CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212122Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212122
Priority or Standard	Priority
Submit Date(s)	January 23, 2020
Received Date(s)	January 23, 2020
PDUFA Goal Date	July 23, 2020
Division/Office	Division of Pulmonology, Allergy, and Critical Care Products/OII
Review Completion Date	July 23, 2020
Established/Proper Name	Budesonide, glycopyrrolate, and formoterol fumarate
(Proposed) Trade Name	Breztri Aerosphere
Pharmacologic Class	Inhaled corticosteroid, LAMA, LABA combination
Code name	PT010
Applicant	AstraZeneca AB
Dosage form	Inhalation aerosol
Applicant proposed Dosing Regimen	Two inhalations (budesonide 320 µg, glycopyrrolate 18 µg, and formoterol fumarate 9.6 µg) twice daily
Applicant Proposed Indication(s)/Population(s)	Maintenance treatment of adult patients with chronic obstructive pulmonary disease (COPD)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	13645005
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with COPD
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	13645005
Recommended Dosing Regimen	Two inhalations (budesonide 320 µg, glycopyrrolate 18 µg, and formoterol fumarate 9.6 µg) twice daily

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Linda Ebonine, PA-C
Nonclinical Reviewer	Ijeoma Uzoma, PhD
Nonclinical Team Leader	Timothy Robison, PhD
Office of Clinical Pharmacology Reviewer(s)	Yunzhao Ren, MD, PhD
Office of Clinical Pharmacology Team Leader(s)	Bhawana Saluja, PhD
Clinical Reviewer	Aishah Ali, MD
Clinical Team Leader	Robert Lim, MD
Statistical Reviewer	Mingyu Xi, PhD
Statistical Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Robert Lim, MD
Division Director (DPACC)	Sally Seymour, MD
Office Director (or designated signatory authority)	Sally Seymour, MD

Additional Reviewers of Application

OPQ/ONDP	Craig Bertha(ATL), Renishkumar Delvadia, Soumya Mitra, Donna Christner
OPQ/OPMA	Ramesh Dandu, PhD; Yong Hu, PhD
OPQ/OPRO	Florence Aisida/Grace Gnall
ORA Lead/CDRH OC	Emre Genca
OPDP	Taylor Burnett / Kathleen Klemm
OSI	Tina Chang / Min Lu
OSE/DEPI	
OSE/DMEPA	Cristina Attinello / Ashleigh Lowery
OSE/DRISK	
Other/Patient Labeling	Sharon Williams / Marcia Williams

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

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ijeoma Uzoma, Ph.D.	Division of Pharmacology-Toxicology for Immunology & Inflammation, Office of Immunology and Inflammation	Section: 5	Select one: _X_ Authored ___ Approved
	Signature: Ijeoma K. Uzoma -S Digitally signed by Ijeoma K. Uzoma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002231243, cn=Ijeoma K. Uzoma -S Date: 2020.07.23 09:13:20 -04'00'			
Nonclinical Supervisor	Timothy W. Robison, Ph.D., D.A.B.T.	Division of Pharmacology-Toxicology for Immunology & Inflammation, Office of Immunology and Inflammation	Section: 5	Select one: _X_ Authored _X_ Approved
	Signature: Timothy W. Robison -S Digitally signed by Timothy W. Robison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300110610, cn=Timothy W. Robison -S Date: 2020.07.23 09:20:34 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Yunzhao Ren	OTS/OCP/DIIP	Section: 6	Select one: _X_ Authored ___ Approved
	Signature: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yunzhao Ren -S, 0.9.2342.19200300.100.1.1=2000971048 Date: 2020.07.23 09:31:05 -04'00'			
Clinical Pharmacology Team Leader	Bhawana Saluja	OTS/OCP/DIIP	Section: 6	Select one: ___ Authored _X_ Approved
	Signature: Jianmeng Chen on behalf of Bhawana Saluja Jianmeng Chen -S Digitally signed by Jianmeng Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianmeng Chen -S, 0.9.2342.19200300.100.1.1=2000743816 Date: 2020.07.23 09:34:49 -04'00'			
Clinical Reviewer	A'ishah Ali, MD	OND/ODEII/DPACC	Sections: 1-4, 7-13, 19	Select one: _X__ Authored ___ Approved
	Signature: A'ishah Ali -S Digitally signed by A'ishah Ali -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=A'ishah Ali -S, 0.9.2342.19200300.100.1.1=1001476496 Date: 2020.07.23 09:57:43 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Robert Lim, MD	OND/ODEII/DPACC	Sections: All	Select one: _X_ Authored _X_ Approved
	Signature: Robert H. Lim -S Digitally signed by Robert H. Lim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Robert H. Lim -S, 0.9.2342.19200300.100.1.1=2000596695 Date: 2020.07.23 10:26:06 -04'00'			
Division Director (Clinical)	Sally Seymour, MD	OND/ODEII/DPACC	Sections: All	Select one: ___ Authored _X__ Approved
	Signature: Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour -S Date: 2020.07.23 10:55:47 -04'00'			
Statistical Reviewer	Mingyu Xi, PhD	OB/DBIII	Sections: 8.1, 8.3	Select one: _X_ Authored ___ Approved
	Signature: Mingyu Xi -S Digitally signed by Mingyu Xi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mingyu Xi -S, 0.9.2342.19200300.100.1.1=2001034850 Date: 2020.07.23 09:40:33 -04'00'			
Statistical Team Leader	Yongman Kim, PhD	OB/DBIII	Sections: 8	Select one: ___ Authored _X__ Approved
	Signature: Yongman Kim -S Digitally signed by Yongman Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yongman Kim -S, 0.9.2342.19200300.100.1.1=1300218531 Date: 2020.07.23 09:49:31 -04'00'			
Division Director (OB)	Laura Lee Johnson, PhD	OB/DBIII	Sections: 8	Select one: ___ Authored __X_ Approved
	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2020.07.23 10:53:09 -04'00'			

APPEARS THIS WAY ON ORIGINAL

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
ICH	International Conference on Harmonisation
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

1 Executive Summary

1.1. Product Introduction

The Applicant, AstraZeneca (AZ), has a submitted an NDA Class 2 Resubmission for the fixed-dose combination (FDC) of budesonide (BD), glycopyrrolate (GP), and formoterol fumarate (FF) inhalation aerosol (combination referred to as BGF). BGF (tradename: Breztri) is an FDC of the inhaled corticosteroid (ICS) BD, the long-acting muscarinic antagonist (LAMA) GP, and the long-acting β2-adrenergic receptor agonist (LABA) FF delivered by a pressurized metered dose inhaler (MDI). BGF is to be administered as two inhalations twice daily. Each inhalation contains budesonide 160 µg, glycopyrrolate (glycopyrronium bromide) 9 µg, and formoterol fumarate 4.8 µg for a total dose of 320, 18, and 9.6 µg of each component, respectively, twice daily. The FDC of glycopyrrolate/formoterol fumarate (GFF) is approved in the United States under the tradename Bevespi Aerosphere at the same dose for the glycopyrrolate (160 µg) and formoterol fumarate (9.6 µg) components using the same delivery device as the BGF combination. The FDC of BFF is not approved, nor are the mono-components BD, GP, and FF in this delivery device. However, they are approved alone and in combination in other delivery devices for inhalation.

The initial 505(b)(2) NDA for BGF for the maintenance treatment of chronic obstructive pulmonary disease (COPD) was submitted on November 30, 2018. A Complete Response (CR) action was taken on September 30, 2019 as the results from the single phase 3 trial [BGF Trial PT010006 (referred to as Trial 06)] meant as primary support for safety and efficacy did not demonstrate the contribution of the ICS monocomponent to the combination and did not provide substantial evidence of efficacy.

In Trial 06, BGF was compared to the dual combinations glycopyrrolate/formoterol fumarate (GFF, an approved LAMA/LABA combination) and budesonide/formoterol fumarate (BFF) for efficacy. In that trial, compared to GFF, BGF did not show a statistically significant improvement in the co-primary endpoint of morning pre-dose trough forced expiratory volume in 1 second (FEV1) at Week 24. As such, there was no demonstration that BD contributed to the bronchodilatory effect of BGF. For the other co-primary endpoint of Trial 06, BGF did show a statistically significant improvement in FEV1, demonstrating the contribution of GP to BGF. Because of the failure to achieve statistical significance for both components of the co-primary endpoint, all secondary endpoints, including exacerbation, were considered not statistically significant. Therefore, Trial 06 was insufficient to support the efficacy of BGF in terms of bronchodilation, exacerbation, and contribution of the BD component to the combination.

The deficiency cited in the CR letter issued on September 30, 2019 stated:

> "The single Breztri Aerosphere phase 3 pivotal trial failed on the co-primary endpoint of change from baseline in trough FEV1 for the comparison of Breztri Aerosphere and the glycopyrrolate and formoterol fumarate combination. Therefore, the submitted data do not establish the contribution of budesonide to the Breztri Aerosphere combination product. Furthermore, due to failure at the co-primary endpoint, all secondary endpoints in the

> single phase 3 pivotal trial failed to show statistical significance and did not provide supportive evidence of efficacy. Moreover, as only a single Breztri Aerosphere phase 3 pivotal trial was submitted with this application, there was no additional data to directly support the efficacy and safety of Breztri Aerosphere."

In order to address the CR deficiency, the Agency advised to "conduct an additional trial or trials to provide data to demonstrate the efficacy of the Breztri Aerosphere combination product and the contribution of budesonide to the combination product." To address the CR deficiency, the Applicant submitted an NDA Class 2 Resubmission for BGF on January 22, 2020; which included results from a new single phase 3 study, BGF Trial PT010005, referred to as Trial 05.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for BGF for the indication of maintenance treatment for adult patients with COPD.

The support for efficacy is primarily derived from two phase 3 trials comparing BGF to BFF and GFF (previously reviewed Trial 06 and newly submitted Trial 05). To address the CR deficiencies and provide substantial evidence of efficacy and the contribution of the ICS and LAMA monocomponents, the Applicant submitted the results from a second phase 3, 52 week, randomized, placebo-controlled trial (Trial 05) with the primary objective of assessing the effect of BGF compared to GFF and BFF on exacerbation. This trial also included a PFT sub-study to support effects on lung function. Trial 05 demonstrated evidence of efficacy as determined by achieving a statistically significant reduction in rate of moderate or severe COPD exacerbations for BGF treated patients versus GFF and BFF treated patients. This also demonstrated the contribution of the ICS (BD) and LAMA (GP) monocomponents to the triple combination in terms of exacerbation. The secondary exacerbation related endpoints were also consistent with the primary endpoint. BGF demonstrated statistically significant improvement over GFF and BFF for time to first moderate or severe COPD exacerbation. Results were similar for severe exacerbations, though not statistically significant for the BGF to BFF comparison. SGRQ results were also generally consistent with the exacerbation data. The PFT sub-study demonstrated statistically significant improvements in lung function for BGF versus GFF and BFF, demonstrating both efficacy and the contribution of the LAMA and ICS monocomponents to the triple combination in terms of bronchodilation. Results from Trial 05, with additional support for the previously reviewed Trial 06, taken together represent substantial evidence of efficacy and the contribution of the relevant monocomponents to the triple combination. The deficiencies outlined in the CR letter have been sufficiently addressed to warrant Approval of BGF for the maintenance treatment of COPD.

Regarding safety, assessment of BGF safety focused on Trial 05, with supporting evidence from Trial 06 and its safety extension Trial 08. No large imbalances in terms of deaths, serious adverse events (SAE), adverse events (AE) leading to discontinuation, or common AEs were observed when

comparing BGF to the active comparators. Observed events were generally consistent with drugs of the same classes. No safety concerns precluding Approval were identified.

In summary, results from BGF Trial 05 adequately addressed the deficiencies that resulted in the initial CR action and the overall BGF development program has provided substantial evidence of efficacy and safety. The overall risk-benefit assessment support approval of BGF. The recommendation is Approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Chronic obstructive pulmonary disease (COPD) is a debilitating respiratory condition that has significant morbidity and mortality; it is the third leading cause of death in the US. Substantial healthcare resources are utilized in managing long-term COPD and in treating acute exacerbations. It is often associated with active or prior cigarette smoking (typically >10 pack-years), but other environmental and genetic factors have been found to contribute to its etiology. Multiple long-acting muscarinic antagonist (LAMA)/long-acting β2-adrenergic receptor agonist (LABA) fixed-dose combination (FDC) and inhaled corticosteroid (ICS)/LABA FDC exist. There is one approved ICS/LAMA/LABA FDC. This product potentially provides another alternative ICS/LAMA/LABA treatment for patients with COPD.

Breztri Aerosphere is a FDC of the inhaled corticosteroid (ICS) budesonide (BD), the LAMA glycopyrrolate (GP), and the LABA formoterol fumarate (FF) (combination referred to as BGF) delivered by a pressurized metered dose inhaler (MDI). To support the safety and efficacy for the indication of maintenance treatment of COPD, in the initial new drug application (NDA) submission, the Applicant included data from a single phase 3, 24-week, randomized, placebo-controlled trial with the primary objective of assessing the effect of BGF compared to the double combination of GP/FF (referred to as GFF and approved for the treatment of COPD) and BD/FF (referred to as BFF) on lung function (Trial 06). Results from this trial were insufficient to support the contribution of the ICS monocomponent to BGF, though contribution of the LAMA monocomponent was supported. As a result, a Complete Response (CR) action was taken, and the product was not approved. To address the CR deficiencies and provide substantial evidence of efficacy and the contribution of the ICS and LAMA monocomponents, the Applicant submitted the results from a second phase 3, 52 week, randomized, placebo-controlled trial (Trial 05) with the primary objective of assessing the effect of BGF compared to GFF and BFF on exacerbation. This trial also included a PFT sub-study to support effects on lung function. Trial 05 demonstrated evidence of efficacy as determined by achieving a statistically significant reduction in rate of moderate or severe COPD exacerbations for BGF treated patients versus GFF and BFF treated patients. This also demonstrated the contribution of the ICS (BD) and LAMA (GP) monocomponents to the triple combination in terms of exacerbation. The secondary exacerbation related endpoints were also consistent with the primary endpoint. BGF demonstrated statistically significant improvement over GFF and BFF for time to first moderate or severe COPD exacerbation. Results were similar for severe exacerbations, though not statistically significant for the BGF to BFF comparison. SGRQ results were also generally consistent with the exacerbation data. The PFT sub-study demonstrated statistically significant improvements in lung function for BGF versus GFF and BFF, demonstrating both efficacy and the contribution of the LAMA and ICS monocomponents in terms of bronchodilation. Results from Trial 05, with additional support for the previously reviewed Trial 06, taken together represent substantial evidence of efficacy and the contribution of the relevant monocomponents to the triple combination. The deficiencies outlined in the CR letter have been sufficiently addressed to warrant Approval of BGF for the maintenance treatment of COPD. Safety findings from BGF Trials 05 and 06 were consistent with products in this class.

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 of <0.7 is used for diagnosis of COPD in the 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.	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.
Current Treatment Options	Several classes of inhaled medications exist for the long-term maintenance treatment of COPD: Anticholinergics, LABA, and ICS (ICS is only available for combination products).	Multiple inhaled medications including LAMA/LABA/ICS fixed-dose combination inhalers exist, and this product provides another alternative treatment for patients with COPD.
Benefit	Support for efficacy is based primarily on two phase 3 trials comparing BGF to BFF and GFF, Trials 05 and 06. In Trial 05, a 52-week exacerbation study, BGF demonstrated a statistically significant reduction in rate of moderate or severe COPD exacerbations compared to BFF and GFF, the primary endpoint. BGF also demonstrated a statistically significant improvement in the secondary endpoints of time to first moderate or severe COPD exacerbation. In the Trial 05 pulmonary function sub study, BGF also showed a statistically	BGF provides an improvement in lung function and reduces COPD exacerbations. BGF also has an impact on health-related quality of life as measured by the SGRQ. BGF provides an alternative ICS/LAMA/LABA combination product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	significant improvement in the spirometric primary endpoints compared to both GFF and BFF. In Trial 06, a 24-week bronchodilator trial, BGF demonstrated a statistically significant improvement in lung function compared to BFF, but not to GFF. In both Trial 05 and 06 BGF treatment positively impacted St. George's Respiratory Questionnaire (SGRQ) scores when compared to BFF and GFF. Therefore results from Trial 05 with additional support from Trial 06 provide substantial evidence of efficacy for BGF as well as the contribution of the BD and GP monocomponents to the combination.	
Risk and Risk Management	The safety program for BGF demonstrated no new concerning safety signals compared to the BFF and GFF treatment arms. Common adverse events including upper respiratory tract infection. Known class safety issues associated with ICS in patients with COPD include oropharyngeal candidiasis, reduction in bone mineral density, glaucoma, cataracts and pneumonia. Known class safety issues associated with LAMA in patients with COPD include worsening of urinary retention. Known class safety issues associated with LABA include cardiovascular effects, such as tachycardia, increased blood pressure, and arrhythmias. These risks are adequately described in product labeling. No additional risk mitigation strategy is necessary.	The safety profile of BGF is similar to other medications in its class. The safety profile of ICS/LAMA/LABA are well known and are adequately described in product labeling.

1.4. Patient Experience Data

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

☒	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Section 8.1 (SGRQ)
		☐	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

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition that results in significant morbidity and mortality; it is the third leading cause of death in the United States. Given its high prevalence and disease burden, maintenance therapy requirement and management of acute exacerbations result in a significant societal and economic burden. Cigarette smoking is most often associated with the disease, but it is increasingly understood that alternative noxious exposures, as well as a variety of host-specific factors, contribute to COPD pathogenesis.

COPD is characterized by persistent respiratory symptoms and airflow limitations. Chronic inflammation resulting from inhaled irritants causes structural changes, small airways narrowing, mucociliary dysfunction, and destruction of lung parenchyma. Common symptoms include dyspnea, fatigue and cough, which often impact a patient's quality of life and ability to perform activities of daily living. Physical exam findings include wheezing, prolonged expiration, diminished breath sounds, and increased chest diameter. Spirometry is used to diagnose COPD. A FEV/FEV1 ratio below 0.7 establishes the diagnosis, and percent of predicted FEV1 determines the severity of airflow obstruction. COPD exacerbation history and dyspnea scoring provide an additional layer of formal disease assessment. [1] Other diagnostic considerations are increases in lung volume measurements, decreased diffusing capacity, decreased pulse oximetry, and evidence of chronic hypercapnia. Radiographic studies may reveal changes such as vascular tapering, radiolucency, flattened diaphragms, bullous disease, emphysema, thickened airways, and prominent hilar vascularity.

In conclusion, COPD is a serious disease with societal and individual impacts. It is a leading cause of death globally, and it's increasing prevalence and associated morbidity result in utilization of healthcare resources and loss of productivity. It also has significant impact on afflicted individuals, leading to reduced quality of life and difficulty performing regular activities. 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 the table below.

[1] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 at http://goldcopd.org

Table 1. Current COPD Treatment Options

Class		Generic Name	Brand Name	Approval
Beta2-adrenergic agonists	Short-acting (SABA)*	Albuterol sulfate	Accuneb ProAir HFA Proventil HFA Ventolin HFA	1981
		Levalbuterol tartrate	Xopenex HFA	1999
	Long-acting (LABA)	Salmeterol xinofoate	Serevent Diskus	1997
		Formoterol fumarate	Foradol Aerolizer**	2001
		Arfomoterol 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
		Aclidinium bromide	Tudorza Pressair	2012
		Umeclidinium bromide	Incruse Ellipta	2014
		Glycopyrrolate	Seebri Neohaler	2015
			Lonhala Magnair	2017
		Revefenacin	Yupelri	2018
	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
		Aclidinium/formoterol	Duaklir Pressair	2019
	ICS/LAMA/LABA	Fluticasone/Umeclidinium/ Vilanterol	Trelegy	2017
Xanthine		Theophylline	Multiple	1992
Phosphodiesterase inhibitors	PDE4 Inhibitors	Roflumilast	Daliresp	2011

Abbreviations: LABA = long-acting β2-adrenergic receptor agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; SABA = short-acting beta agonist; HFA = hydrofluoroalkane; PDE = Phosphodiesterase; COPD = chronic obstructive pulmonary disease
*General bronchodilator claim, not specifically indicated for COPD
** No longer marketed

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BGF is not marketed or approved in the United States. GFF, which contains the same LAMA/LABA at the same dose and delivery platform as BGF, was approved on April 25, 2016 under NDA 208294 with the tradename Bevespi Aerosphere. GFF is approved for the (b) (4) - (b) (4), maintenance treatment of airflow obstruction in patients with COPD, and it does not carry an exacerbation indication. Under this delivery platform, BFF, which contains the same ICS/LABA at the same dose as BGF, is not approved, nor are the mono-components BD and FF. However, these drug combinations have been approved for COPD in other delivery devices. This includes Symbicort (budesonide/formoterol fumarate), Foradil Aerolizer (formoterol fumarate, no longer marketed), Perforomist (formoterol), Seebri Neohaler (glycopyrrolate), and Lonhala Neohaler (glycopyrrolate). Additionally, Pulmicort (budesonide) is approved for asthma but not for COPD.

3.2. Summary of Presubmission/Submission Regulatory Activity

BGF was studied under investigational new drug (IND) 118313, opened on October 11, 2013. Relevant regulatory interactions are summarized below:

Pre-IND Meeting on July 17, 2013

(b) (4)

Written Responses on April 11, 2014

- Advised that a single trial may be adequate for approval of the triple combination if both dual combination products demonstrate an added benefit in lung function over their respective mono-products and the trial demonstrates robust, clinically meaningful efficacy for reduction in exacerbation or other relevant endpoints such as mortality

Written Responses on May 18, 2015

- Advised that moderate and severe exacerbations are the events of clinical significance to regulatory decision-making
- All exacerbations should also be reported as AEs

Teleconference on September 9, 2016

- The FDA advised that developing fixed-dose triple-combination products based solely on a lung function claim will ultimately be a review issue

EOP2 meeting on November 7, 2016

- The FDA agreed with the dose of BD and FF selected for the Phase 3 program
- The Applicant agreed to proceed to Phase 3 with the GP dose that was approved for COPD at the time.

Pre-NDA Meeting on March 31, 2017

- The FDA agreed with the Applicant's proposal to include full study reports and data for both BFF and BGF (b) (4)
- The FDA advised that if the BFF development program demonstrates an exacerbation benefit, then a lung function benefit for the BGF product may be a viable path to registration but would be a review issue
- The FDA did not agree with the 'efficacy' estimand as the primary estimand and recommend that the primary analyses should target the 'treatment policy' estimand

Initial NDA Review and Complete Response Action

- NDA submitted on November 30, 2018
- A Complete Response for BGF was issued on September 30, 2019 after the single phase 3 pivotal trial BGF Trial 06 failed on the co-primary endpoint of change from the baseline in trough FEV1 for the comparison of BGF to GFF. The submitted data failed to establish contribution of budesonide to the BGF combination product, and as only a single phase 3 trial was submitted, there was no additional data to directly support the efficacy and safety of BGF.
- The FDA recommended that in order to address the deficiency, an additional trial or trials to provide data to demonstrate the efficacy of the BGF combination product and the contribution of budesonide to the combination product was needed

Type A meeting on December 4, 2019

- Statistical comments were provided by the FDA for the Applicant to include additional analyses including additional estimands and type 1 error control data for the resubmission
- The FDA noted literature and clinical guidelines regarding ICS withdrawal, and the need for more analyses to evaluate this issue. The FDA provided additional analyses for the sponsor to include in the NDA Resubmission to explore the effect of ICS removal

(b) (4)

The Applicant submitted an NDA Class 2 Resubmission (Complete Response to CR action) for BGF on January 23, 2020.

