	9		
Rat	Inhalation	130	6	780	52.70	55		

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/s/

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02/04/2019 12:05:55 PM

CAROL M GALVIS
02/04/2019 01:14:57 PM
I concur.