BFF was studied under IND (b) (4), opened on July 18, 2014. Relevant regulatory interactions are summarized below:

<u>EOP2 Meeting on October 15, 2015</u>

- The proposed budesonide doses of 320 and 160 µg were considered acceptable by FDA
- The FDA recommended removal of the placebo group in study PT009002

(b) (4)

<u>Teleconference on September 9, 2016</u>

- The FDA agreed with an alternative development plan in which the BFF program would only pursue a lung function indication in order to qualify as the appropriate ICS/LABA comparator in the BGF program
- The FDA stated that development of a fixed-dose triple-combination products solely on a lung function claim was a review issue

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

4.1. Office of Scientific Investigations (OSI)

No investigations were performed during this review, as they were performed in the previous cycle review. No evidence of analysis-altering misconduct was identified in the three sites evaluated in the previous review.

4.2. Product Quality

No product quality issues were present in the previous cycle.

4.3. Clinical Microbiology

None.

4.4. Devices and Companion Diagnostic Issues

None.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Supporting nonclinical pharmacology and toxicology studies were reviewed under the original NDA submission. No new nonclinical were provided in the resubmission. See the following documents:

- Review and evaluation of supporting nonclinical pharmacology and toxicology studies authored by Dr. Ijeoma Uzoma can be found in the UniReview dated September 30, 2019
- Review and evaluation of the 2-year carcinogenicity studies in mice and rats can be in found in the review authored by Dr. Ijeoma Uzoma dated August 19, 2019
- Statistical evaluation of 2-year carcinogenicity studies in mice and rats can be found in review authored by Dr. Malick Mbodj dated April 23, 2019
- Minutes of the Executive Carcinogenicity Assessment Committee dated April 16, 2019 (DARRTS date April 18, 2019)
- Labeling review authored by Dr. Ijeoma Uzoma dated November 6, 2019
- Review of Extractables and Leachables Data from the Container Closure System authored by Dr. Ijeoma Uzoma dated November 12, 2019

6 Clinical Pharmacology

6.1. Executive Summary

The applicant, AstraZeneca resubmitted NDA 212122 (SDN 0027) for the triple combination (BD, GP, FF) product on January 23, 2020. The resubmission is to address the clinical deficiencies identified in the Complete Response Letter dated September 30, 2019.

During the review of the original submission, the Office of Clinical Pharmacology Divisions of Clinical Pharmacology II and Pharmacometrics concluded that the NDA was approvable. For details, refer to the UniReview dated September 30, 2019.

In this resubmission package, AstraZeneca included an updated "Summary of Clinical Pharmacology Studies" under section 2.7.2, study report D5980C00007 under section 5.3.4.1, and an addendum of study report PT010006 under section 5.3.5.1.

After a careful assessment, the review team decided not to review the gamma scintigraphy study D5980C00007 on pulmonary deposition of technetium-99m pertechnetate due to limited clinical utility (see section 6.2).

In the addendum of study report PT010006, the Applicant re-analyzed the PK data from a sub-population in Phase 3 Study PT010006. (b) (4)

Of note, it is not uncommon that the sample size for certain PK parameters, such as AUCs, are smaller than the studied subjects. In the original submission, the Applicant used extrapolation method to calculate AUC_{0-12}. Using this approach, the AUC_{0-12} value is not available for subjects whose elimination clearance cannot be reasonably estimated. This phenomenon may be contributed by the following two factors:

- Considerable number of PK samples are below the lower limit of quantification (BLQ) for products via inhalation administration route;
- The last PK sampling time point, i.e., 12 hour post-dose, may not be sufficient to characterize the elimination phase of formoterol and glycopyrronium, the half-life of which is about 10 hours and 15 hours, respectively.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology, has reviewed the re-analysis of PK results from Study PT010006 contained in NDA 212122

resubmission (SDN 0027) and considers this approach is acceptable. The changes in PK results from Study PT010006 do not warrant changes to the prescribing information.

6.2. Assessment of Study D5980C00007

Study D5980C00007 is a Phase 1, randomized, two-period, single-dose study to assess the pulmonary deposition of technetium-99m pertechnetate (^{99m}Tc) as delivered by commercially available BGF MDI device in healthy subjects. In total 10 subjects were randomized and all of them completed the study. During each treatment period, subjects inhaled two actuations of BGF (160/7.2/4.8 µg per actuation) mixed with ^{99m}Tc (≤ 5 MBq per actuation). The subjects were instructed to hold their breath for 3 seconds or 10 seconds after each inhalation in different periods. There was a minimum washout period of 7 ± 2 days between the two periods.

The primary endpoint of the study is the proportion of emitted dose of ^{99m}Tc deposited in the lungs following a 10 second breath-hold. Gamma scintigraphy images were used to capture the deposition of ^{99m}Tc. The results demonstrated that 38% and 62% of the emitted ^{99m}Tc dose was deposited in the lungs and oropharyngeal + stomach region, respectively. About 10% of the ex-valve dose was deposited on the actuator.

These results are limited by deposition of ^{99m}Tc, but not the active ingredients (i.e., budesonide, glycopyrronium bromide, and formoterol fumarate). Therefore, the clinical utility of pulmonary deposition of ^{99m}Tc is unclear. The charcoal PK Study PT010011 included in the original submission of NDA 212122 indicates that pre-ingestion of charcoal had an impact on the systemic PK of budesonide, glycopyrrolate, and formoterol, which may be partly explained by their differential oral/pulmonary deposition patterns.

Therefore, no further detailed clinical pharmacology review is conducted for this radio-labeled study.

6.3. Assessment of Re-analyzed PK results from Study PT010006

Study Overview

Study PT010006 was a multi-center, randomized, double-blind, parallel-group, 24-week, active-controlled study to assess the efficacy and safety of BGF MDI, GFF MDI, BFF MDI, compared with Symbicort TBH as an active control in subjects with moderate-to-very severe COPD. Approximately 600 subjects each were randomized to the BGF MDI and GFF MDI treatment groups, and 300 subjects each were randomized to the BFF MDI and Symbicort TBH treatment groups.

Steady-state PK of BD, formoterol, and glycopyrronium was assessed in a subset of COPD patients who participated in the pulmonary function test sub-study. Approximately 240 randomized subjects (80 subjects from each of the BGF MDI and GFF MDI treatment groups,

and 40 subjects from each of the BFF MDI and Symbicort TBH treatment groups) were assessed at Week 24. PK samples were collected within 30 minutes prior to dosing, and 2, 5, 20 minutes, 1, 2, 4, 8, 10, and 12 hours post-dose. Assessment of the quality of the PK data demonstrated that each subject had an average of 9.8 PK samples collected (Table 2). The proportion of BLQ PK samples were 1.4%, 9.0%, and 5.9% for BD, formoterol, and glycopyrronium, respectively.

Table 2. Summary of PK Samples in Study PT010006

	# of subjects with PK samples collected	Total listed PK samples	BLQ	ULQ	NR
Budesonide	141	1386	19	3	8
Formoterol	175	1729	156	0	7
Glycopyrronium	136	1350	80	1	5

Source: Reviewer's analysis

(b) (4)

The Applicant attributes the discrepancy to the method used for calculating AUC_{0-12}; when the PK samples were obtained earlier than 12-hour post-dose, a portion of AUC_{0-12} was extrapolated from the actual final time point to the nominal final time point (12-hour). In order to do this, subjects with earlier final time point needed to have a valid elimination half-life estimated, which was not available for each subject.

Table 3. Summary of Subject Numbers by PK Parameters in Study PT010006 from Original Submission

	# of subjects with PK samples collected	# of subjects with reported C_{max}	# of subjects with reported AUC_{0-12}
Budesonide	141	141	124
Formoterol	175	174[1]	129
Glycopyrronium	136	135[2]	107

[1] All PK samples from Subject (b) (6) on BGF MDI 320/14.4/9.6 µg treatment were BLQ.
[2] All post-dose PK samples from Subject (b) (6) on BGF MDI 320/14.4/9.6 µg treatment were BLQ.
Source: pt010006-clinical-study-report.pdf, page 219, Table 64; page 223, Table 66; and page 226, Table 68

To reduce the data loss from some subjects, the Applicant performed re-analysis by avoiding extrapolation, and instead calculated the AUC_{0-12} values by non-compartment analysis with the actual collection time, since the majority of subjects had planned 12-hour PK sample collected and the actual collection times were reasonably within the range (Table 4). The reviewer considers the justification reasonable.

Table 4. Evaluation of Actual Time point Collected at Planned 12-Hour from Study PT010006

	# of subjects with PK samples collected	# of subjects with a 12-hour sample	Time range of available 12-hour sample (hour)
Budesonide	141	138	11.5 – 12.3
Formoterol	175	171	11.5 – 12.3
Glycopyrronium	136	132	11.5 – 12.3

Source: reviewer's analysis

With this approach, more AUC_{0-12} values can be calculated for subjects without elimination clearance available in the original submission. However, it appeared that some subjects were kept excluded from the analysis:

- Subject with most PK samples missing
- Subject's last PK sample collected at or earlier than 10-hour post-dose
- Subject with most PK samples BLQ.
- Subjects with unexplained PK profile (the drug concentration fluctuated throughout 12 hours)

The following IR was conveyed to the Applicant on February 28, 2020, requesting an additional PK parameter, AUC_{last} to be estimated for sensitivity analysis:

FDA acknowledges the re-analysis of AUC0-12 of budesonide, formoterol, and glycopyrronium from study pt01006 by using actual sampling time and the exclusion criterion of subjects without any post-dose samples above LLOQ used for PK re-analysis. Provide results of AUC0-12 using non-compartment model in the format of Table 1, 3, 5, 7, 9, and 11 of pt1006-csr-addendum.pdf, but includes subjects whose plasma concentrations fell BLQ prior to the 12-hour post-dose timepoint (AUC0-12 same value as AUClast) and subjects whose lambda z could not be calculated. Clarify if reanalyzed AUC0-12 was calculated by using nominal/planned time point.

The Applicant responded to the IR on March 9, 2020 with following clarifications:

In order to address the FDA request, a non-compartmental analysis of AUClast has been performed using actual time points.

- *In this analysis, for subjects who had quantifiable concentrations through 12 hours, the AUClast value is the same as the AUC0-12 value provided in the re-analysis since a full 12 hours of data was available.*
- *For subjects whose concentrations fell BLQ prior to the 12-hour time point, AUClast is presented without extrapolation to 12 hours for all subjects, including those for whom extrapolation was previously done in the re-analysis of AUC0-12, as well as subjects for whom extrapolation was not possible (i.e., those who could not have lambda z calculated).*

The re-analyzed PK parameters of BD (Table 5), formoterol (Table 6), and glycopyrronium (Table 7) provided by the Applicant are listed below and compared side-by-side with the results from the original submission. The reviewer conducted independent analysis and confirmed the results. Therefore, the Applicant's re-analysis of PK data from Study PT010006 included in this resubmission is acceptable.

Table 5. Descriptive Statistics for PK Parameters of Budesonide by Treatment at Week 24 from Study PT010006

	BGF MDI 320/14.4/9.6 µg MDI (N=75)		BFF MDI 320/9.6 µg MDI (N=39)		Symbicort TBH 400/12 µg (N=27)	
	Re-analysis	Original	Re-analysis	Original	Re-analysis	Original
C_{max} (pg/mL)[1]	631 (80%, N=75)		654 (59%, N=39)		635 (55%, N=27)	
T_{max} (hour)[2]	0.37 (0.0, 12.1, N=75)	0.37 (0.0, 12.1, N=73)	0.97 (0.03, 4.18, N=39)		0.33 (0.03, 1.02, N=27)	
AUC_{0-12} (h·pg/mL)[1]	2516 (71%, N=73)	2551 (70%, N=65)	2573 (54%, N=39)	2583 (56%, N=35)	2300 (46%, N=26)	2285 (48%, N=24)
AUC_{last} (h·pg/mL)[1]	2281 (137%, N=75)	N/A	2573 (54%, N=39)	N/A	2137 (63%, N=27)	N/A

[1] geometric mean (CV%, N)
[2] median (min, max, N)
Source: clinical-information-amendment.pdf dated 3/9/2020, page 3, Table 1; pt010006-clinical-study-report.pdf dated 11/30/2018, page 219, Table 64

Table 6. Descriptive Statistics for PK Parameters of Formoterol by Treatment at Week 24 from Study PT010006

	BGF MDI 320/14.4/9.6 µg MDI (N=75)		GFF MDI 14.4/9.6 µg MDI (N=61)		BFF MDI 320/9.6 µg MDI (N=39)	
	Re-analysis	Original	Re-analysis	Original	Re-analysis	Original
C_{max} (pg/mL)[1]	8.4 (70%, N=74)		10.5 (80%, N=61)		7.5 (57%, N=39)	
T_{max} (hour)[2]	0.96 (0.03, 12.1, N=74)		0.63 (0, 12.07, N=61)[3]	0.92 (0.03, 12.07, N=59)	1.00 (0, 9.97, N=39)	1.00 (0.07, 9.97, N=38)
AUC_{0-12} (h·pg/mL)[1]	54.9 (62%, N=67)	55.1 (57%, N=53)	61.9 (63%, N=56)	56.2 (53%, N=49)	48.6 (47%, N=35)	47.3 (44%, N=27)
AUC_{last} (h·pg/mL)[1]	41.2 (210%, N=74)	N/A	56.8 (73%, N=61)	N/A	45.7 (51%, N=39)	N/A

[1] geometric mean (CV%, N)
[2] median (min, max, N)
[3] confirmed by the reviewer
Source: clinical-information-amendment.pdf dated 3/9/2020, page 5, Table 3; pt010006-clinical-study-report.pdf dated 11/30/2018, page 223, Table 66

Table 7. Descriptive Statistics for PK Parameters of Glycopyrronium by Treatment at Week 24 from Study PT010006

	BGF MDI 320/14.4/9.6 µg MDI (N=75)		GFF MDI 14.4/9.6 µg MDI (N=61)	
	Re-analysis	Original	Re-analysis	Original
C_{max} (pg/mL)[1]	17.5 (94%, N=75)	17.8 (92%, N=74)	19.8 (97%, N=61)	
T_{max} (hour)[2]	0.08 (0, 12.1, N=75)	0.08 (0.02, 12.1, N=74)	0.08 (0, 12.0, N=61)	0.08 (0.03, 12.0, N=60)
AUC_{0-12} (h·pg/mL)[1]	83.2 (72%, N=67)	74.0 (69%, N=53)	83.1 (92%, N=60)	79.3 (84%, N=54)
AUC_{last} (h·pg/mL)[1]	64.2 (207%, N=74)	N/A	80.7 (96%, N=61)	N/A

[1] geometric mean (CV%, N)
[2] median (min, max, N)
[3] confirmed by the reviewer
Source: clinical-information-amendment.pdf dated 3/9/2020, page 7, Table 5; pt010006-clinical-study-report.pdf dated 11/30/2018, page 226, Table 68

In general, the PK results for BD, formoterol, and glycopyrronium following re-analysis were similar to the PK results in the original submission. Therefore, all the conclusions derived from Study PT010006 PK results in the Clinical Pharmacology review section of Multi-Disciplinary Review dated September 30, 2019 during the original review cycle remain unchanged:

1. The systemic exposure of BD is comparable with or without coadministration of glycopyrronium and/or formoterol in healthy subjects (Study PT010002) and patients with COPD [Study PT0090001 and PT010006] (page 67).
2. Glycopyrronium systemic exposure was compared between BGF MDI 320/18/9.6 µg and the approved GFF MDI 18/9.6 µg (NDA 208294, Bevespi Aerosphere). Glycopyrronium systemic exposure is generally comparable between BGF MDI 320/18/9.6 µg and Bevespi Aerosphere both in healthy subjects following single dose inhalation and in patients with COPD following BID chronic treatment (Table 31). Therefore, BD is unlikely to affect glycopyrronium systemic exposure when the two drugs are co-administered. (page 72).
3. Formoterol systemic exposure was compared between BGF MDI 320/18/9.6 µg and the approved GFF MDI 18/9.6 µg (NDA 208294, Bevespi Aerosphere). The formoterol systemic exposure was generally comparable between BGF MDI 320/18/9.6 µg and Bevespi Aerosphere both in healthy subjects following single dose inhalation and in patients with COPD following BID chronic treatment (Table 32). Therefore, BD is unlikely to affect formoterol systemic exposure when the two drugs are co-administered (page 72).
4. The BD systemic exposure was generally comparable between BGF MDI 320/18/9.6 µg and BFF MDI 320/9.6 µg in patients with COPD following BID chronic treatment (Table

34). Therefore, glycopyrronium is unlikely to affect BD systemic exposure when two components are co-administered (page 73-74).

5. Median T_{max} of BD ranged from 20 minutes to 40 minutes from Studies PT010018 and PT010006 following single or multiple dose inhalation of BGF MDI 320/18/9.6 µg in patients with COPD (page 83).
6. Median T_{max} of glycopyrronium was 6 minutes following multiple dose inhalation of BGF MDI 320/18/9.6 µg in patients with COPD from both Studies PT010018 and PT010006 (page 85).
7. Median T_{max} of formoterol ranged from 20 to 60 minutes following inhalation of BGF MDI 320/18/9.6 µg in patients with COPD from both Studies PT010018 and PT010006 (page 87).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Phase 3 clinical trials reviewed to evaluate the safety and efficacy of BGF are shown in Table 8. Note that only Trial 05 was new for this submission, and the other listed trials (grayed out) were previously reviewed during the initial NDA review cycle. Also note that this table does not contain all clinical studies submitted with the initial NDA and complete response to CR submission.

Table 8. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Trials to Support Efficacy and Safety						
PT010005 (Trial 05)[a]	02465567	R, DB, PB, AC	BGF 320/18/9.6 BID BGF 160/18/9.6 BID GFF 18/9.6 BID BFF 320/9.6 BID	- Rate of moderate or severe COPD exacerbation - Time to first moderate of severe COPD exacerbation - PFT sub-study for bronchodilation	52 weeks	8588	Moderate to very severe COPD	812 study centers, 26 countries
PT010006 (Trial 06)[b]	02497001	R, DB, PG, AC	BGF 320/18/9.6 BID GFF 18/9.6 BID BFF 320/9.6 BID TBH (OL) 400/12 BID	- Change from baseline FEV1 AUC_{0-4} at week 24 (BGF vs. BFF) -Change from baseline through FEV1 at week 24 (BGF vs. GFF)	24 weeks	1902	Moderate to very severe COPD	215 (CA, JP, US, CN)
		Studies to Support Safety						
PT010008 (Trial 08)[b]	03313570	R, DB, PG, AC, extension study	BGF 320/18/9.6 BID GFF 18/9.6 BID BFF 320/9.6 BID	- Safety	28- week extension in a subset of PT010006 subjects	627	Moderate to very severe COPD	71 (all US)
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
PT009002 (Trial 02)[b]	02766608	R, DB, PG, AC	BFF 320/9.6 BID BFF 160/9.6 BID FF 9.6 BID BD 320 BID TBH (OL) 400/12 BID	-Change from baseline FEV1 AUC_{0-4} at week 24 (BFF vs. FF) -Change from baseline through FEV1 at week 24 (BFF vs. BD)	24 weeks	2389	Moderate to very severe COPD	253 (CA, CZ, DE, HU, PL, RU, US)
PT009003 (Trial 03)[b]	02727660	R, DB, PG, AC	BFF 320/9.6 BID BFF 160/9.6 BID FF 9.6 BID	-Change from baseline through FEV1 at week 24	12 weeks	1876	Moderate to very severe COPD	292 (AR, AT, BE, BR, CA, CL, DE, DK, IT, MX, NO, PE, RU, ZA, ES,

Abbreviations: AUC0-4 = area under the curve from 0 to 4 hours; AC = active comparator; AR = Argentina; AT = Austria; BD = budesonide; BE = Belgium; BFF = budesonide/formoterol fumarate; BGF = budesonide/glycopyrrolate/formoterol fumarate; BID = twice daily; BR = Brazil; CA = Canada; CL = Chile; CN = China; COPD = chronic obstructive pulmonary disease; CZ = Czech Republic; DB = double-blinded; DE = Germany; DK = Denmark; ES = Spain; FEV1 = forced expiratory volume in 1 second; FF = formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; HU = Hungary; IT = Italy; JP = Japan; MX = Mexico; NO = Norway; OL = open-label; PC = placebo-controlled; PE = Peru; PG = parallel group; PL = Poland; R = randomized; RU = Russia; SE = Sweden; TBH = Symbicort Turbuhaler; UK = United Kingdom; US = United States; ZA = South Africa;

[a]Reviewed in current Unireview;

[b]Reviewed in previous cycle Unireview

7.2. Review Strategy

Support for the efficacy and safety of BGF is primarily based on two phase 3 trials, Trials 05 and 06, with supporting evidence derived from BGF safety extension Trial 08, and the BFF development program (Trial 02 and Trial 03). This Unireview will focus on Trial 05, as BGF Trials 06 and Trial 08 and BFF Trial 02 and Trial 03 were previously reviewed in the initial NDA cycle (see Unireview dated September 30, 2019 for complete review). However, results from the previously reviewed trials will be summarized in this review where appropriate. Note that BFF is not an approved product and a full development program for BFF was necessary to demonstrate that BFF was an appropriate comparator in the BGF program to demonstrate added benefit of the triple combination (BGF). GFF (Bevespi Aerosphere) is an approved product and evidence for its efficacy and safety is derived from its approval (NDA 208294).

Efficacy analysis was performed by FDA Biostatisticians to confirm the data shown in support of the Applicant's primary and secondary endpoints, as well as for additional analyses necessary to support this submission. The review of the Trial 05 protocol and efficacy is in Section 8.1. Support for the safety of BGF is primarily based on the results of Trial 05 and previously reviewed Trials 06/08. Safety analyses were performed by the Clinical Reviewer and are in Section 8.2.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BGF Protocol Review: Trial 05

8.1.1.1. Trial 05 (PT010005) – BGF 52 week Exacerbation Trial

Title: "A Randomized, Double-Blind, Multi-Center, Parallel-Group Study to Assess, the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52-Week Treatment Period in Subjects with Moderate to Very Severe COPD"

- Study dates: July 15, 2015 – July 26, 2019
- Study report date: July 26, 2019
- Study sites: 812 study centers in 26 countries

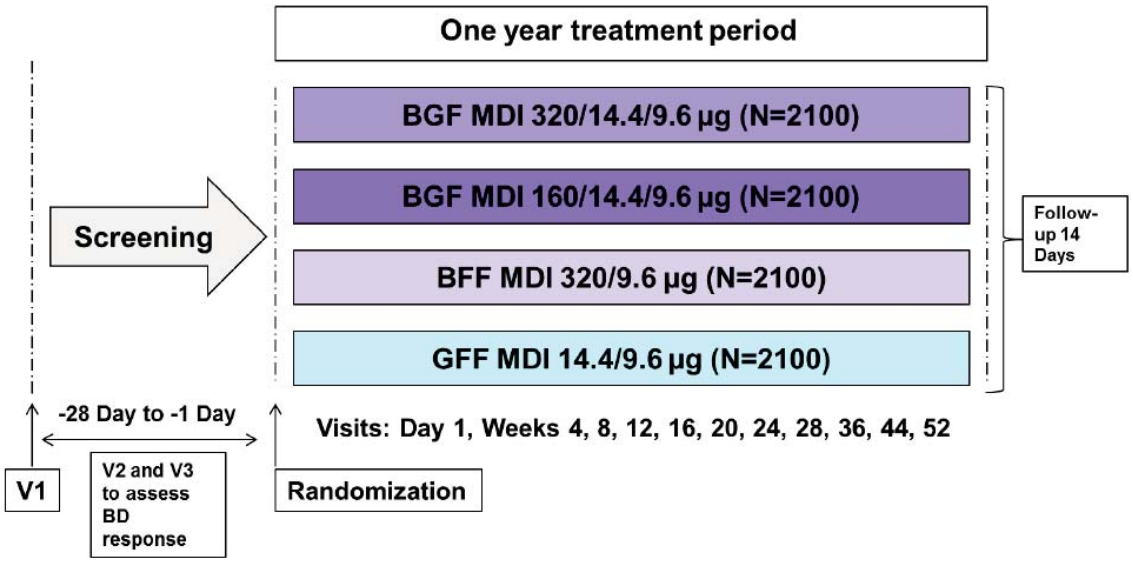
Trial Design

This was a multicenter, randomized, double-blind, parallel-group, 52 week treatment period trial to assess the efficacy and safety of budesonide/glycopyrrolate/formoterol (BGF) metered dose inhaler (MDI), relative to glycopyrrolate/formoterol (GFF) MDI, and budesonide/formoterol (BFF) MDI, in patients with moderate to very severe COPD with an increased risk of experiencing a COPD exacerbation and that remain symptomatic (COPD Assessment Test (CAT) ≥ 10) on two or more inhaled maintenance treatments. Subjects must have had a documented history of COPD exacerbation(s). Patients with post-bronchodilator FEV1 <50% were required to have ≥ 1 moderate or severe COPD exacerbation in the 12 months prior to Screening (Visit 1), and subjects with post-bronchodilator FEV1 ≥ 50% were required to have ≥2 moderate COPD exacerbations or ≥1 severe COPD exacerbation (hospitalized) in the 12 months prior to Screening. At Visit 1, patients signed an informed consent form (ICF) prior to the conduct of any screening assessments and must have met spirometry criteria as re-screening was not allowed after Visit 1. Patients who met all entry criteria discontinued any prohibited COPD medications for the duration of the trial, with a minimum washout period observed between Visits 1 and 2. The screening period lasted a total of 4 weeks. Randomization occurred at Visit 4 and was followed by a 52-week double-blind treatment period ending at Visit 14. Patients were randomized in a 1:1:1:1 ratio (BGF MDI 320/14.4/9.6 µg BID, BGF MDI 160/14.4/9.6 µg BID, BFF MDI 320/9.6 µg BID, or GFF MDI 14.4/9.6 µg BID, respectively). There was a vital status check at week 52. The trial schematic is shown in Figure 1 and the schedule of assessments is shown in Table 9 and Table 10.

This trial included the following 2 sub-studies: a pulmonary function test (PFT) sub-study and a 24-hour Holter Monitoring sub-study. Subject participation in the sub-studies was determined at Screening, prior to any trial procedures. Individual subjects were allowed to participate in

both sub-studies.

Figure 1. BGF Trial 05 Schematic



Abbreviations: BFF=Budesonide and Formoterol Fumarate; BGF=Budesonide, Glycopyrronium, and Formoterol Fumarate; GFF=Glycopyrronium and Formoterol Fumarate; BD=Bronchodilator, MDI=metered dose inhaler
Source: PT010005 Protocol Version 6.0, Figure 1, page 41

Table 9. BGF Trial 05 Schedule of Assessments

Procedures	Screening			52-Week Treatment Period											Follow-up TC
	Visit 1	Visit 2	Visit 3	Visit 4 (Rand)	Visit 5 Week 4	Visit 6 Week 8	Visit 7 Week 12	Visit 8 Week 16	Visit 9 Week 20	Visit 10 Week 24	Visit 11 Week 28	Visit 12 Week 36	Visit 13 Week 44	Visit 14 Week 52	
Study Day[a]	Day -28 to 12	Day -16 to -2	Day -15 to -1	Day 1	Day 29±2	Day 57±5	Day 85±5	Day 113±5	Day 141±5	Day 169±5	Day 197±5	Day 253±5	Day 309±5	Day 366±5	Day 380
IN-CLINIC	X	X	X	X	X		X			X		X		X	
TELEPHONE CONTACT						X		X	X		X		X		X
Informed Consent	X														
Eligibility Criteria	X	X	X	X											
Verify Continued Eligibility					X		X			X		X		X	
Reversibility Testing[b]		X	X												
Demographics and Medical/Surgical History	X														
Smoking Status	X	X	X	X	X		X			X		X		X	
Chest Imaging	X[q]														
CAT[c]	X			X											
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]	X
Spirometry (All subjects)[e]	X	X	X												
Spirometry (PFT Sub-study)[e]				X	X		X			X		X		X	
Physical Examination[f]	X													X[p]	
Vital Signs	X	X	X	X	X		X			X		X		X[p]	
12-Lead ECG[g]	X			X	X					X				X[p]	
Pregnancy Test[h]	X			X	X		X			X		X		X[p]	
Clinical Laboratory Testing[i]	X			X	X					X				X[p]	
Adjust COPD Medications[j]	X													X[p]	
Adverse Events/COPD Exacerbations.	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]	X

Procedures	Screening			52-Week Treatment Period											Follow-up TC
	Visit 1	Visit 2	Visit 3	Visit 4 (Rand)	Visit 5 Week 4	Visit 6 Week 8	Visit 7 Week 12	Visit 8 Week 16	Visit 9 Week 20	Visit 10 Week 24	Visit 11 Week 28	Visit 12 Week 36	Visit 13 Week 44	Visit 14 Week 52	
Study Day[a]	Day -28 to 12	Day -16 to -2	Day -15 to -1	Day 1	Day 29±2	Day 57±5	Day 85±5	Day 113±5	Day 141±5	Day 169±5	Day 197±5	Day 253±5	Day 309±5	Day 366±5	Day 380
IN-CLINIC	X	X	X	X	X		X			X		X		X	
TELEPHONE CONTACT						X		X	X		X		X		X
Inhalation Device and Dose Indicator Training	X	X	X	X											
Study Drug Dispensing[j]	X[J]			X	X		X			X		X		X	
24-hour Holter Monitoring[k]			X					X							
Study Drug Collection				X	X		X			X		X		X[p]	
Study Drug Administration[l]				X	X		X			X		X		X	
BDI/TDI[m]				X	X		X			X		X		X[p]	
SGRQ[m]				X	X		X			X		X		X[p]	
EQ-5D-5L[m]				X	X		X			X		X		X[p]	
HCRU					X	X	X	X	X	X	X	X	X	X[p]	X
eDiary Dispensing/Collection	X													X[p]	
eDiary Training[n]	X														
eDiary Review[o]		X	X	X	X		X			X		X		X	
Vital Status Check														X	

Abbreviations: BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; eDiary=electronic diary; ECG=electrocardiogram; EQ-5D=EuroQol 5 Dimensions Questionnaire; Exac.=exacerbations; EXACT =Exacerbations of Chronic Pulmonary Disease Tool; hCG=human chorionic gonadotropin; HCRU=health care resource utilization; MDI=metered dose inhaler; PFT=pulmonary function test; Rand=randomization; SGRQ=St. George's Respiratory Questionnaire; TC=Telephone Call
Source: PT010005 Protocol Version 6.0, Figure 1, page 91-92

Table 10. Timed Assessments in PFT Sub-Study

Clinical Variable	Pre-dose		Post-dose					
	-1 hour	-30 minutes	5 minutes	15 minutes	30 minutes	1 hour	2 hours	4 hours
Review of Electronic Diary[a]	X							
Vital Signs[b,c]	X				X		X	
Spirometry (FEV_1, FVC, PEFR, FEF_{25-75})[f]	X	X	X[f]	X	X	X	X	X
Study Drug Collection/Dispensing[g,h]	X†							
TDI[i]	X†							
SGRQ[i]	X†							
EQ-5D-5L[i]	X†							
Assessments to be performed at Visits 4, 5, 10, and 14 (Day 1, Weeks 4, 24, and 52)								
12-Lead ECG[b,d]	X				X		X	
Clinical Laboratory Testing[b,e]	X†						X	

Abbreviations: BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire; EXACT =Exacerbations of Chronic Pulmonary Disease Tool; FEF25-75=forced expiratory flow between 25% to 75% of FVC; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; hCG=human chorionic gonadotropin; PEFR=peak expiratory flow rate; PFT=pulmonary function test; SGRQ=St. George's Respiratory Questionnaire
Source: PT010005 Protocol Version 6.0, Figure 1, page 94

Overall, the design of the trial is reasonable to assess exacerbation and consistent with other programs for COPD inhaled products.

Objectives

- Primary objective: To assess the effects of BGF MDI relative to GFF MDI and BFF MDI on rate of COPD exacerbations.
- Secondary objectives:
    - To assess the effects of BGF MDI relative to GFF MDI and BFF MDI on symptoms of COPD.
    - To assess the effects of BGF MDI relative to GFF MDI and BFF MDI on quality of life.
    - To assess the effects of BGF MDI relative to GFF MDI and BFF MDI on all-cause mortality.
    - To assess the effects of BGF MDI relative to GFF MDI and BFF MDI on COPD exacerbations.
    - To assess the safety of BGF MDI relative to GFF MDI and BFF MDI.

- 4-hour PFT sub-study: To assess the effect of BGF MDI relative GFF MDI and BFF MDI on lung function.
- 24-Hour Holter Monitoring sub-study: To evaluate the cardiovascular safety of BGF MDI relative to GFF MDI and BFF MDI as evaluated by 24-hour Holter monitoring.
- Health Care Resource Utilization (HCRU) Objective: To assess overall and COPD-specific Healthcare Resource Utilization of BGF MDI, MDI GFF MDI, and BFF MDI.

Trial Population

The trial consisted of 8588 randomized COPD patients.

Key Inclusion Criteria

1. Signed informed consent to participate.
2. Were at least 40 years of age and no older than 80 at Visit 1.
3. A female was eligible to enter and participate in the study if she was of:
    a. Non-childbearing potential.
    b. Childbearing potential had a negative serum pregnancy test at Visit 1 and agreed to an acceptable form of contraception.
4. COPD diagnosis as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) or by locally applicable guidelines.
5. Current or former smokers with a history of at least 10 pack-years of cigarette smoking.
6. Patients with an established clinical history of COPD and severity defined as:
    a. At Visit 1, FEV1/FVC ratio was <0.70 and FEV1 was <65% predicted normal value.
    b. At Visit 2, post-bronchodilator FEV1/FVC ratio was <0.70 and post-bronchodilator FEV1 was ≥25% to <65% predicted normal value.
    c. At Visit 4, the average of the 60 minutes and 30 minutes predose FEV1 assessments was <65% predicted normal value.
    d. Symptomatic (CAT ≥10) at Screening (Visit 2).
7. Use of 2 or more inhaled maintenance therapies for the management of their COPD for at least 6 weeks prior to Screening.
8. Subject was willing and, in the opinion of the Investigator, able to adjust current COPD therapy, as required by the protocol.
9. Screening clinical laboratory tests were acceptable to the Investigator.
10. Screening ECG was acceptable to the Investigator.
11. Chest X-ray or CT scan of the chest/lungs within 6 months prior to Visit 1 was acceptable to the Investigator.
12. Patients must have been willing to remain at the study center as required per protocol to complete all visit assessments.

Key Exclusion Criteria

1. Significant diseases or conditions other than COPD that in the opinion of the Investigator, may have put the patient at risk because of participation in the study or may have influenced either the results of the study or the subject's ability to participate in the study.
2. Women who were pregnant or lactating, or were planning to become pregnant during the course of the study, or women of childbearing potential who were not using an acceptable method of contraception.
3. Respiratory diseases including asthma, alpha-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, idiopathic pulmonary fibrosis, primary pulmonary hypertension, and uncontrolled sleep apnea.
4. Patients who had undergone lung volume reduction surgery, lobectomy, or bronchoscopic lung volume reduction within 6 months
5. Hospitalization for COPD within 6 months prior to Visit 1 with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1.

6. Acute worsening of COPD that required treatment with oral steroids or antibiotics within 6 weeks prior to Visit 1 with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1.
7. Lower respiratory tract infection that required antibiotics within 6 weeks prior to Visit 1 with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1.
8. Upper respiratory tract infection not resolved at least 7 days prior to screening.
9. Chest X-ray abnormalities requiring additional investigation/treatment or may put subject at risk because of study participation.
10. Substantial risk of pneumonia in the opinion of the Investigator.
11. Pneumonia not clinically resolved within 14 days of Visit 1.
12. Patients who could not perform acceptable and repeatable spirometry by ATS/ERS acceptability criteria.
13. Long term oxygen therapy except for as needed oxygen.
14. Use of non-invasive positive pressure ventilation device.
15. Change in smoking status within 6 weeks of Visit 1.
16. Pulmonary rehabilitation within 4 weeks prior to Visit 1.
17. Initiated or altered use of intranasal corticosteroids and/or antihistamines within 7 days prior to Visit 1.
18. Cardiac diseases including unstable ischemic heart disease, left ventricular failure, documented myocardial infarction within 6 months, percutaneous coronary intervention within 3 months, and coronary artery bypass graft within 3 months.
19. Congestive heart failure with New York Heart Association Class III/IV symptoms.
20. Clinically significant abnormal ECG including conduction abnormalities, arrhythmias, prolonged QT interval, ventricular bradycardia, significant ST-T wave abnormalities, or any other ECG abnormalities that are clinically significant in the opinion of the Investigator.
21. Uncontrolled hypertension.
22. Neurologic conditions including seizures requiring anticonvulsants within 12 months, changes in dose of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors within 4 weeks, or cerebrovascular accident within 6 months.
23. Renal/urinary disorders including symptomatic prostatic hypertrophy or prostate resection within 6 months, bladder neck obstruction, urinary retention, and calculated creatinine clearance ≤30 mL/minute.
24. Endocrine disorders including uncontrolled thyroid disease, hypokalemia, hyperadrenergic state, or diabetes.
25. Abnormal liver function tests.
26. Cancer that has not been in complete remission at least 5 years.
27. Inadequately treated glaucoma.
28. Drug allergy to BGF components or drugs of the same class.
29. Substance abuse.
30. Subjects who were unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each visit were unable to participate in the PFT sub-study.

31. Subjects who received live attenuated vaccinations within 7 days prior to Visit 1.
32. Non-compliance.
33. Treatment with investigational drug or device within the last 30 days or within 5 half-lives prior to Visit 1.
34. Subjects who required use of spacer device or use of nebulizer to deliver maintenance COPD medication.
35. Previous enrollment in PT009 or PT010 studies.

Key Withdrawal Criteria

1. Patient personal request.
2. Calculated QTcF >500 msec and increased by 60 msec or more over baseline value
3. Abnormal LFT ≥3 x ULN
4. Use of prohibited medications.
5. The Investigator will determine the suitability of the subject continuing on study drug if any of the following occur: Increase in heart rate >40 bpm or systolic blood pressure >40 mmHg after dosing, or decrease in creatinine clearance ≤30 mL/min.

The inclusion criteria and exclusion criteria are reasonable and consistent with other programs for COPD inhaled products. Based on these criteria, the study population will likely be representative of the target population.

Treatments

The trial consisted of 4 treatment groups. All treatments were taken twice daily. The treatment groups are as follows:

- BGF (budesonide/glycopyrrolate/formoterol) 320/18/9.6 µg
- BGF (budesonide/glycopyrrolate/formoterol) 160/18/9.6 µg
- GFF (glycopyrrolate/formoterol) 18/9.6 µg (approved dose in US)
- BFF (budesonide/formoterol) 320/9.6 µg

BGF, GFF, and BFF were all administered via MDI. All patients were provided with albuterol sulfate inhalation aerosol 90 µg to be taken as directed on an as needed basis during the trial.

Restricted Medications

Prohibited medications with minimum washout period or prohibited time period are shown in Table 11. Subjects who were on an ICS as a part of an approved fixed-dose combination therapy must have been on the ICS component for at least 4 weeks prior to visit 1 (Screening) and maintained on a stable dose for at least 4 weeks prior to Visit 1 (Screening). These subjects were switched to the corresponding dose of the ICS administered as a single agent BID, with LABA portion provided by Sponsor. Subjects receiving a maintenance dose of an ICS not administered as a fixed-dose combination together with a LABA continued their ICS provided they were maintained on a stable dose for at least 4 weeks prior to Visit 1 (Screening). All ICS was abruptly stopped, without washout, at randomization (Visit 4). The subjects who were on ICS prior to the study and were randomized to the GFF group which contained no ICS component had abrupt discontinuation of their ICS at randomization.

Note that patients who were dependent on steroids and maintained on an equivalent of up to 5 mg oral prednisone daily or up to 10 mg oral prednisone every other day for at least 3 months prior to Visit 1 were eligible for enrollment provided the dose remained consistent. Patients may have been treated with systemic corticosteroids during the treatment period if required.

Table 11. Prohibited Medications

Class of Medication	Minimum Washout Period Prior to Visit 2 or Minimum Cessation Period Prior to Visit 1
Long-acting muscarinic antagonists (LAMA)	Tiotropium: 14 days Aclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
Short-acting muscarinic antagonists (SAMA)	6 hours
Short-acting β2-adrenergic agonists (SABA)	6 hours
Long-acting β2-adrenergic agonists (LABA; inhaled)	7 days (14 days for indacaterol and olodaterol)
Fixed-combinations of LABA/LAMA	7 days (14 days for indacaterol/glycopyrronium and olodaterol/tiotropium)
Fixed-combinations of LABA/ICS	7 days
Fixed combinations of SABAs and SAMAs	6 hours
Oral beta-agonists	2 days
Theophylline (total daily dose >400 mg/day)	7 days
Leukotriene antagonists	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen (eye drops allowed)	7 days
Any drug with significant QT-prolonging potential	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Non-selective beta-blocking agents (carvedilol allowed for treatment of heart failure when appropriate)	7 days
Cardiac antiarrhythmics class Ia, III	7 days (amiodarone 3 months)
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and free of seizures for 1 year
Tricyclic antidepressants (allowed if stable dose for at least 6 weeks and Investigator allows)	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor alpha antibodies	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies (may be allowed on case-by-case basis after discussion with Medical Monitor)	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs (allowed if stable dose for at least 6 weeks and Investigator allows)	30 days
Systemic calcineurin inhibitors, systemic antifungal	30 days

agents, protease inhibitors, and cimetidine	
Systemic anticholinergics (unless used for overactive bladder and treatment is stable for 1 month)	7 days
Chinese complementary and alternative bronchodilatory medicines	10 days (Investigator may determine appropriate washout on case-by-case basis.

Source: PT01000 Protocol Version 6.1; Tables 1, 2, and 4; consolidated by Clinical Reviewer

The medication restrictions are typical for a COPD trial.

Study Endpoints

Primary Endpoints

- Rate of moderate or severe COPD exacerbations

Secondary Endpoints

- Time to first moderate or severe COPD exacerbation
- Rate of severe COPD exacerbations
- Rate of moderate or severe COPD exacerbations in subjects with ≥ 2 moderate or severe COPD exacerbations in the prior year
- Change from baseline in the SGRQ total score over 24 weeks (This endpoint was included to satisfy non-US regulatory bodies)
- Percentage of subjects achieving a minimally clinical important difference (MCID) of ≥4 units in St George's Respiratory Questionnaire (SGRQ) (50-item version with 4-week recall period) total score at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- TDI focal score of 24 weeks (This endpoint was included to satisfy non-US regulatory bodies)
- Change from baseline in EXAcerbation of Chronic Pulmonary Disease Toll (EXACT) total score over 52 weeks (This endpoint was included to satisfy non-US regulatory bodies)
- Time to death (all-cause)

A COPD exacerbation was defined as a change in the subject's usual COPD symptoms that lasted 2 or more days, was beyond normal day-to-day variation, was acute in onset, and may have warranted a change in regular medication. The change in symptoms must have included at least 1 major COPD symptom (dyspnea, change in sputum volume, and change in sputum color) and at least 1 other major or minor symptom (cough, wheeze, sore throat, cold symptoms (rhinorrhea or nasal congestion), and fever without other cause). An exacerbation was considered moderate if it resulted in use of systemic corticosteroids and/or antibiotics for at least 3 days. Exacerbations were considered severe if they resulted in an inpatient COPD-related hospitalization or death. This definition is consistent with other COPD exacerbation programs.

Safety Endpoints

- Adverse Events (AE)
- ECGs
- Clinical laboratory testing
- Vital signs measurement

The trial endpoints and definition of COPD exacerbation are reasonable and consistent with the trial objectives and are similar to other COPD development programs. The co-primary endpoints are chosen to demonstrate the contribution of GP and BD to the triple combination (BGF vs. GFF) (BGF vs. BFF). Overall the trial design is adequate to support the efficacy of BGF given that GFF is approved and provided that the BFF program demonstrates the efficacy of BFF.

PFT Sub-study Endpoints

Primary Endpoints

- Change from baseline in morning pre-dose trough FEV_1 at week 24 (US) for the comparison of BGF MDI to GFF MDI
- FEV1 area under the curve from 0 to 4 hours (AUC_{0-4}) at week 24 (US) for the comparison of BGF MDI to BFF MDI
- To satisfy non-US regulatory bodies, the PFT sub-study endpoints were also analyzed over 24 weeks

Additional PFT endpoints

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks, over Weeks 12 to 24, over 52 weeks, and at each post-randomization visit
- FEV_1 AUC_{0-4} over 24 weeks, over Weeks 12 to 24, over 52 weeks, and at each post-randomization visit where measured
- Peak change from baseline in FEV_1 over 24 weeks, over Weeks 12 to 24, over 52 weeks, and at each post-randomization visit where measured
- Rate of decline in pre-dose FEV_1 over 52 weeks
- Rate of decline in FEV_1 AUC_{0-4} over 52 weeks
- Time to onset of action on Day 1

24-Hour Holter Monitoring Sub-study Endpoints (Assessed at Week 16)

Primary Endpoint

- Change from baseline in mean heart rate averaged over 24 hours

Secondary Endpoints

- Change from baseline in mean nighttime (22:00 to 06:00) and day time (6:00 to 22:00) heart rate
- Change from baseline in the maximum 24-hour heart rate
- Change from the baseline in the minimum 24-hour heart rate
- Change from baseline in the frequency of isolated ventricular ectopic events (including a single premature ventricular contraction [PVC])
- Change from baseline in the frequency of ventricular couplets (defined as two PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of ventricular runs (defined as three of more PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of supraventricular ectopic beats

- Change from baseline in the frequency of isolated supraventricular ectopic events
- Change from baseline in the frequency of supraventricular couplets
- Change from baseline in the frequency of supraventricular runs
- Incidence of withdrawal criteria being met during 24-hour Holter monitoring
- Incidence of atrial fibrillation with rapid ventricular response (>100 beats per minute [bpm]).

Statistical Analysis Plan

Analysis Population and Estimand

The Applicant defined four analysis populations in this trial: intent-to-treat (ITT) population, modified intent-to-treat (mITT) population, per-protocol (PP) population and safety population.

The ITT Population was defined as all subjects who were randomized to treatment and received at least one dose of the study treatment.

The mITT Population was a subset of the ITT Population, defined as all subjects with post randomization data obtained prior to discontinuation from treatment.

The PP Population was a subset of the ITT Population, defined as all subjects with post randomization data obtained prior to any major protocol deviations. If the first treatment received is the wrong treatment, then the subject was excluded entirely from the PP population.

The safety population was defined as all subjects who are randomized to treatment and received at least one dose of the study treatment. Subjects who had no postdose safety assessments were excluded.

The Applicant defined four estimands for this trial: efficacy estimand, attributable estimand, treatment policy estimand and per protocol estimand. The labels and definitions, in general different than those found in ICH E9(R1), are described below.

The efficacy estimand is the effect of the randomized treatments in all subjects assuming continuation of randomized treatments for the duration of the trial regardless of actual compliance. This assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomized treatment had they remained on treatment.

The attributable estimand is the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized medication for reasons such as tolerability or lack of efficacy is considered a bad outcome.

The treatment policy estimand is the effect of randomized treatment over the trial period regardless of whether randomized treatment is continued.

The per protocol estimand is the effect of treatment on subjects who are compliant with the protocol without major protocol deviation, including the use of randomized medication. All the primary efficacy analyses targeted the efficacy estimand. Only data obtained prior to subjects discontinuing from randomized treatment were utilized in the analyses.

For each dose level, there are two pairwise comparisons of treatments of interest, namely:

- BGF MDI vs. GFF MDI
- BGF MDI vs. BFF MDI

In the next section of the review we focus on the comparison of high dose BGF (320/18/9.6 µg) to GFF and BFF. All references to BGF refer only to the 320/18/9.6 µg arm unless otherwise noted.

Statistical Analysis Model and Additional Analyses

Primary Endpoint

The rate of moderate or severe COPD exacerbations were analyzed using a negative binomial regression model. The model included baseline post-bronchodilator percent predicted FEV1 and log baseline blood eosinophil count as continuous covariates, and baseline COPD exacerbation history, region (US & Canada, Asia, Western Europe, Eastern Europe, Mexico & Central America & South America, Australia & New Zealand & South Africa), and ICS use at screening as categorical covariates. The logarithm of time at risk of experiencing an exacerbation was used as an offset variable in the model. Point estimates of rate ratio with two-sided 95% CIs and two-sided p-values were produced for each treatment comparison.

Secondary Endpoints

The time to first moderate or severe COPD exacerbation was analyzed using a Cox regression model. The model included treatment, baseline post-bronchodilator percent predicted FEV1, and log baseline blood eosinophil count as continuous covariates, and baseline COPD exacerbation history (1, ≥ 2), region (US & Canada, Asia, Western Europe, Eastern Europe, Mexico & Central America & South America, Australia & New Zealand & South Africa), and ICS use at screening (Yes/No) as categorical covariates. Estimated adjusted hazard ratios relative to the comparator were displayed along with the associated Wald two-sided 95% confidence interval and p-values for all treatment comparisons.

Change from baseline in rescue Ventolin HFA use was analyzed using a linear mixed model. The model included treatment, 4-week time interval (Interval 1- Interval 13), the treatment by time interval interaction, and screening ICS use as categorical covariates and baseline post-bronchodilator percent predicted FEV1, baseline rescue Ventolin HFA use, log baseline blood eosinophil count, and percent reversibility to bronchodilator as continuous covariates. Point

estimates of treatment difference with two-sided 95% CIs and two-sided p-values were produced for each treatment comparison.

St. George's Respiratory Questionnaire (SGRQ) was analyzed using a linear mixed model. The model included treatment, visit, and the treatment by visit interaction, and ICS use at screening as categorical covariates and log baseline blood eosinophil count, baseline SGRQ, baseline post-bronchodilator percent predicted FEV1, and percent reversibility to bronchodilator as continuous covariates. Point estimates of treatment difference with two-sided 95% CIs and two-sided p-values were produced for each treatment comparison. SGRQ responder analysis used Logistic regression model. The model included baseline SGRQ Score, log baseline blood eosinophil count, and baseline post-bronchodilator percent predicted FEV1 and percent reversibility to bronchodilator as continuous covariates and treatment, and ICS use at screening as categorical covariates. P-values and odds ratios with 95% CIs were produced for each treatment comparison.

Time to death (All Cause) was analyzed using Cox regression model based on treatment policy estimand. The model adjusted for baseline post-bronchodilator percent-predicted FEV1 and baseline age as covariates. Hazard ratios with Wald 2-sided 95% CIs for these ratios were reported for all treatment comparisons.

The change from baseline in morning pre-dose trough FEV1 was analyzed using an repeated measures (RM) linear mixed model. The RM linear mixed model included baseline FEV1, log baseline blood eosinophil count, and percent reversibility to bronchodilator as continuous covariates and visit, treatment, the treatment by visit interaction, and ICS use at screening as categorical covariates. Point estimates of treatment difference of FEV1 with two-sided 95% CIs and two-sided p-values were produced for each treatment comparison.

The change from baseline in FEV1 AUC_{0-4} was analyzed using an RM linear mixed model similar to that used for pre-dose trough FEV1. The RM linear mixed model included baseline FEV1, log baseline blood eosinophil count, and percent reversibility to bronchodilator as continuous covariates and visit, treatment, the treatment by visit interaction, and ICS use at screening as categorical covariates. Point estimates of treatment difference of FEV1 AUC_{0-4} with two-sided 95% CIs and two-sided p-values were produced for each treatment comparison.

Missing Data Handling and Sensitivity Analysis

For the primary analysis of the primary endpoints and secondary endpoints data collected after discontinuing the study treatment was excluded from the primary analysis and treated as missing.

The sponsor also conducted analyses including data collected after discontinuing study treatment. In this review we will report results on both analyses.

The Applicant has conducted tipping point analysis based on the efficacy estimand as a sensitivity analysis to assess the impact of missing data to the efficacy results.

Multiplicity

The Applicant proposed the overall type I error probability was controlled using a hierarchical testing procedure combined with a Hochberg procedure. Following are the endpoints in the order of hypothesis testing.

- Rate of moderate or severe COPD exacerbations (Efficacy estimand; mITT population): BGF vs GFF & BGF vs BFF
- Rate of moderate or severe COPD exacerbations (Attributable estimand; mITT population): BGF vs GFF & BGF vs BFF
- FEV1 AUC_{0-4} in PFT Sub-study (Efficacy estimand; mITT population): BGF vs BFF
- CFB trough FEV1 (Efficacy estimand; mITT population): BGF vs GFF

After the above testing, the following 3-groups of tests were conducted simultaniously :

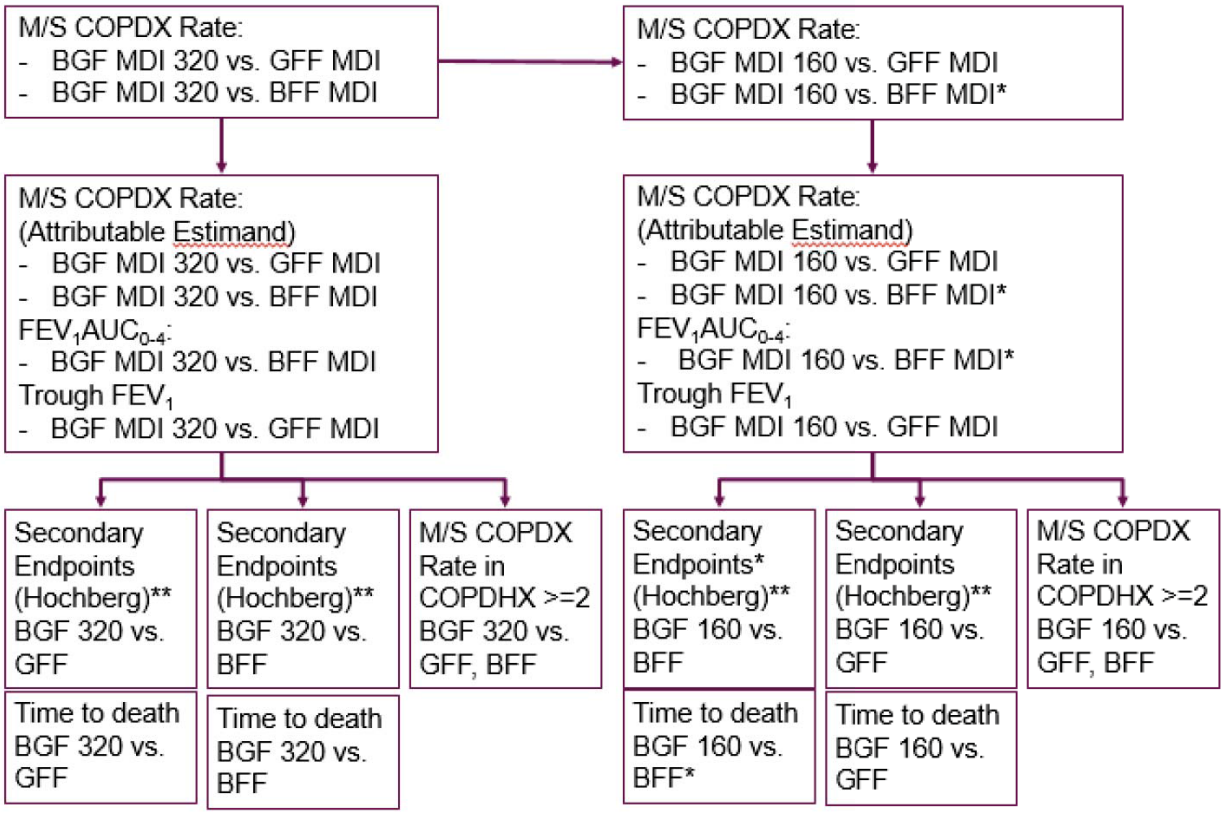
1. Rate of moderate or severe COPD exacerbations in subjects with ≥2 exacerbations in the year before Screening (Efficacy Estimand; mITT Population): BGF vs GFF & BGF vs BFF
2. Hochberg tests:
    - Time to first moderate or severe COPD exacerbation: BGF vs GFF
    - CBF in average daily rescue Ventolin Hydrofluoroalkane (HFA) use over 24 weeks: BGF vs GFF
    - Percentage of subjects achieving a minimal clinically important difference (MCID) of 4 units or more in SGRQ total score at week 24: BGF vs GFF
    - Rate of severe COPD exacerbations: BGF vs GFF
3. Hochberg tests:
    - Time to first moderate or severe COPD exacerbation: BGF vs BFF
    - CBF in average daily rescue Ventolin Hydrofluoroalkane (HFA) use over 24 weeks: BGF vs BFF
    - Percentage of subjects achieving a minimal clinically important difference (MCID) of 4 units or more in SGRQ total score at week 24: BGF vs BFF
    - Rate of severe COPD exacerbations: BGF vs BFF

After the above testing, the following two tests were conducted:

- Time to death (all cause): BGF vs GFF
- Time to death (all cause): BGF vs BFF

Figure 2 presents the diagram of hypothesis testing order.

Figure 2: Order of Hypothesis Testing for Type I Error Control



Source: Statistical Analysis Plan Page 76; Figure 2.
*All comparisons of BGF MDI 160/14.4/9.6 µg vs BFF MDI were for non-inferiority using the PP Estimand followed by superiority. Superiority was not required to advance to the next comparison. All other comparisons were for superiority and used the Efficacy Estimand unless otherwise stated.
**Hochberg-controlled secondary endpoints: Time to first moderate or severe COPD exacerbation, rescue use, rate of severe COPD exacerbation, SGRQ responders.

Subgroup Analysis and Bayesian Shrinkage Subgroup Analysis

For the primary endpoint, subgroup analyses were conducted by the following categories:

- Region (North America, Europe, Asia, Other)
- Age (<65, >=65)
- Gender (Male, Female)
- Race (Black or African American, White, Asian, Other)
- Baseline blood eosinophil counts (<cells/mm3, ≥ cells/mm3)
- COPD exacerbation history (1, ≥2)
- Percent predicted post-bronchodilator FEV1 (50<%, 50≥%)
- Baseline blood eosinophil count and COPD exacerbation history (<150 cells/mm3 and 1 exacerbation, <150 cells/mm3 and ≥2 exacerbations, ≥150 cells/mm3 and 1 exacerbation, ≥150 cells/mm3 and ≥2 exacerbations)

- ICS use (Yes, No)

In this review, we focused on the following subgroup analyses using both traditional subgroup analysis and Bayesian shrinkage subgroup analysis:

- Region
- Age
- Gender
- Race

Protocol Amendments

The first version of the protocol dated May 18, 2015 was amended eight times globally (all countries affected) on July 4, 2015, August 17, 2015, January 8, 2016, August 25, 2016, September 19, 2016, November 3, 2017, March 27, 2018, and June 21 2019. Japan-specific amendments were also made. Global protocol amendments are summarized as follows:

July 4, 2015 Amendment

- Clarified that all subjects must have a documented history of COPD
- More specific guidance added for the minimum duration of corticosteroid and/or antibiotic washout used to treat COPD exacerbation or lower respiratory tract infection
- Provided guidance that COPD exacerbation could be treated as appropriate by healthcare provider
- Noted that pneumococcal and influenza vaccine should be considered versus required to account for regional differences
- Clarified that steroids were allowed in Screening Period for treatment of COPD exacerbation. Added guidance on subjects who were steroid dependent.
- ICS/LABA combinations were updated
- Severely reduced kidney function included as a reason for treatment discontinuation or study withdrawal

August 17, 2015 Amendment

- The end of the study date was defined as the date on which data were collected for last subject's follow-up telephone call. Timing of the interim efficacy analysis was clarified

January 8, 2016 Amendment

- Revised post-bronchodilator FEV1 requirement for subjects during screening
- Percentage of subjects achieving a MCID of ≥ 4 units in SQRG total score was added as a secondary and other endpoint
- Statistical methods regarding the primary efficacy analysis of rate of moderate of severe COPD exacerbations was revised
- Clarity was added regarding timing of interim analysis
- The end date defined as the date on which data were collected for the last subject's follow-up telephone call
- Clarified that visit 4 FEV_1 was only required for those subjects in the PFT sub-study
- Chest X-ray was allowed in the study

- Nebulized albuterol was acceptable with a minimum 6 hour washout prior to visit 1
- Follow-up spirometry assessments added for early discontinuations
- Analysis of Transition Dyspnea Index (TDI) was revised
- Analysis of percentage of days with "no rescue Ventolin HFA use" over the Treatment Period was revised
- Analysis of change from baseline was revised
- Time to onset on Day 1 analysis text was added

August 25, 2016 Amendment

- Secondary efficacy endpoints and other endpoints were revised
- Text regarding blood eosinophil count covariate used in efficacy analysis was revised
- Caffeine containing medications were added to restricted medications
- Allowed subjects who failed acceptability and repeatability spirometry criteria to have these criteria reassessed at Visit 2
- Limit of calculated creatinine clearance was lowered
- Nebulized products were permitted only prior to Visit 1
- Aligned pneumococcal and annual influenza vaccination recommendations per local policies, availability, and affordability
- Changes to prohibited COPD medications, other medications, and required washout were revised
- Reasons for treatment discontinuation and study withdrawal were clarified
- Hy's law criteria were added, which were initially omitted in error
- Added testing BGF MDI 160/14/9.6 µg MDI to BFF MDI for non-inferiority (NI) followed by superiority and specified the order of efficacy comparisons
- Removed texts on handling missing data, as they were not finalized yet
- Analysis of rescue Ventolin revised
- Testing was added in the "baseline eosinophil count high" subgroup for the comparisons of triple therapy vs GFF MDI

September 19, 2016 Amendment

- Updated exclusion criterion numbering

November 3, 2017 Amendment

- Removal of need for confirmation by central reading for exclusion criterion 4
- Clarified treatment discontinuation language and allowed medications to treat COPD exacerbation
- Clarification that antibiotics with the potential to prolong QT interval are not prohibited
- Clarified that AEs occurring between informed consent signing and randomization would be summarized as medical history unless they met definition of serious adverse event (SAE)
- Removed 14 day follow up phone call after the last study visit for subjects who discontinue study drug but continue in study
- Updated sample size calculations to increase sample size by 400 subjects
- Clarified data included in and analysis to be completed with the mITT population
- Added region as a covariate for rate of moderate or severe COPD exacerbation and time to first COPD exacerbation

- Replaced high eosinophils subgroup with history of exacerbations, and added the comparison of BGF 320/14.4/9.6 µg vs BFF MDI for the subgroup
- Clarified the primary and secondary Holter monitoring endpoint analyses
- Specified the details on the potential impact of missing data

March 27, 2018 Amendment

- Requirement of an enrolled target to achieve twice as many randomized subjects in the high blood eosinophil stratum (≥150 cells/mm^3) versus low eosinophil stratum (<150 cells/mm3)
- Enrollment into PFT sub-study targeted only subjects with a high blood eosinophil count of ≥150 cells/mm^3 at Visit 1

June 21, 2019 Amendment

- Added secondary objective and moved rate of severe COPD exacerbation from other efficacy endpoint to secondary efficacy endpoint
- Removed several other efficacy endpoints and revised 24-hour Holter monitoring sub-study and HCRU endpoints
- Updated definition of duration of moderate or severe COPD exacerbation
- Clarified start date of COPD exacerbation was not excluded from time-at-risk of a COPD exacerbations
- Updated analysis to include the log baseline blood eosinophil count as a covariate instead of baseline blood eosinophil count
- Clarified FEV_1 AUC analysis model
- Added treatment and smoking status terms for rate of decline in predose FEV_1 and FEV_1 AUC_{0-4}
- Corrected NI margin from 0.1 to 1.1 for the comparisons of the two BGF groups on COPD exacerbations
- Upper limit criteria for glucose changed

The protocol amendments submitted do not affect the interpretation of results for Trial 05.

8.1.2. Study Results

This section of the review of efficacy is for BGF Trial 05, the dedicated BGF phase 3 exacerbation trial. Previously reviewed BGF phase 3 studies (Trial 06 and Trial 08), and BFF phase 3 studies (Trial 02 and Trial 03) will be summarized where appropriate (see review by Dr. Clerman dated September 30, 2019 for complete review). The efficacy for the dual component GFF was established under the approval of NDA 208294 (see review by Dr. Chin dated March 21, 2016) and will not be discussed here.

Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in the clinical study report in Trial 05.

Financial Disclosure

See Section 19.2.

Patient Disposition

Patient analysis sets are presented in Table 12. In Trial 05, the BGF 52-week exacerbation trial, 8588 patients were randomized and 8573 received at least one dose of study drug. Of these, 79 (0.7%) were not included in the intent-to-treat population (ITT) or modified ITT (mITT) population and 44 (0.5%) were not included in the Safety Population. The ITT population is identical to the mITT population in terms of included patients. The primary reason for patient exclusion from the ITT/mITT and safety population was participation in multiple Applicant phase 3 trials and/or multiple study sites. The ITT/mITT population included 8509 subjects and the Safety Population include 8529 patients.

Table 12. Analysis Sets (All Subjects Randomized)

	BGF 320/14.4/9.6 µg (N=2157) n (%)	BGF 160/14.4/9.6 µg (N=2137) n (%)	GFF 14.4/9.6 µg (N=2143) n (%)	BFF 320/9.6 µg (N=2157) n (%)	Total (N=8588) n (%)
Treated subjects	2156 (100.0)	2132 (99.8)	2139 (99.8)	2146 (99.8)	8573 (99.8)
ITT Population	2137 (99.1)	2121 (99.5)	2120 (99.1)	2131 (99.3)	8509 (99.3)
mITT Population	2137 (99.1)	2121 (99.5)	2120 (99.1)	2131 (99.3)	8509 (99.3)
Safety Population	2144 (99.4)	2124 (99.6)	2125 (99.3)	2136 (99.5)	8529 (99.5)
4-hour PFT Sub-study mITT Population	747 (34.6)	807 (37.9)	779 (36.4)	755 (35.2)	3088 (36.0)
Holter Monitoring Sub-study Population	180 (8.3)	196 (9.2)	161 (7.5)	184 (8.6)	721 (8.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; ITT: intention to treat; mITT: modified intention to treat;
Source: PT010005 CSR Edition 1; Table 23; pg 121; confirmed by Clinical Reviewer

Overall, the number of patients excluded from the ITT, mITT, and Safety Population was small (<1%) and similar across treatment groups and not likely to affect interpretation or analyses of results.

Of the 8588 randomized patients, 7187 completed the trial and 6654 completed treatment. Patient disposition for Trial 05 is presented in Table 13.

Table 13. BGF Trial 05 Subjects Disposition (All Subjects Randomized)

	BGF 320/14.4/9.6 µg (N=2157) n (%)	BGF 160/14.4/9.6 µg (N=2137) n (%)	GFF 14.4/9.6 µg (N=2143) n (%)	BFF 320/9.6 µg (N=2151) n (%)	All Subjects (N=8588) n (%)
Not treated	1 (<0.1)	5 (0.2)	4 (0.2)	5 (0.2)	15 (0.2)
Treated	2156 (100.0)	2132 (99.8)	2139 (99.8)	2146 (99.8)	8573 (99.8)
Completed 52 weeks of treatment with study drug	1711 (79.4)	1715 (80.4)	1584 (74.1)	1644 (76.6)	6654 (77.6)
Discontinued from study drug	445 (20.6)	417 (19.6)	555 (25.9)	502 (23.4)	1919 (22.4)
Completed study	104 (4.8)	105 (4.9)	180 (8.4)	144 (6.7)	533 (6.2)
Withdrawn from study	342 (15.9)	317 (14.9)	379 (17.7)	363 (16.0)	1401 (16.3)
Completed Study	1815 (84.2)	1820 (85.4)	1764 (82.5)	1788 (83.3)	7187 (83.8)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate;
Source: PT010005 CSR Edition 1; Table 20; pg 117; confirmed by Statistical Reviewer

In terms of treatment discontinuations in Trial 05, the GFF 14.4/9.6 µg group had the highest rate of discontinuation (25.69) and BGF 160/14.4/9.6 µg had the lowest (19.6%). Reasons for discontinuation in Trial 05 for the Safety Population are shown in Table 14. Reasons for discontinuation were similar across groups except for the reason of lack of efficacy, where the GFF group had a higher rate of discontinuations while the other groups were similar in rates. The most common reason for discontinuation was adverse events. The discontinuation results are shown for the Safety Population as it is slightly larger than the ITT population. Similar analyses were performed with the ITT population with similar results.

Table 14. BGF Trial 05 Reasons for Discontinuation From Study Drug (Safety Population)

Reason for Discontinuation	BGF 320/14.4/9.6 µg (N=2144)	BGF 160/14.4/9.6 µg (N=2124)	GFF 14.4/9.6 µg (N=2125)	BFF 320/9.6 µg (N=2136)	Total (N=8529) n (%)
Discontinued from the study drug	437 (20.4)	412 (19.4)	544 (25.6)	492 (23.0)	1885[a] (22.1)
Adverse events	118 (4.8)	114 (5.4)	147 (6.9)	138 (6.5)	517 (6.1)
Lack of efficacy	103 (4.8)	102 (4.8)	171 (8.0)	136 (6.4)	512 (6.0)
Subject discretion	104 (4.9)	94 (4.4)	123 (5.8)	130 (6.1)	451 (5.3)
Investigator or designee considers it to be in subject's best interest	23(1.1)	33 (1.6)	38 (1.8)	28 (1.3)	122 (1.4)
Major protocol deviation	30 (1.4)	27 (1.3)	26 (1.2)	28 (1.3)	111 (1.3)
Subject lost to follow-up	25 (1.2)	21 (1.0)	19 (0.9)	15 (0.7)	80 (0.9)
Protocol-specified discontinuation criteria	20 (0.9)	10 (0.5)	9 (0.4)	12 (0.6)	51 (0.6)
Administrative reason	13 (0.6)	10 (0.5)	11 (0.5)	5 (0.2)	39 (0.5)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate;
[a]Two subjects did not have a reason for discontinuation
Source: PT010005 CSR Edition 1; Table 21; pg 118; confirmed by Clinical Reviewer

Overall, patient disposition and treatment discontinuation across the BGF program is not likely to affect the interpretation of safety or efficacy results.

Protocol Violations/Deviations

In the BGF safety population, there were 59 (0.7%) subjects with a major protocol deviation. Major protocol deviations included but were not limited to: enrollment in more than one sponsor Phase 3 study (0.5%) and randomized but not dosed (0.2%).

Overall, the protocol violations were similar between treatment groups and not likely to affect the interpretation of results.

Table of Demographic Characteristics

Patient demographic characteristics for the ITT populations are shown in Table 15. The ITT demographics are presented as this population was the basis for the efficacy analyses. The average age was 64.7 years and the majority of patients were ≥65 years. There were more males than

females and the most common race was White followed by Asian. The demographics were similar in the Safety Population.

Table 15. Demographics (ITT Population)

	BGF 320/14.4/9.6 µg (N=2137)	BGF 160/14.4/9.6 µg (N=2121)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=2131)	All Subjects (N=8509)
Age					
N	2137	2121	2120	2131	8509
Mean	64.6 (7.6)	64.6 (7.6)	64.8 (7.6)	64.6 (7.6)	64.7
Median	65.0	65.0	65.0	65.0	65.0
Min, Max	43, 81	41, 81	40, 80	40, 80	40, 81
Age group, n (%)					
<65 years	1037 (48.5)	1028 (48.5)	992 (46.8)	1022 (48.0)	4079 (47.9)
≥ 65 years	1100 (52.5)	1093 (51.5)	1128 (53.2)	1109 (52.0)	4430 (52.1)
Gender, n(%)					
Male	1260 (59.0)	1298 (61.2)	1244 (58.7)	1279 (60.0)	5081 (59.7)
Female	877 (41.0)	823 (38.8)	876 (41.3)	852 (40.0)	3428 (40.3)
Race, n(%)					
Black or African American	78 (3.6)	88 (4.1)	75 (3.5)	64 (3.0)	305 (3.6)
White	1819 (85.1)	1783 (84.1)	1808 (85.3)	1816 (85.2)	7226 (84.9)
Native Hawaiian or Pacific Islander	2 (0.1)	0	0	0	2 (<0.1)
Asian	162 (7.6)	166 (7.8)	157 (7.4)	166 (7.8)	651 (7.7)
Other	43 (2.0)	44 (2.1)	50 (2.4)	46 (2.2)	183 (2.2)
Ethnicity, n(%)					
Hispanic or Latino	400 (18.7)	393 (18.5)	426 (20.1)	401 (18.8)	1620 (19.0)
Not Hispanic or Latino	1690 (79.1)	1680 (79.2)	1649 (77.8)	1683 (79.0)	6702 (78.8)
Unknown	21 (1.0)	27 (1.3)	24 (1.1)	25 (1.2)	97 (1.1)
Not Reported	26 (1.2)	21 (1.0)	21 (1.0)	22 (1.0)	90 (1.1)
BMI (kg/m2)					
N	2136	2120	2120	2131	8507
Mean (SD)	27.6 (6.2)	27.5 (6.3)	27.6 (6.2)	27.1 (6.2)	27.4 (6.2)
Median	26.9	26.5	26.7	26.3	26.6
Min,max	14.3, 60.9	14.0, 65.3	14.5, 70.3	12.6, 60.2	12.6, 70.3

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate;
Source: PT010005 CSR Edition 1; Table 24; pg 123; confirmed by Clinical Reviewer

The demographics are similar across groups. Overall, the demographic were well-balanced and fairly representative of the COPD population.

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

In Trial 05, COPD symptom scores, COPD severity, smoking history, baseline spirometry and cardiovascular disease history were similar across groups. Background COPD medication use was also similar between groups. ICS use at Screening was similar among all treatment groups, with 80.5% of subjects using ICS at Screening.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The treatment compliance was approximately 93% across groups and the majority of subjects in each treatment group were 80% to 100% complaint. Compliance was defined as the total number of puffs per day divided by the total expected puffs per day averaged across all days of dosing multiplied by 100. Concomitant medications that were initiated after study entry were similar across groups in both rates and medication used. The most common concomitant non-COPD medications were acetylsalicylic acid, atorvastatin, and amlodipine. The most common COPD-related medications were oxygen, theophylline, and salbutamol.

Efficacy Results – Primary Endpoint

The presentation of efficacy data will focus on the BGF dose for which the sponsor is seeking approval for, BGF MDI 320/14.4/9.6 µg. For the following efficacy section, BGF MDI 320/14.4/9.6 µg will be referred to as BGF, GFF MDI 14.4/9.6 µg will be referred to as GFF, and BFF MDI 320/14.4 µg will be referred to as BFF. Results for the lower dose, BGF 160/14.4/9.6 µg are summarized in the subsection titled Dose/Dose Response.

For Trial 05, the primary endpoint was the rate of moderate or severe COPD exacerbations (Efficacy Estimand).

To support the contribution of the ICS component (budesonide) and the LAMA component (glycopyrrolate) to BGF, the rate of moderate or severe exacerbations (Efficacy Estimand) for BGF was compared to GFF and BFF. The treatment rate ratio was 0.76 between BGF and GFF (95% CI: 0.69, 0.83; p<0.0001) and was statistically significant. The treatment rate ratio was 0.87 between BGF and BFF (95% CI: 0.79, 0.95; p=0.0027) and was statistically significant. Based on the comparisons of BGF to BFF and GFF, both the LAMA (glycopyrrolate) and ICS (budesonide) appear to contribute to a decrease in moderate or severe exacerbation following treatment with BGF. These data are summarized in Table 16.

Table 16. Rate of Moderate or Severe COPD Exacerbations (Efficacy Estimand; mITT Population)

	BGF 320/14.4/9.6 µg (N=2137)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=2131)
Subject with moderate or severe COPD exacerbations n (%)	1026 (48.0)	1056 (49.8)	1085 (50.9)
Adjusted rate per year (SE)	1.08 (0.04)	1.42 (0.05)	1.24 (0.04)
Treatment Rate ratio, 95% CI	N/A	0.76 (0.69, 0.83)	0.87 (0.79, 0.95)
p-value	N/A	<0.0001	0.0027

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 38; pg 150; confirmed by Statistical Reviewer

Results based on the Treatment Policy Estimand are considered important from the regulatory standpoint. Therefore, the results using the treatment policy estimand are summarized in Table 17, although the analysis was not included in the multiplicity hierarchy. The results are consistent with the results from the primary efficacy estimand and support the efficacy of BGF and the contribution of the ICS and LAMA monocomponents to the combination.

Table 17: Rate of Moderate or Severe COPD Exacerbations (Treatment Policy Estimand; ITT Population)

	BGF 320/14.4/9.6 µg (N=2137)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=2131)
Subject with moderate or severe COPD exacerbations n (%)	1062 (49.7)	1093 (51.6)	1135 (53.3)
Adjusted rate per year (SE)	1.07 (0.03)	1.31 (0.04)	1.20 (0.04)
Treatment Rate ratio, 95% CI	N/A	0.82 (0.75, 0.89)	0.89 (0.82, 0.97)
p-value	N/A	<0.0001	0.0107

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease
Source: Statistical Reviewer

Results for the primary endpoint in the BGF Trial 05 demonstrate contribution of ICS and LAMA monocomponents in reducing moderate or severe COPD exacerbations. While in the previously reviewed BGF Trial 06, a statistically significant reduction in exacerbations was not demonstrated when comparing BGF to GFF or BFF, trends were similar with point estimates for rate ratios at <1.

Overall, these exacerbation data from the BGF program demonstrate that BGF reduces moderate and severe exacerbations and that both the ICS and LAMA monocomponents contribute to that 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

The secondary endpoints for Trial 05 are as follows:

- Rate of moderate or severe COPD exacerbations (Attributable Estimand)
- Time to first moderate or severe COPD exacerbation
- Rate of severe COPD exacerbations
- Rate of moderate or severe COPD exacerbations in subjects with ≥2 moderate or severe COPD exacerbations in the prior year
- Percentage of subjects achieving an MCID of ≥4 units in SQRQ total score at week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to death (all-cause)

Exacerbation

To provide additional support for the contribution of the ICS and LAMA monocomponents to BGF, the rate of moderate or severe exacerbations for BGF was compared to GFF and BFF using the Attributable Estimand. The treatment rate ratio was 0.76 between BGF and GFF (95% CI: 0.71, 0.83; p<0.0001) and was statistically significant. The treatment rate ratio was 0.85 between BGF and BFF (95% CI: 0.78, 0.92; p<0.0001) and was also statistically significant. Based on these comparisons, and consistent with the primary endpoint, both the LAMA and ICS monocomponents contribute to the exacerbation effect observed with BGF. These data are summarized in Table 18.

The time to first moderate or severe exacerbations for BGF was longer in months than for GFF and BFF. The hazard ratio was 0.880 between BGF and GFF (95% CI: 0.807, 0.959; p=0.0035) and was statistically significant. The hazard ratio was 0.887 between BGF and BFF (95% CI: 0.814, 0.966; p=0.0057) and was statistically significant. These data also support the primary analysis and are presented in Table 19.

Table 18. Rate of Moderate or Severe COPD Exacerbations (Attributable Estimand; mITT Population)

	BGF 320/14.4/9.6 µg (N=2137)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=2131)
Subject with moderate or severe COPD exacerbations n (%)	1026 (48.0)	1056 (49.8)	1085 (50.9)
Adjusted rate per year (SE)	1.25 (0.04)	1.63 (0.06)	1.47 (0.05)
Treatment Rate ratio, 95% CI	N/A	0.76 (0.71, 0.83)	0.85 (0.78, 0.92)
p-value	N/A	<0.0001	<0.0001

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 38; pg 151; confirmed by Statistical Reviewer

Table 19. Time to First Moderate or Severe COPD Exacerbation (Efficacy Estimand, mITT)

	BGF 320/14.4/9.6 µg (N=2137)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=21310)
Subject with moderate or severe COPD exacerbations n (%)	1026 (48.0)	1056 (49.8)	1085 (50.9)
Time to first exacerbation (months)	3.7	2.6	3.1
Hazard ratio, 95% CI	N/A	0.880 (0.807, 0.959)	0.887 (0.814, 0.966)
p-value	N/A	0.0035	0.0057

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease; mITT: modified intention to treat
Source: PT010005 CSR Edition 1; Table 40; pg 155; confirmed by Statistical Reviewer

The rate of severe COPD exacerbations with BGF relative to BFF (rate ratio [95% CI]: 0.80 [0.66, 0.97], p=0.0221) was statistically significant. The rate of severe COPD exacerbations with BGF relative to GFF (rate ratio [95% CI]: 0.84 [0.69, 1.03], p=0.0944) was numerically lower, but was not statistically significant. Similar analyses were performed by FDA biostatisticians using the Treatment Policy Estimand in the ITT population. In contrast to the mITT analyses, the rate of severe exacerbation when comparing BGF to BFF had a rate ratio with a 95% CI that did not exclude null, though the point estimate was <1. These data are presented in Table 20.

Table 20. Rate of Severe COPD Exacerbations

	BGF 320/14.4/9.6 µg (N=2137)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=2131)
Efficacy Estimand; mITT population			
Subject with severe COPD exacerbations n (%)	219 (10.2)	239 (11.3)	261 (12.2)
Adjusted rate per year (SE)	0.13 (0.01)	0.15 (0.01)	0.16 (0.01)
Rate Ratio, 95% CI	N/A	0.84 (0.69, 1.03)	0.80 (0.66, 0.97)
p-value	N/A	0.0944	0.0221
Treatment Policy Estimand; ITT population			
Subject with severe COPD exacerbations n (%)	247 (11.6)	261 (12.3)	278 (13.0)
Adjusted rate per year (SE)	0.14 (0.01)	0.15 (0.01)	0.16 (0.01)
Rate ratio, 95% CI	N/A	0.91 (0.75, 1.10)	0.87 (0.72, 1.04)
p-value	N/A	0.3165	0.1279

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease; mITT: modified intention to treat ; ITT= intent to treat
Source: PT010005 CSR Edition 1; Table 41; pg 157; confirmed and generated by Statistical Reviewer

Overall, while the severe exacerbation data are generally consistent with primary analyses, in that they trend in the positive direction, they do not warrant inclusion in the label.

The rate of moderate or severe COPD exacerbations in subjects with a history of ≥2 moderate of severe COPD exacerbations in the year before screening was lower with BGF relative to GFF

(rate ratio [95% CI]: 0.73 [0.65, 0.83], p<0.0001) and was statistically significant. The rate of moderate or severe COPD exacerbations in subjects with a history of ≥2 moderate of severe COPD exacerbations in the year before screening was numerically lower with relative to BFF (rate ratio [95% CI]: 0.89 [0.79, 1.01, p=0.0680]. These data are presented in Table 21. Similar analyses were performed using treatment policy estimand in the ITT population. Results were similar (Table 22).

Table 21. Rate of Moderate of Severe COPD Exacerbations in Subjects with a History of ≥2 Moderate or Severe COPD exacerbations in the Year before Screening (mITT population)

	BGF 320/14.4/9.6 µg (N=1195)	GFF 14.4/9.6 µg (N=1211)	BFF 320/9.6 µg (N=1217)
Subject with moderate or severe COPD exacerbations n (%)	600 (50.2)	632 (52.2)	642 (52.8)
Adjusted rate per year (SE)	1.17 (0.05)	1.60 (0.07)	1.32 (0.06)
Rate Ratio, 95% CI	N/A	0.73 (0.65, 0.83)	0.89 (0.79, 1.01)
p-value	N/A	<0.0001	0.0680

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease; mITT: modified intention to treat
Source: PT010005 CSR Edition 1; Table 39; pg 153; confirmed by Statistical Reviewer

Table 22: Rate of Moderate of Severe COPD Exacerbations in Subjects with a History of ≥2 Moderates or Severe COPD exacerbations in the Year before Screening (ITT population)

	BGF 320/14.4/9.6 µg (N=1195)	GFF 14.4/9.6 µg (N=1211)	BFF 320/9.6 µg (N=1217)
Subject with moderate or severe COPD exacerbations n (%)	622 (52.1)	649 (53.6)	661 (54.3)
Adjusted rate per year (SE)	1.16 (0.05)	1.47 (0.06)	1.26 (0.05)
Treatment Rate ratio, 95% CI	N/A	0.79 (0.71, 0.89)	0.92 (0.82, 1.04)
p-value	N/A	<0.0001	0.1746

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease; mITT: modified intention to treat
Source: Statistical Reviewer

Overall, the results of the secondary endpoints related to exacerbation in Trial 05 were generally consistent with the results of the primary endpoint, supporting the efficacy of BGF and the contribution of ICS and LAMA monocomponents to the triple combination.

SGRQ

A higher proportion of subjects achieved an improvement of ≥4 units in the SGRQ total score over their baseline scores at Week 24 with BGF (50.4%) relative to both GFF (42.6%) and BFF (44.7%). The number of responders was statistically greater in the BGF group at Week 24 when compared with GFF (treatment difference of 7.60%, odds ratio of 1.358, p<0.0001) and BFF (treatment difference of 5.47%, odds ratio of 1.246, p=0.0005). These data are presented in Table 23.

Table 23. Subjects Achieving an Improvement of ≥4 units in SGRQ Total Score at Week 24

	BGF 320/14.4/9.6 µg (N=2119)	GFF 14.4/9.6 µg (N=2096)	BFF 320/9.6 µg (N=2122)
Efficacy Estimand; mITT population			
Responder, n(%)	1068 (50.4)	893 (42.6)	949 (44.7)
Difference, 95% CI	N/A	7.60 (4.52, 10.68)	5.47 (2.39, 8.55)
Odds ratio, 95% CI	N/A	1.358 (1.199, 1.539)	1.246 (1.100, 1.410)
p-value	N/A	<0.0001	P=0.0005
Treatment Policy Estimand; ITT population			
Responder n (%)	1097 (51.8)	956 (45.6)	997 (47.0)
Difference, 95% CI	N/A	5.9 (2.8, 9.00)	4.53 (1.43, 7.62)
Odds ratio, 95% CI	N/A	1.267 (1.118, 1.435)	1.199 (1.059, 1.357)
p-value	N/A	P=0.0002	P=0.0042

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease; mITT= modified in intent to treat; ITT= intent to treat
Source: PT010005 CSR Edition 1; Table 45; pg 166; confirmed and generated by Statistical Reviewer

At Week 52, a higher proportion of subjects achieved an improvement of ≥4 units in the SGRQ total score over their baseline scores with BGF (44.2%) relative to both GFF (36.5%) and BFF (39.5%). The number of responders was greater in the BGF group at Week 52 when compared with GFF (treatment difference of 7.51%, odds ratio of 1.368) and BFF (treatment difference of 4.89%, odds ratio of 1.224). The treatment differences of BGF vs GFF and BGF vs BFF at Week 52 were similar to the differences observed at Week 24.

Overall, the results of the improvement in SGRQ responses provide evidence supporting the effectiveness of BGF over GFF and BFF and demonstrate the contribution of ICS (BGF vs. GFF) and LAMA (BGF vs. BFF). These data also warrant inclusion in the label, as information regarding the domains covered in the SGRQ are relevant to patients and informative to healthcare providers.

Rescue Medication Use

Subjects treated with BGF used less rescue Ventolin HFA on average over 24 weeks relative to both GFF (LS mean difference of -0.51 puffs/day; 95%CI -0.68, -0.34; p<0.0001) and BFF (LS mean difference of -0.37 puffs/day; 95%CI -0.54, -0.2; p<0.0001). Ventolin use decrease in the BGF group compared to both GFF and BFF was not statistically significant due to earlier failure in the analysis hierarchy.

Mortality

A lower proportion of subjects died during the study with BGF (1.3%) relative to GFF (2.3%) and BFF (1.6%). The time to death (all cause) was defined as the number of days from randomization to the date of death. As assessed by the Cox proportional hazards model, the risk of death (all cause) was lower during treatment with BGF relative to GFF (HR [95%CI]: 0.544 [0.340, 0.870], p=0.0111) and were not statistically significant due to earlier failure in the

analysis hierarchy. The risk of death (all cause) was numerically lower during treatment with BGF relative to BFF (HR [95%CI]: 0.782 [0.472, 1.296], p=0.3401), but not statistically significant. These data are presented in Table 24.

Table 24. Time to Death (All Cause) (Treatment Policy Estimand, ITT Population)

	BGF 320/14.4/9.6 µg (N=2137)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=2131)
Subject deaths, n (%)	28 (1.3)	49 (2.3)	34 (1.6)
Hazard Ratio, 95% CI	N/A	0.544 (0.340, 0.870)	0.782 (0.472, 1.296)
p-value	N/A	0.0111	0.3401

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate;
Source: PT010005 CSR Edition 1; Table 48; pg 174; confirmed by Statistical Reviewer

Dose/Dose Response

The doses for GP and FF were established in the GFF program reviewed under NDA 208294 (see review by Dr. Stacy Chin dated March 21, 2016), and so only the dose for BD needed to be established in this development program. The data to support the BD and BFF dose used in the BGF combination in the phase 3 studies was previously reviewed (see Unireview dated September 30, 2019). Trial 05 included two doses of the BGF combination, 320/14.4/9.6µg and 160/14.4/9.6µg. The treatment effect in terms of primary endpoint of rate of moderate or severe exacerbation was statistically significant for both doses and similar when comparing the two doses and not suggestive of a dose-response. With regard to spirometry endpoints, in the spirometric substudy both doses demonstrated statistically significant improvements versus the comparators. The BGF 320/14.4/9.6 µg had slightly numerically larger effect size compared to BGF 160/14.4/9.6 µg in terms of FEV1 AUC(0-4), which may suggest some dose response. Results were similar for the trough FEV1. These results are summarized in Table 25.

Table 25. Overview of Results of Primary and Secondary Efficacy Endpoints

Comparisons	BGF 320/14.4/9.6 µg vs GFF MDI	BGF 320/14.4/9.6 µg vs BFF MDI	BGF 160/14.4/9.6 µg vs GFF MDI	BGF 160/14.4/9.6 µg vs BFF MDI
Primary endpoint				
Rate of moderate or severe COPD exacerbations (Efficacy Estimand; mITT population)				
Treatment Rate Ratio	0.76	0.87	0.75	0.86
95% CI	0.69, 0.83	0.79, 0.95	0.69, 0.83	0.79, 0.95
p-value	<0.0001*	0.0027*	<0.0001*	0.0020*
Primary PFT Sub-study endpoints				
FEV_1 AUC_{0-4} at Week 24 (mL) (Efficacy Estimand; mITT Population)				
LS mean (SE)	53 (12.1)	119 (12.1)	43 (11.9)	109 (11.9)

95% CI	29, 77	95, 143	19, 66	85, 132
p-value	<0.0001§	<0.0001*	0.0004§	<0.0001§
Change from baseline in morning predose trough FEV1 at Week 24 (mL) (Efficacy Estimand; mITT Population)				
LS mean (SE)	35 (11.5)	76 (11.4)	33 (11.3)	74 (11.2)
95% CI	12, 57	54, 99	11, 55	52, 96
p-value	0.0025*	<0.0001§	0.0035*	<0.0001§

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate;
Note: *=statistically significant; § = p<0.046 but not included in Type I error control
Source: PT010005 CSR Edition 1; Table 36; pg 145; confirmed by Statistical Reviewer

These data suggest that the treatment effect of the higher BGF dose is not substantially higher than the lower dose. However, as the results for the safety analyses are similar between the two BGF doses (see 8.2) and there is more safety data for the higher dose, as the lower dose was not studied in trial 06, (b) (4) (b) (4)

Durability of Response

In BGF Trial 06, studies supporting the durability of effect for BGF were completed (see review by Dr. Andrew Clerman dated September 30, 2019).

Persistence of Effect

No analysis was performed to assess the persistence of effect because the effects of BGF are not expected to persist following treatment discontinuation.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

SGRQ responder analysis of the percentage of patients achieving an improvement of 4 units in SGRQ total score revealed a statistically significant difference for BGF over GFF (p<0.0001) and BFF (p=0.0005). These data are presented in Table 23.

Additional Analyses Conducted on the Individual Trial

PFT Sub-study

A PFT sub-study was included in Trial 05 to evaluate the effect of BGF relative to GFF and BFF on lung function. A subset of 3088 subjects from the overall mITT/ITT Population was included in the PFT Sub-study. The 2 primary endpoints of this sub-study were:

- FEV_1 AUC_{0-4} at Week 24 for the comparison of BGF to BFF
- Change from the baseline in the morning predose trough FEV1 at Week 24 for the comparison of BGF to GFF

FEV_1 AUC_{0-4} at Week 24

The use of BGF resulted in a statistically significant improvement in LS mean FEV_1 AUC_{0-4} at Week 24 compared to BFF (119ml; 95%CI 95, 143mL; p<0.0001). This demonstrated that the LAMA monocomponent contributed to the bronchodilatory effect of BGF. When comparing BGF with GFF, an improvement in LS mean FEV1 AUC_{0-4} at Week 24 was demonstrated (53ml;

95%CI 29, 77mL; p<0.0001). However, these results were not considered statistically significant as the BGF vs. GFF comparison was not included in the testing hierarchy. That being said, this does suggest that the ICS monocomponent also contributes to the bronchodilatory effect. Similar analyses using the Treatment Policy Estimand on the ITT population yielded similar results. These data are presented in Table 26.

Table 26. FEV_1 AUC_{0-4} (mL) at Week 24 - PFT Sub-study

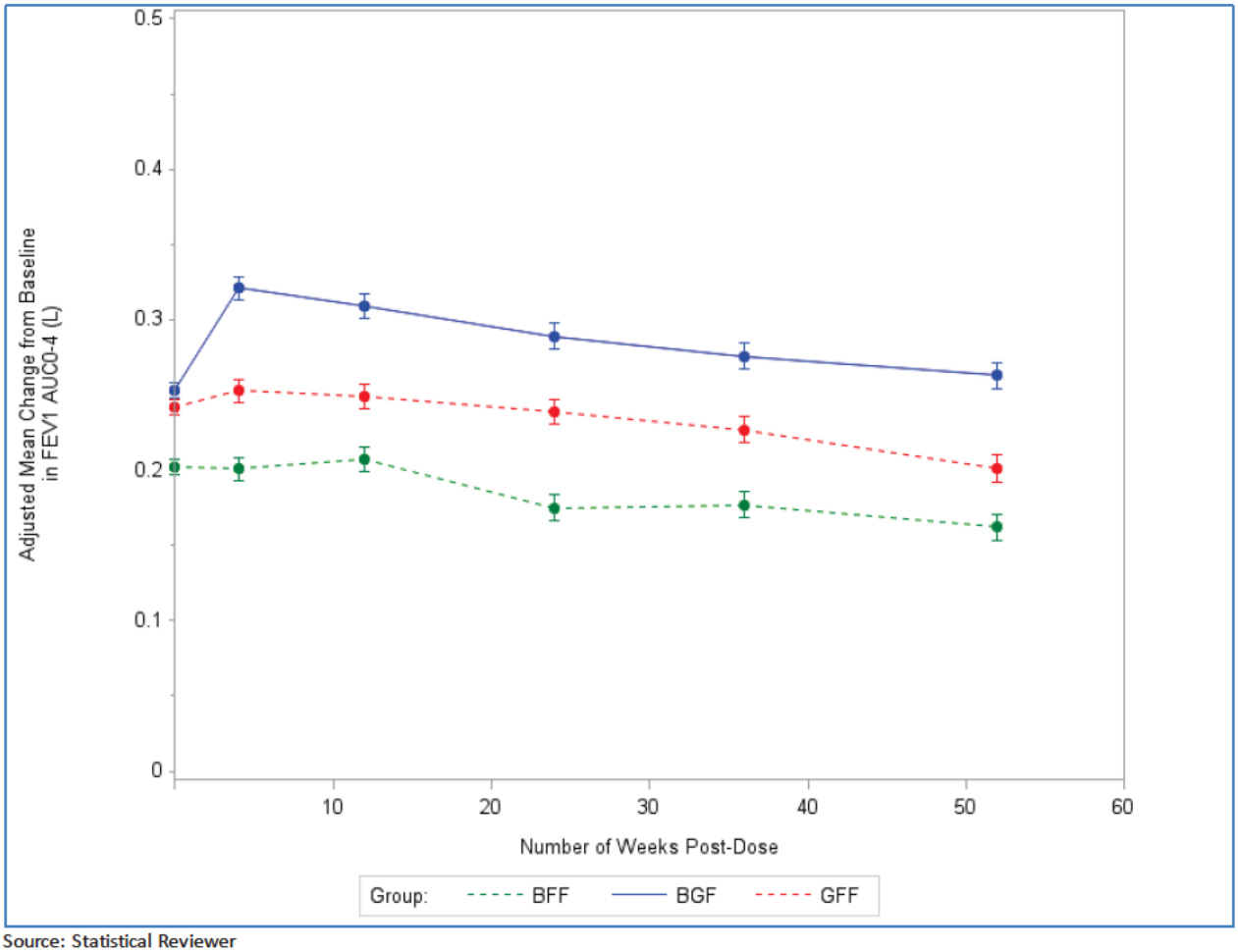
	BGF 320/14.4/9.6 µg (N=747)	GFF 14.4/9.6 µg (N=779)	BFF 320/9.6 µg (N=755)
Efficacy Estimand; mITT population			
n	633	588	605
LS mean (SE)	290 (8.5)	237 (8.7)	171 (8.7)
Difference: BGF - treatment LS mean (SE)		53 (12.1)	119 (12.1)
95% CI	N/A	(29, 77)	(95, 143)
p-value	N/A	<0.0001	<0.0001
Treatment Policy Estimand; ITT population			
n	660	647	649
LS mean (SE)	289 (8.5)	239 (8.5)	175 (8.5)
Difference: BGF - treatment LS mean (SE)	N/A	50 (11.9)	114 (11.9)
95% CI		(27, 74)	(91, 137)
p-value	N/A	<0.0001	<0.0001

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate;
Note: Comparison of BGF to GFF was not in the testing hierarchy.
Source: PT010005 CSR Edition 1; Table 52; pg 181; confirmed and generated by Statistical Reviewer

FEV1 AUC_{0-4} over the treatment period is summarized in

Figure 3 and suggests that the effect on FEV1 AUC_{0-4} are maintained over 52-weeks.

Figure 3: Adjusted Mean FEV1 AUC_{0-4} (L) ± SE Over Time PFT Sub-study (ITT Population)



Source: Statistical Reviewer

Morning Predose Trough FEV1 at Week 24

The use of BGF resulted in a statistically significant improvement in LS mean change from baseline in morning predose trough FEV1 at Week 24 compared with GFF (35ml; 95%CI 12, 57ml; p=0.0025). This demonstrated that the ICS monocomponent contributed to the bronchodilatory effect of BGF. When comparing BGF with BFF, a nominally significant improvement of LS mean change from baseline in morning predose trough FEV1 at Week 24 was seen (76ml; 95%CI 54, 99ml; p<0.0001). The BGF vs. BFF comparison was not included in the testing hierarchy. However, this does suggest that the LAMA monocomponent also contributes to the bronchodilatory effect. Similar analyses using the Treatment Policy Estimand on the ITT population yielded similar results. These data are presented in Table 27.

Table 27. Change from Baseline in Morning Predose Trough FEV_1 at Week 24 – PFT Sub-study

	BGF 320/14.4/9.6 µg (N=747)	GFF 14.4/9.6 µg (N=779)	BFF 320/9.6 µg (N=755)
Efficacy Estimand; mITT population			
n	634	586	609
LS mean (SE)	111 (8.0)	76 (8.3)	35 (8.2)
Difference: BGF – treatment LS mean (SE)		35 (11.5)	76 (11.4)
95% CI	N/A	(12, 57)	(54, 99)
p-value	N/A	p=0.0025	<0.0001
Treatment Policy Estimand; ITT population			
n	662	650	651
LS mean (SE)	112 (7.9)	83 (7.9)	40 (7.9)
Difference: BGF – treatment LS mean (SE)	N/A		
95% CI		29 (11.1) (7, 51)	72 (11.1) (51, 94)
p-value	N/A	0.0085	<0.0001

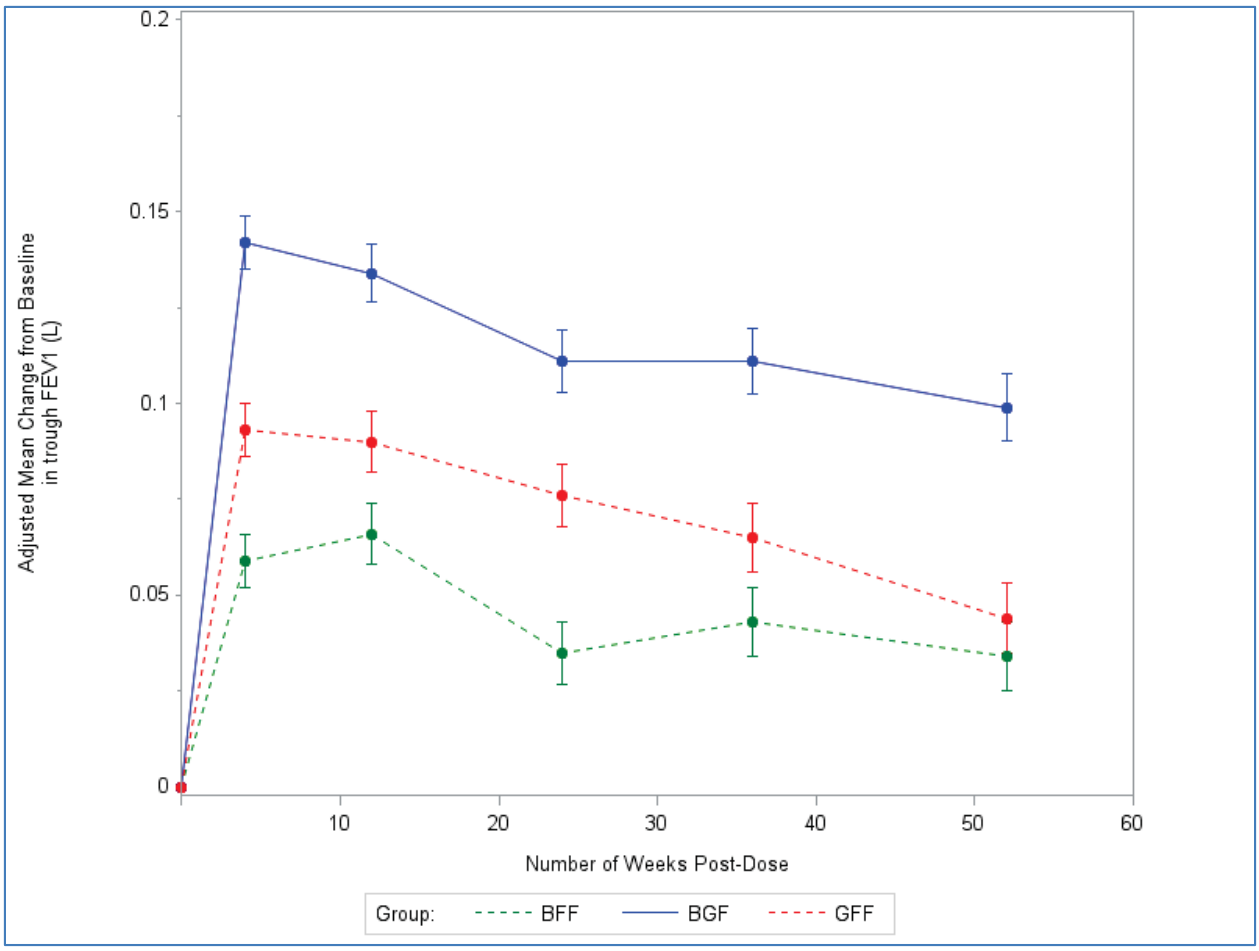
Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate;

Note: Comparison of BGF to BFF was not in the testing hierarchy.

Source: PT010005 CSR Edition 1; Table 53; pg 185; confirmed and generated by Statistical Reviewer

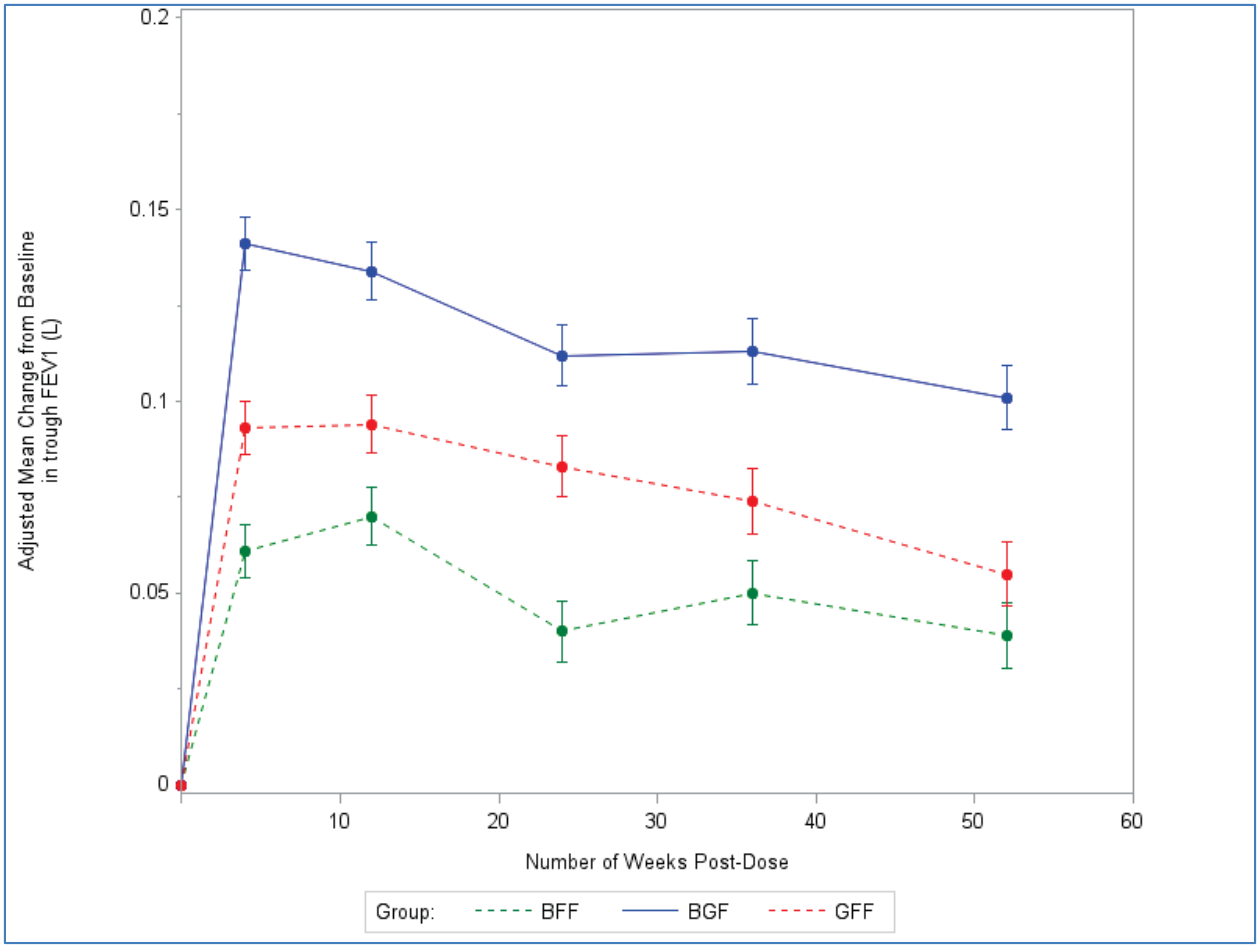
Nominally significant improvements in LS mean change from baseline in morning predose trough FEV_1 were maintained at Week 52 for the comparison of BGF to both GFF and BFF. This data is presented in Figure 4 and Figure 5. Figure 3 using the mITT population and treatment policy estimand with the ITT population, respectively.

Figure 4. Adjusted Mean Change from Baseline in Morning Predose Trough FEV_1 (L) ± SE Over Time PFT Sub-study (Efficacy Estimand, mITT Population)



Source: Statistical Reviewer

Figure 5: Adjusted Mean Change from Baseline in Morning Predose Trough FEV1 (L) ± SE Over Time PFT Sub-study (Treatment Policy Estimand, ITT Population)



Source: Statistical Reviewer

Peak change from baseline in FEV1 was measured within 4 hours postdose for the PFT sub-study visits, and the mean peak change from those visits was determined. The use of BGF resulted in numerical increases in LS mean peak change at Week 24 compared with both GFF (54ml; 95%CI 29, 79) and BFF (126ml; 95%CI 101, 151). This analysis was not included in the testing hierarchy.

Subgroup Analyses – Prior ICS Use

In Trial 05, patients who were on prior ICS therapy at Screening abruptly stopped ICS treatment if they were randomized to the GFF treatment group. There are several studies to support the trend of clinical deterioration following after ICS removal [1; 2; 3; 4; 5; 6]. Given the concern for possible effects of ICS withdrawal, it becomes difficult to determine if a positive exacerbation effect is due to an added benefit of the ICS containing combination product over a non-ICS containing comparator, or a detrimental effect of removal of ICS.

To assess whether abrupt ICS removal may have had an effect on study results in Trial 05, the Applicant submitted sub-group analyses ICS use (yes/no) prior to Screening and ICS/muscarinic antagonist (MA)/beta agonist (BA) use (yes/no) prior to Screening. In Trial 05, 80.5% of subjects overall used ICS at baseline, and 45.8% of subjects used triple therapy (ICS/MA/BA). ICS was removed abruptly at randomization for patients previously on ICS containing therapies who were randomized to the GFF arm. The Applicant submitted exploratory analyses to help differentiate between the effect of ICS removal versus the effectiveness of a triple therapy. These sub-group analyses included time to first moderate or severe COPD exacerbation and rate of moderate or severe COPD exacerbation. Analyses were conducted overall, excluding the first 30, 60, and 90 days, and including only the first 90 days. The comparison of BGF to GFF in subjects with and without prior ICS use was the most direct comparison for assessing the impact of removing ICS treatment.

Rate of moderate or severe COPD exacerbations by ICS use

The data for ICS sub-group analysis for BGF vs. GFF and BFF for the rate of moderate or severe COPD exacerbation is shown in Table 28. In the subgroup of patients who used ICS prior to Screening, the adjusted annual rate of exacerbation was numerically higher for the GFF (1.51) compared to BFF (1.27). The numerically increased rate of exacerbation observed for patients on ICS at baseline who were randomized to GFF (i.e., withdrawn from ICS) compared those who were randomized to BFF (i.e. remained on ICS) suggests that there may have been an ICS withdrawal effect. In contrast, in the subgroup of patients who did not use ICS prior to Screening, the adjusted annual rate of exacerbation for GFF and BFF were numerically similar (1.11 and 1.12, respectively). This observation raises concerns that the observed effect of exacerbation reduction may be due to ICS withdrawal, rather than a true exacerbation reduction effect. However, results for treatment rate ratios for rate of moderate or severe exacerbations based on ICS use at Screening (yes/no), suggest that the exacerbation reduction effect cannot be entirely attributed to ICS withdrawal. In the subgroup of patients who used ICS prior to Screening, the BGF vs. GFF comparison treatment rate ratio was 0.76 (95%CI 0.68, 0.84; p<0.0001), and the BGF to BFF comparison treatment rate ratio was 0.90 (95%CI 0.81, 1.00; p=0.0473). In the subgroup of patients who did not use ICS prior to Screening, the BGF vs. GFF comparison treatment rate ratio was 0.75 (95%CI 0.61, 0.94; p=0.0117), and the BGF to BFF comparison treatment rate ratio was 0.75 (95%CI 0.60, 0.93;p=0.0091). The ICS use prior to Screening sub-group and the no ICS use prior to Screening sub-group had similar treatment rate ratios for the comparison of BGF vs. GFF, and trended in the same direction for the BGF vs BFF. These data show an exacerbation reduction effect for BGF compared to GFF, regardless of ICS use at Screening and with point estimates of similar magnitude. This suggests that, regardless of ICS use at screening (and ICS withdrawl), treatment with BGF results in exacerbation reduction. Analysis comparing treatment rate ratios for BGF v. GFF excluding the first 30, 60, and 90 days were consistent with the overall treatment period in that point estimates for the treatment rate ratios were generally similar between the ICS use prior to Screening subgroup and no ICS use prior to screening subgroup. In analysis including only the first 90 days, BGF to GFF treatment rate ratios were also similar between ICS use at screening yes/no subgroups, though the treatment rate ratios in both subgroups were lower in magnitude compared the

overall treatment period (data not shown). Overall, based on these data, while an ICS withdrawal effect may be present, it is not the primary/sole contributor to the observed exacerbation reduction effect of BGF.

Table 28: : Rate of Moderate or Severe COPD Exacerbations by ICS Use (Efficacy Estimand; mITT Population)

	BGF 320/14.4/9.6 µg (N=2137)	GFF 14.4/9.6 µg (N=2120)	BFF 320/9.6 µg (N=2131)
ICS Use: YES			
N	1706	1707	1704
Subject with moderate or severe COPD exacerbations n (%)	845 (49.5)	871 (51.0)	872 (51.2)
Adjusted rate per year (SE)	1.14 (0.04)	1.51 (0.06)	1.27 (0.05)
Treatment Rate ratio, 95% CI	N/A	0.76 (0.68, 0.84)	0.90 (0.81, 1.00)
p-value	N/A	<0.0001	0.0473
ICS Use: NO			
N	431	413	427
Subject with moderate or severe COPD exacerbations n (%)	181 (42.0)	185 (44.8)	213 (49.9)
Adjusted rate per year (SE)	0.84 (0.07)	1.11 (0.09)	1.12 (0.09)
Treatment Rate ratio, 95% CI		0.75 (0.61, 0.94)	0.75 (0.60, 0.93)
p-value		0.0117	0.0091

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease
Source: Statistical Reviewer

Time to first moderate or severe COPD exacerbation by ICS use

The data for ICS sub-group analysis for BGF vs. GFF and BFF for the time to first moderate or severe COPD exacerbation are shown in Table 29. For BGF vs. GFF, the sub-groups of ICS use prior to Screening and no ICS use prior to Screening had similar hazard ratios in all analysis sub-groups. For the comparison of BGF vs. BFF, the sub-group who used ICS prior to Screening had higher hazard ratios than the sub-group who did not use ICS prior to Screening in all sub-group analyses. When excluding the first 30, 60, and 90 days and including just the first 90-days, results remained similar to the overall treatment period in terms of hazard ratios when comparing subgroups. The benefits of BGF relative to GFF and BFF continued to be seen beyond the early time periods in both subjects with and without prior ICS therapy.

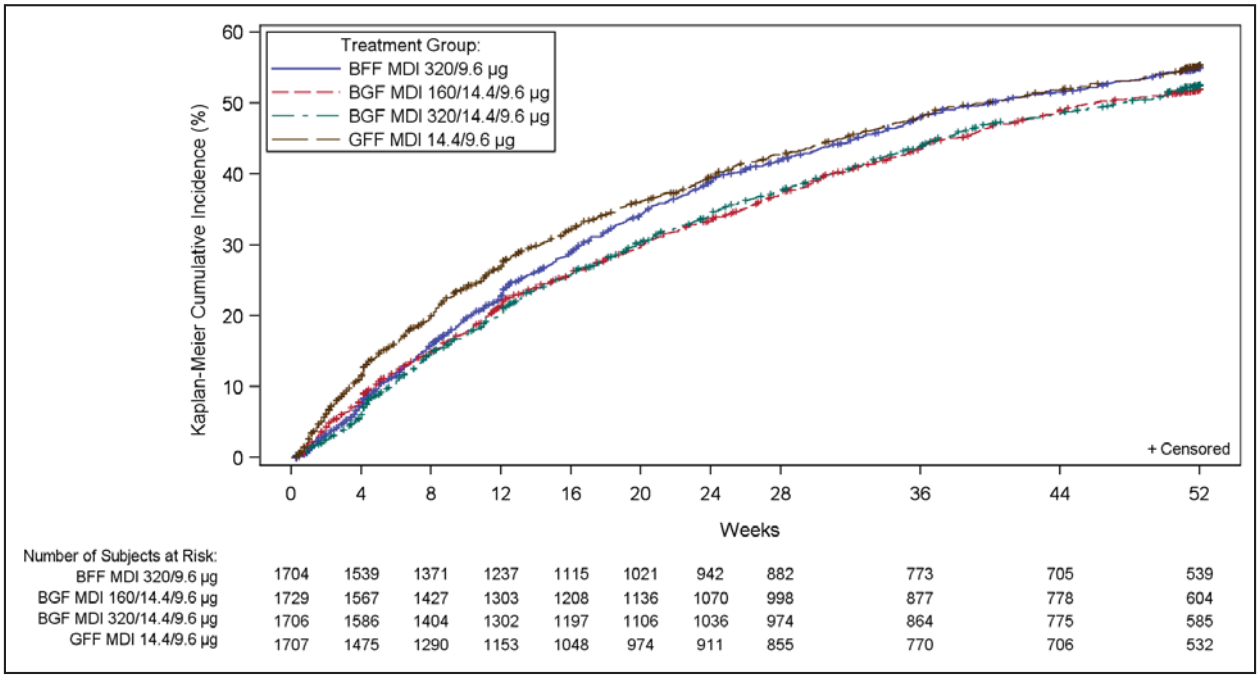
Table 29. Hazard Ratios for Time to First Moderate or Severe COPD exacerbation: ICS use subgroups (yes/no)

Hazard ratio (p-value)	BGF vs. GFF		BGF vs. BFF	
	Used ICS prior	Did not use ICS prior	Used ICS prior	Did not use ICS prior
Entire treatment period	0.896 (95%CI 0.816, 0.984) p=0.0211)	0.884 (95%CI 0.724, 1.079) (p=0.2241)	0.925 (95%CI 0.843, 1.015) (p=0.1008)	0.764 (95%CI 0.631, 0.926) (p=0.0060)
Excluding first 30 days	0.943 (95%CI 0.856, 1.039) (p=0.2349)	0.925 (95%CI 0.753, 1.136) (p=0.4560)	0.934 (95%CI 0.848, 1.028) (p=0.1609)	0.773 (95%CI 0.634, 0.941) (p=0.0103)
Excluding first 60 days	0.969 (95%CI 0.877, 1.070) (p=0.5309)	0.923 (95%CI 0.747, 1.141) (p=0.4584)	0.932 (95%CI 0.845, 1.029) (p=0.1623)	0.756 (95%CI 0.617, 0.927) (p=0.0071)
Excluding first 90 days	0.968 (95%CI 0.873, 1.074) (p=0.5417)	0.968 (95%CI 0.775, 1.210) (p=0.774)	0.924 (95%CI 0.834, 1.024) (p=0.1310)	0.756 (95%CI 0.612, 0.634) (p=0.0096)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; ICS: inhaled corticosteroid
Source: pg 36, Table 5 of Sponsor submitted Kaplan Meier, compiled by Clinical Reviewer

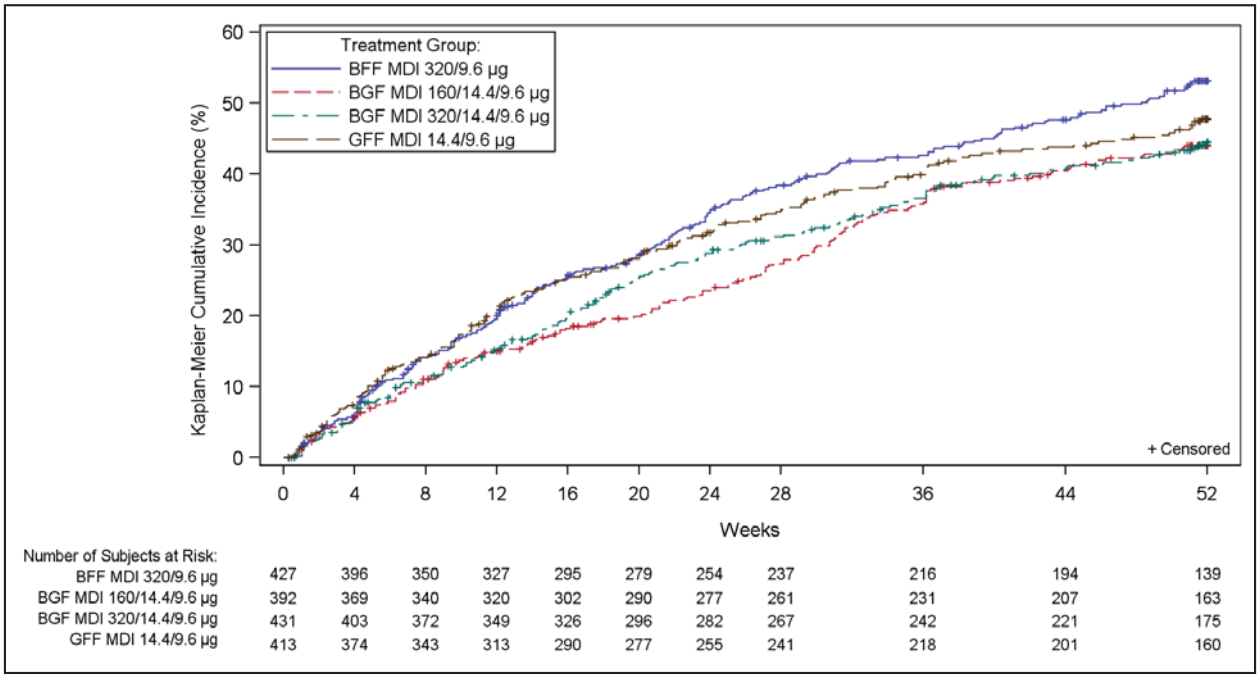
Kaplan-Meier (KM) curves for time to first moderate or severe COPD exacerbation, time to first severe COPD exacerbation, and time to first moderate or severe COPD exacerbation in subjects with ≥2 moderate or severe COPD exacerbations in the prior year were assessed for all treatment groups with and without prior ICS use. This was analyzed overall, excluding the first 30, 60, 90 days, and including the first 90 days. The time to first moderate or severe COPD exacerbation was longer following treatment with BGF relative to both GFF and BFF for the overall study period in the sub-groups of ICS use prior to Screening and no ICS use prior to Screening (Figure 6, Figure 7), as well as time to first severe COPD exacerbation, and time to first moderate or severe COPD exacerbations in subjects with ≥2 moderate or severe COPD exacerbations in the prior year (not shown).

Figure 6. Kaplan-Meier curve for time to first moderate or severe COPD exacerbation for patients using ICS during 30 days prior to Screening



Source: Statistical Reviewer

Figure 7. Kaplan-Meier curve for time to first moderate or severe COPD exacerbation for patients not using ICS during 30 days prior to Screening



Source: Statistical Reviewer

For the comparison of BGF vs. GFF, the treatment effect on rate of moderate or severe exacerbation and time to moderate or severe exacerbation were consistent in subgroups with and without a history of prior ICS use, and these effects were consistent excluding the first 30, 60, and 90 days. Overall, while there may be suggestion of an ICS withdrawal effect, the results of the analyses support that the observed benefits of BGF treatment are not solely or primarily driven by the changes of treatment at randomization, in particular the change from an ICS containing therapy to a non-ICS-containing therapy (i.e., ICS withdrawal). For the BGF to BFF comparison, it is unclear why the hazard ratios for those with a history of prior ICS use were higher than those not on prior ICS use.

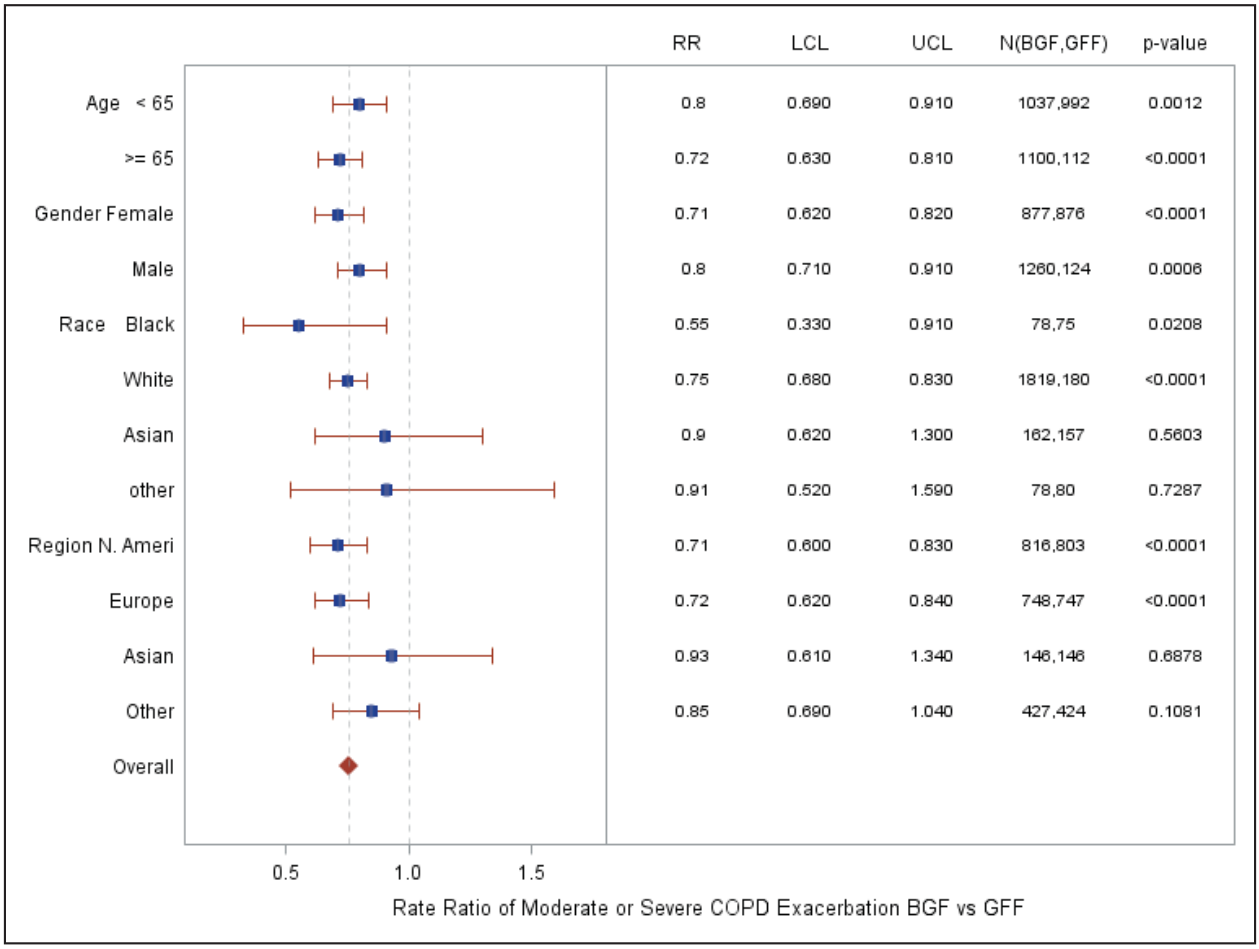
Traditional Subgroup Analysis

To examine whether the treatment effects vary among the levels of a baseline factor, such as age, gender, race or country (region), we conducted subgroup analyses on the primary endpoint(s) in these four factors. These subgroup analyses used the same analysis model, but a subset of the dataset used in the overall analyses.

Figure 8 presents the subgroup analysis results of primary endpoint moderate or severe COPD exacerbation over 52 weeks comparing BGF to GFF. Figure 9 presents the subgroup analysis results of primary endpoint moderate or severe COPD exacerbation over 52 weeks comparing BGF to BFF. The results showed that subgroups with small number of subjects have large variability while

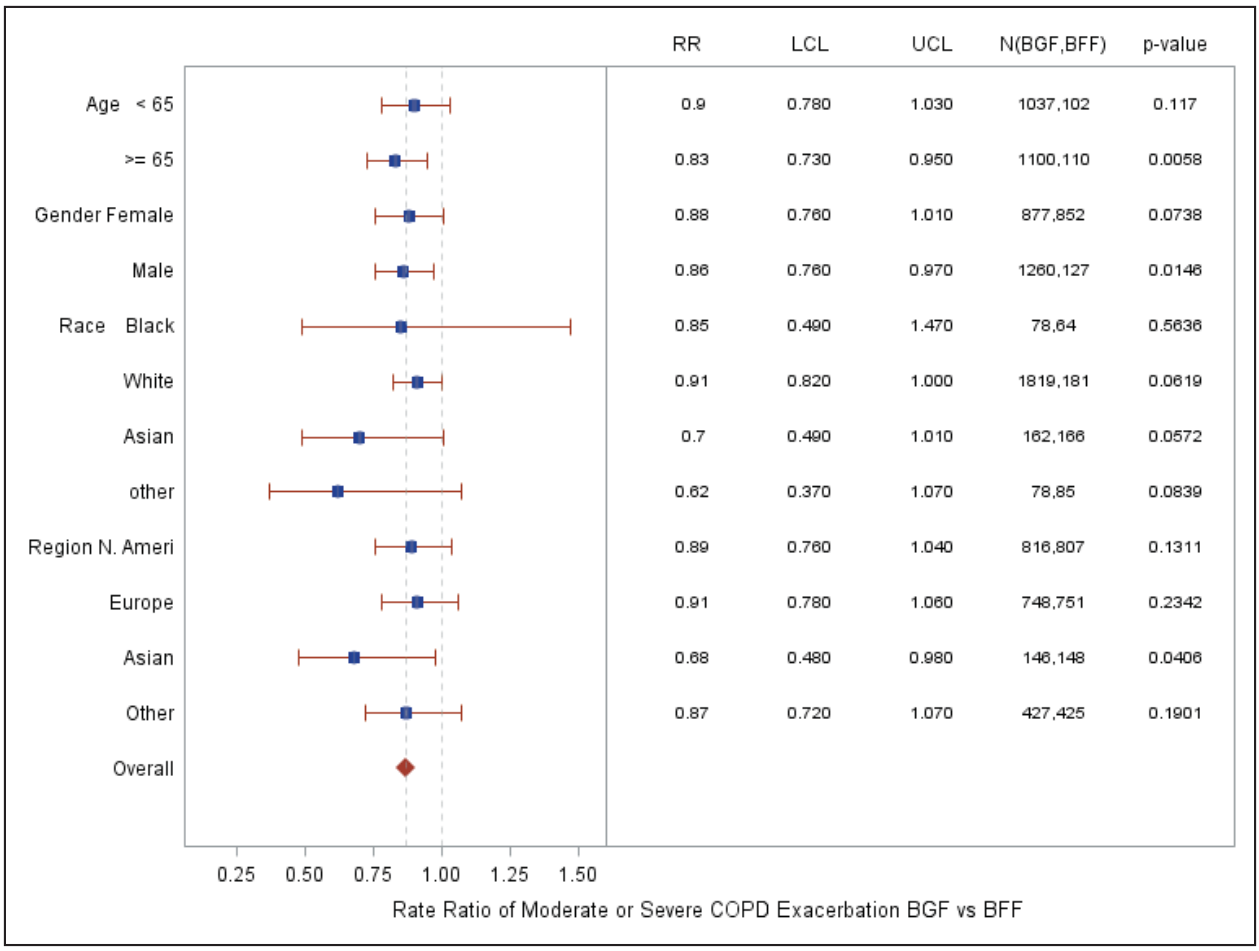
overall there were no significant difference between the subgroups examined. The results were consistent to the overall results across the subgroups.

Figure 8: Forest Plot of Subgroup Analysis of Moderate or Severe COPD Exacerbation Over 52 Weeks (BGF vs GFF, mITT Population)



Abbreviations: N. Ameri = North America
Source: Statistical Reviewer

Figure 9: Forest Plot of Subgroup Analysis of Moderate or Severe COPD Exacerbation Over 52 Weeks (BGF vs BFF, mITT Population)



Abbreviations: N. Ameri = north America
Source: Statistical Reviewer

Bayesian Shrinkage Subgroup Analysis

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

In traditional subgroup analyses, there are some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size or large variability for some subgroups. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. With a shrinkage method, sample estimate is "shrunk" towards the overall estimate. The weights are

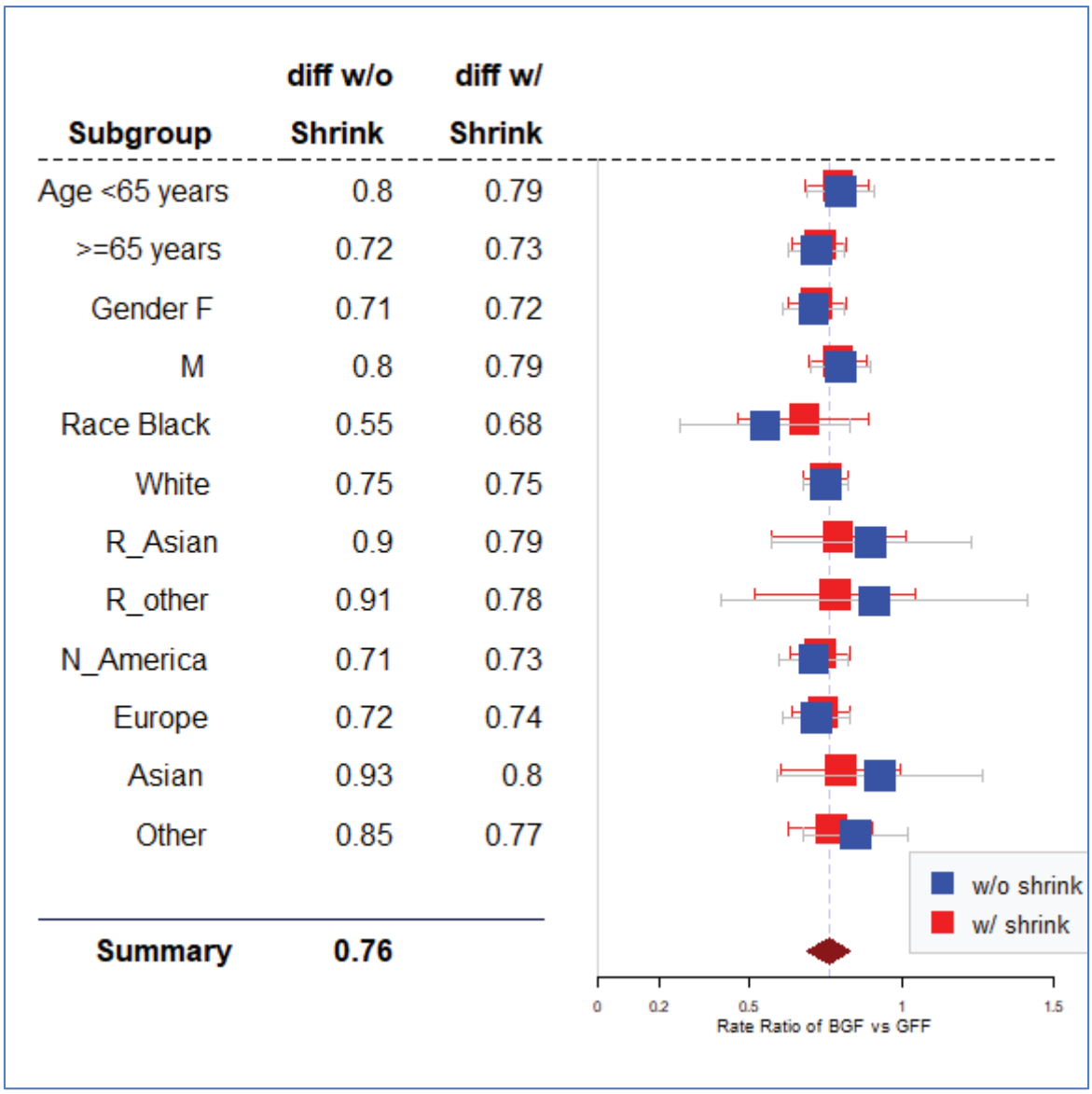
based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage).

The Bayesian hierarchical model was used in this review as a shrinkage method with sample estimates from the traditional subgroup analysis with the same flat prior to derive shrinkage estimates for all subgroups and assumptions as followings:
Y_i: the observed sample estimate of treatment effect in a subgroup level i (i=1,2, …, total number of subgroups), assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$ with $\mu \sim N(0, c^2)$, $1/\tau^2 \sim$ Gamma (0.001, 0.001) (noted as "shrinkage", c from patient-level standard deviation)

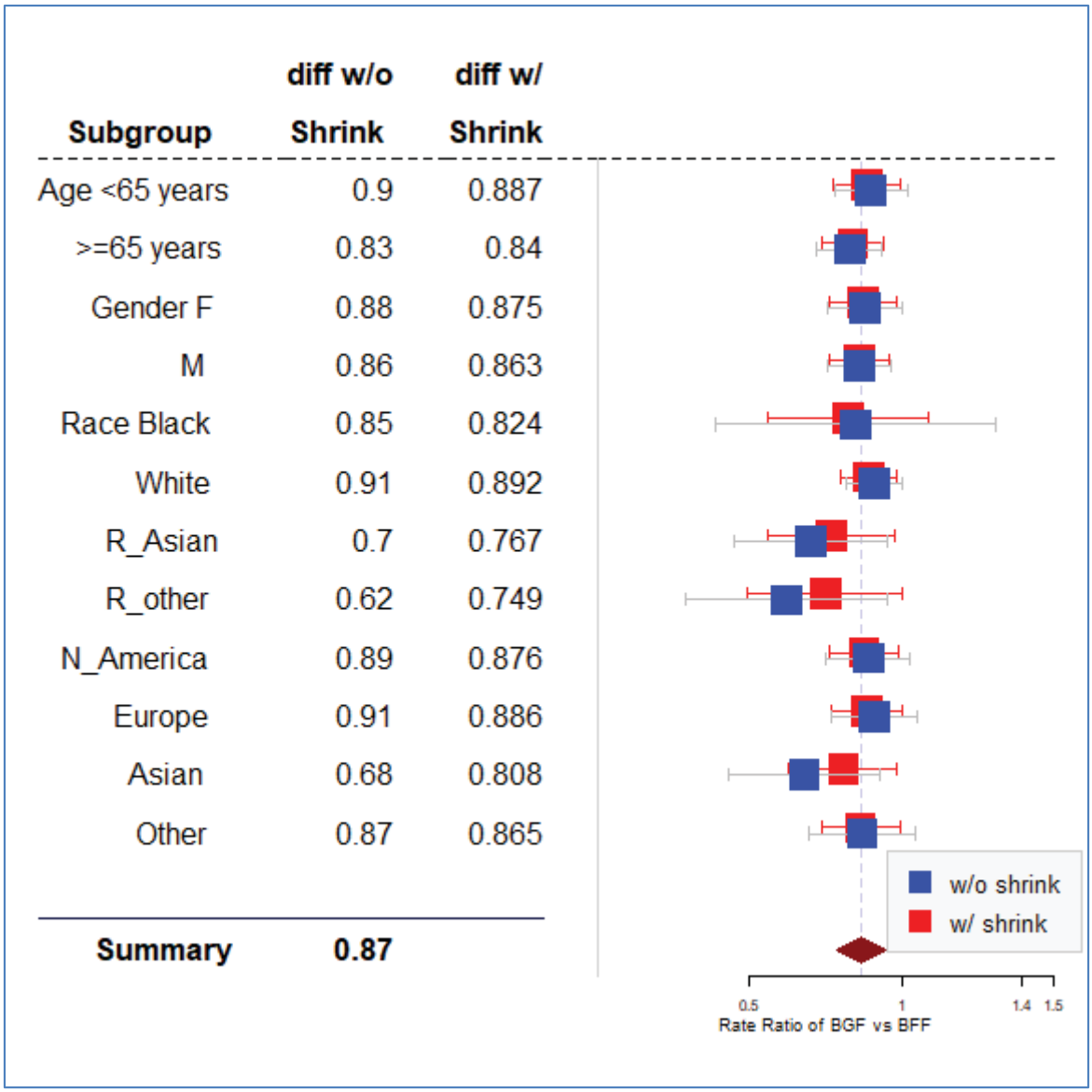
Shrunken estimates and 95% credible interval (equivalent to confidence interval of sample estimate) are calculated and depicted in the forest plot.

Figure 10 : Forest Plot of Bayesian Shrinkage Subgroup Analysis of Moderate or Severe COPD Exacerbation Over 52 Weeks with Comparison to Traditional Subgroup Analysis (BGF vs. GFF, mITT Population)



Abbreviations: F = female; M = male; R_Asian = race Asian; R_other = race other; N_America = North America
Source: Statistical Reviewer

Figure 11: Forest Plot of Bayesian Shrinkage Subgroup Analysis of Moderate or Severe COPD Exacerbation Over 52 Weeks with Comparison to Traditional Subgroup Analysis (BGF vs. BFF, mITT Population)



Abbreviations: F = female; M = male; R_Asian = race Asian; R_other = race other; N_America =north America
Source: Statistical Reviewer

Examining Figure 9 and Figure 10 , we found that:

- All the subgroup means from the Bayesian shrinkage subgroup analysis shrunk to the overall mean
- All the 95% credible intervals of subgroup mean from Bayesian shrinkage subgroup analyses were narrower than the sample estimates' 95% confidence interval

- Although the Bayesian shrinkage subgroup analysis produced more accurate subgroup means and their credible intervals, the difference compared to the traditional subgroup analysis results were minimal.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

This section will focus on the results from Trial 05, as efficacy data from BGF Trial 06 and BFF Trials 02 and 03 were previously reviewed (see Unireview dated September 30, 2019). However, results from these previously reviewed trials will be summarized as applicable.

Primary Endpoints

Trial 05 had the primary endpoint of rate of moderate or severe COPD exacerbation for the comparison of BGF relative to GFF and BFF. The improvement in rate of moderate or severe exacerbations was statistically significant for the comparison of BGF to GFF and BGF to BFF (Table 16).

As GFF is an approved product (Bevespi) and as results from the BFF Trials 02 and 03 supported a spirometric and exacerbation benefit for BFF, the demonstration of superiority of BGF to BFF and GFF in terms of the primary endpoint represents evidence of efficacy for BGF, as well as the contribution of the ICS and LAMA monocomponents.

Secondary and Other Endpoints

Exacerbation
For Trial 05, the improvement of time to first moderate or severe exacerbation was statistically significant for the comparison of BGF to GFF and BGF to BFF (Table 19). For rate of severe exacerbations, results were statistically significant for the comparison of BGF to BFF (Table 20), with similar, though not statistically significant, results for the BGF to GFF comparison. Results were generally similar for rate of moderate or severe COPD exacerbations in subjects with a history ≥2 moderate or severe COPD exacerbations in the year before screening and was statistically significant for the comparison of BGF to GFF (Table 21, Table 22). Overall, exacerbation related secondary endpoint results were consistent with the primary endpoint in Trial 05.

In previously reviewed Trial 06, a 24-week BGF trial, the annualized rate of moderate or severe COPD exacerbation was a secondary endpoint and BGF was compared to both GFF and BFF. These results were numerically lower during treatment with BGF relative to GFF (rate ratio [95% CI]: 0.48 [0.37, 0.64]) and numerically lower during treatment with BGF relative to BFF (rate ratio [95% CI]: 0.82 [0.58, 1.17]). While the 95% CI for the BGF to GFF comparison excluded null, suggesting ICS contribution to BGF, the results were not considered statistically significant due to the failed co-primary endpoint and the comparison's position in the analysis

hierarchy. While these results were not statistically significant, the observed trends were similar to the larger, dedicated exacerbation trial (BGF Trial 05), and offer some additional support for BGF exacerbation benefit.

Overall exacerbation related secondary endpoints across BGF Trials 05 and 06 are supportive of efficacy and when taken together with primary endpoint for BGF Trial 05, represent substantial evidence of efficacy and contribution of the LAMA and ICS monocomponents.

SGRQ
The percentage of patients achieving an improvement of ≥4 units in the SGRQ total score at Week 24 were statistically significant for the comparison of BGF to GFF and BGF to BFF (Table 23).

In Trial 06, the 24-week BGF trial, the percentage of patients achieving an improvement of ≥4 units in SGRQ total score at Week 24 was included as a secondary endpoint. BGF demonstrated a numerically greater percentage of SGRQ responders at Week 24 compared with GFF (not statistically significant due to hierarchy). Similar trends were observed for the BGF to BFF comparison.

Lung Function
Trial 05 included a PFT sub-study which had the co-primary endpoints of FEV_1 AUC_{0-4} at Week 24 for the comparison of BGF to BFF and change from baseline in morning predose trough FEV_1 at Week 24 for the comparison of BGF to GFF. Both co-primary endpoints showed a statistically significant improvement (Table 26 and Table 27). These results demonstrate the bronchodilator effect of BGF and the contribution of the ICS and LAMA monocomponents to that effect.

In BGF Trial 06, the previously reviewed 24-week lung function trial, the co-primary endpoints were pre-dose trough FEV_1 at Week 24 for the comparison of BGF to GFF and FEV_1 AUC_{0-4} at Week 24 for the comparison of BGF to BFF. The results for pre-dose trough FEV_1 at Week 24 for the comparison of BGF to GFF were not statistically significant. In contrast, the results for FEV_1 AUC_{0-4} at Week 24 for the comparison of BGF to BFF showed a statistically significant improvement. As such, Trial 06 only demonstrated the contribution of GP to BGF, but not the contribution of ICS monocomponent. However, these trends were generally consistent with the PFT sub-study in Trial 05 and offer some additional support for the bronchodilator effect.

Subpopulations

For subgroup analyses, see the section entitled Additional Analyses Conducted on the Individual Trial. No notable differences were observed in comparison of subgroups and the subgroup analyses do not change the overall assessment of effectiveness.

Additional Efficacy Considerations

In Trial 05, patients who were on prior ICS therapy at Screening abruptly stopped ICS treatment if they were randomized to the GFF treatment group. Given the concern for possible effects of ICS withdrawal, additional exploratory subgroup analyses were performed based on ICS use at Screening. When comparing moderate or severe COPD exacerbation in subjects who were on an ICS-containing treatment at Screening (yes/no), for the BGF vs. GFF comparison, the Screening ICS "yes" subgroup and "no" subgroup had similar hazard and rate ratios (Table 28, Table 29, Figure 6, and Figure 7). While there may have been suggestion of an ICS withdrawal effect, these results did not suggest that the exacerbation effect observed in the overall population was solely or primarily driven by the withdrawal of ICS from patients on ICS at baseline.

8.1.4. Integrated Assessment of Effectiveness

To approve a combination product, evidence must support the efficacy of the overall combination, including the contribution of each active ingredient to the effectiveness of the combination. To support efficacy, in the initial NDA submission, the Applicant included data from a single phase 3, 24-week, randomized, placebo-controlled trial with the primary objective of assessing the effect of BGF compared to GFF and BFF on lung function (Trial 06). Results from this trial were insufficient to support the contribution of the ICS monocomponent to BGF, though contribution of the LAMA monocomponent was supported. As a result, a CR action was taken. To address the CR deficiencies and provide substantial evidence of efficacy and the contribution of the ICS and LAMA monocomponents, the Applicant submitted the results from a second phase 3, 52 week, randomized, placebo-controlled trial (Trial 05) with the primary objective of assessing the effect of BGF compared to GFF and BFF on exacerbation. This trial also included a PFT sub-study to support effects on lung function. Trial 05 demonstrated evidence of efficacy as determined by achieving a statistically significant reduction in rate of moderate or severe COPD exacerbations for BGF treated patients versus GFF and BFF treated patients. This also demonstrated the contribution of the ICS (BD) and LAMA (GP) monocomponents to the triple combination. The secondary exacerbation related endpoints were also consistent with the primary endpoint. BGF demonstrated statistically significant improvement over GFF and BFF for time to first moderate or severe COPD exacerbation. Results were similar for severe exacerbations, though not statistically significant for the BGF to BFF comparison. SGRQ results were also generally consistent with the exacerbation data. The PFT sub-study demonstrated statistically significant improvements in lung function for BGF versus GFF and BFF, demonstrating both efficacy and the contribution of the LAMA and ICS monocomponents in terms of bronchodilation. Results from Trial 05, with additional support for the previously reviewed Trial 06, taken together represent substantial evidence of efficacy and the contribution of the relevant monocomponents to the triple combination. The deficiencies outlined in the CR letter have been sufficiently addressed to warrant Approval of BGF for the maintenance treatment of COPD.

Overall, the evidence presented in this application does support Approval of BGF.

8.2. Review of Safety

8.2.1. Safety Review Approach

To support the safety of BGF, the Applicant submitted safety data from BGF Trial 05, BGF Trial 06, and BFF Trials 02 and 03. BGF Trial 05 was 52 weeks in duration. BGF Trial 06 was 24 weeks in duration with a safety extension of an additional 28 weeks (Trial 08). BFF Trial 02 was a 24-week trial and Trial 03 was a 12-week trial. Safety data from BGF Trial 06/08 and BFF Trials 02 and 03 were previously reviewed (see Unireview dated September 30, 2019). The safety of BGF was also supported by the known safety profile of the dual-combination product GFF which was approved on March 25, 2016 (tradename Bevespi, NDA 208294, see review by Dr. Stacy Chin dated March 21, 2016). These trials are sufficient to characterize the safety profile of BGF. All studies utilized active controls, and the BGF studies included BFF and the approved GFF as controls. This safety review focuses primarily on safety analyses from BGF Trial 05, as the other trials mentioned above have been previously reviewed.

For the following safety section that will include discussion of both BGF doses studied, BGF MDI 320/14.4/9.6 µg will be referred to as BGF 320/14.4/9.6 µg, BGF MDI 160/14.4/9.6 µg, GFF MDI 14.4/9.6 µg will be referred to as GFF, and BFF MDI 320/14.4 µg will be referred to as BFF. BFF Trials 06 and its safety extension, Trial 08, will be referred to as Trial 06/08.

8.2.2. Review of the Safety Database

Overall Exposure

Exposure data are taken from Trial 05. Exposure was similar across treatment groups. In Trial 05, median exposure was 365.0 days in all groups. The majority of subjects in the trial were exposed to treatment for over 48 weeks. Exposure data for Trial 05 are summarized in Table 30.

Table 30. Study Drug Exposure (Safety Population)

	BGF 320/14.4/9.6 µg n=2144 n(%)	BGF 160/14.4/9.6 µg n=2124 n(%)	GFF 14.4/9.6 µg n=2125 n(%)	BFF 320/9.6 µg n=2136 n(%)	Totals n=8529 n(%)
Extent of exposure (days)					
n	2144	2124	2125	2136	8529
mean (SD)	322.9 (97.6)	325.0 (95.6)	304.2 (117.9)	313.7 (108.3)	316.5 (105.5)
median	365.0	365.0	365.0	365.0	365.0
range	1 - 439	1 - 444	1 - 466	1 - 422	1466
Total person-years of exposure	1896.68	1891.15	1771.22	1835.84	7394.89
Subjects with exposure	1899 (88.6)	1900 (89.5)	1756 (82.2)	1833 (85.8)	7378 (86.5)

≥24 weeks, n (%)					
Subjects with exposure ≥48 weeks, n (%)	1727 (80.6)	1732 (81.5)	1602 (75.4)	1671 (78.2)	6732 (78.9)

Abbreviations: BGF= budesonide/glycopyrrolate/formoterol fumarate; GFF= glycopyrrolate/formoterol fumarate; BFF= budesonide/formoterol fumarate; SD = standard deviation
Source: PT010005 CSR Edition 1; Table 60; Section 8, pg. 259; confirmed by Clinical Reviewer

Adequacy of the safety database:

The BGF safety database is adequate given the safety data from BGF trials and supportive data from the BFF studies, as well as the GFF studies reviewed under NDA 208294 (see review by Dr. Stacy Chin dated March 21, 2016).

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. See Section 4.1 for additional details.

Categorization of Adverse Events (AE)

In all trials reviewed for safety, an AE was categorized as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE could be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE was considered a treatment emergent adverse event (TEAE) if the event occurred on or after the first day of treatment and up to and including the last day of treatment (+1 day for subjects who permanently discontinued treatment before trial completion). Severity of AEs was graded as mild (no limitation in usual activity or only slight discomfort), moderate (limitation of usual activity or significant discomfort), or severe (inability to carry out usual activity or very marked discomfort).

Adverse events of special interest (AESI) were also assessed and defined as LAMA/LABA class effects (potential anticholinergic events and β2-adrenergic agonist events), local steroid effects, pneumonia, and paradoxical bronchospasm. Major Adverse Cardiovascular Events (MACE) were also analyzed and defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. All deaths, potential pneumonia events, and MACE were reviewed by the Clinical Endpoint Committee (CEC). The CEC was implemented to provide an independent, external, systematic, and unbiased assessment of investigator-reported events in the above categories. Review by the CEC was centralized and independent of the Applicant. The committee was comprised of individuals with experience and expertise in the clinical adjudication of pulmonary, neurological, mortality, and cardio- and cerebrovascular events. They were specifically trained in endpoint review and adjudication.

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 BGF Trial 05, there was a total of 112 on-treatment deaths. There were 20 (0.9%) deaths in the BGF 320/14.4/9.6 µg group, 28 (1.3%) deaths in the BGF 160/14.4/9.6 µg group, 35 (1.6%) deaths in the GFF group, and 29 (1.4%) deaths in the BFF group. There were no clear patterns in cause of death across treatment groups. These findings were consistent with BGF Trials 06/08, BFF Trial 02, and BFF Trial 03, (see Unireview dated September 30, 2019). These results are summarized in Table 31.

Table 31. On Treatment Adverse Events with an Outcome of Death in ≥2 Subjects Overall (Safety Population)

Body System/ Preferred Term	BGF 320/14.4/9.6 µg N=2144 n(%)	BGF 160/14.4/9.6 µg N=2124 N(%)	GFF 14.4/9.6 µg N=2125 n(%)	BFF 320/9.6 µg N=2136 n(%)	Total N=8529 n(%)
Patients with fatal outcomes	20 (0.9)	28 (1.3)	35 (1.6)	29 (1.4)	112 (1.3)
Cardiac disorders	4 (0.2)	7 (0.3)	18 (0.8)	4 (0.2)	33 (0.4)
Acute myocardial infarction	0	0	2 (0.1)	0	2 (<0.1)
Arrhythmia	0	1 (<0.1)	0	0	1 (<0.1)
Atrial fibrillation	0	0	1 (<0.1)	0	1 (<0.1)
Cardiac arrest	3 (0.1)	0	7 (0.3)	0	11 (0.1)
Cardiac disorder	0	1 (<0.1)	0	0	1 (<0.1)
Cardiac failure	0	1 (<0.1)	0	0	1 (<0.1)
Cardiac failure acute	0	1 (<0.1)	1 (<0.1)	0	2 (<0.1)
Cardiac failure congestive	0	1 (<0.1)	0	0	1 (<0.1)
Cardio-respiratory arrest	0	1 (<0.1)	3 (0.1)	2 (0.1)	6 (<0.1)
Cardiovascular disorder	0	0	1 (<0.1)	0	1 (<0.1)
Cardiovascular insufficiency	0	0	0	1 (<0.1)	1 (<0.1)
Myocardial infarction	1 (<0.1)	1 (<0.1)	3 (0.1)	1 (<0.1)	6 (<0.1)
Respiratory, thoracic and mediastinal disorders	6 (0.3)	5 (0.2)	3 (0.1)	9 (0.4)	23 (0.3)
Acute pulmonary edema	0	0	0	1 (<0.1)	1 (<0.1)
Acute respiratory failure	0	0	1 (<0.1)	0	1 (<0.1)
Chronic obstructive pulmonary disease	3 (0.1)	3 (0.1)	2 (0.1)	4 (0.2)	12 (0.1)

Pulmonary embolism	1 (<0.1)	0	0	0	1 (<0.1)
Pulmonary mass	0	0	0	1 (<0.1)	1 (<0.1)
Respiratory arrest	0	0	0	1 (<0.1)	1 (<0.1)
Respiratory failure	2 (0.1)	2 (0.1)	0	3 (0.1)	7 (<0.1)
General disorders and administration site conditions	2 (<0.1)	7 (0.3)	8 (0.4)	4 (0.2)	21 (0.2)
Chest pain	0	1 (<0.1)	0	0	1 (<0.1)
Death	1 (<0.1)	4 (0.2)	7 (0.3)	2 (0.1)	14 (0.1)
Multiple organ dysfunction syndrome	0	1 (<0.1)	0	1 (<0.1)	2 (<0.1)
Sudden cardiac death	0	0	1 (<0.1)	0	1 (<0.1)
Sudden death	1 (<0.1)	1 (<0.1)	0	1 (<0.1)	3 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	2 (<0.1)	3 (0.1)	5 (0.2)	11 (0.1)
Acute myeloid leukemia	0	0	0	1 (<0.1)	1 (<0.1)
Colon cancer metastatic	0	0	0	1 (<0.1)	1 (<0.1)
Lung adenocarcinoma	0	1 (<0.1)	0	0	1 (<0.1)
Lung neoplasm malignant	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	3 (<0.1)
Esophageal carcinoma	0	0	1 (<0.1)	0	1 (<0.1)
Pancreatic carcinoma	1 (<0.1)	0	0	0	1 (<0.1)
Pancreatic carcinoma metastatic	0	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Small cell lung cancer	0	0	0	1 (<0.1)	1 (<0.1)
Infections and infestations	2 (<0.1)	2 (<0.1)	2 (<0.1)	4 (0.2)	10 (0.1)
Diverticulitis	0	1 (<0.1)	0	0	1 (<0.1)
Pneumonia	1 (<0.1)	1 (<0.1)	2 (0.1)	1 (<0.1)	5 (<0.1)
Sepsis	0	0	0	2 (0.1)	2 (<0.1)
Septic shock	1 (<0.1)	0	0	1 (<0.1)	2 (<0.1)
Nervous system disorders	2 (<0.1)	0	1 (<0.1)	1 (<0.1)	4 (<0.1)
Cerebrovascular accident	1 (<0.1)	0	1 (<0.1)	0	2 (<0.1)
Hemorrhagic stroke	1 (<0.1)	0	0	0	1 (<0.1)
Ruptured cerebral aneurysm	0	0	0	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	2 (<0.1)	0	0	1 (<0.1)	3 (<0.1)
Gastrointestinal hemorrhage	1 (<0.1)	0	0	1 (<0.1)	2 (<0.1)
Retroperitoneal hemorrhage	1 (<0.1)	0	0	0	1 (<0.1)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 67; Section 8, pg. 273; confirmed by Clinical Reviewer

Deaths were also subject to adjudication by CEC. If more than 1 AE with an outcome of death was recorded for a subject, the adjudicated results were provided for only 1 of the AEs in the

adjudicated AEs listing. The CEC reviewed and adjudicated events that occurred to determine cause of death. The general principal was that a death would be attributed to COPD if the final illness was precipitated by a COPD exacerbation, regardless of subsequent fatal events such as pneumonia, sepsis, or multi-organ system failure. If the medical record indicated that subjects with advanced COPD were placed into palliative care before death, these would be categorized as COPD deaths. In contrast, subjects dying of myocardial infarction or incurable cancer would not be considered COPD-related even though the incidence of those disorders is increased in subjects with COPD. All death events occurring from the date of screening until the end of the treatment period and during a 14 day follow-up period were adjudicated. There were no clear patterns in cause of death across treatment groups. The on-treatment adjudicated deaths are summarized in Table 32.

Table 32. Adjudicated On Treatment Deaths (Safety Population)

Adjudicated category Subcategory	BGF 320/14.4/9.6 µg N=2144 n(%)	BGF 160/14.4/9.6 µg N=2124 n(%)	GFF 14.4/9.6 µg N= 2125 n(%)	BFF 320/9.6 µg N=2136 n(%)	All Subjects (N=8529) n (%)
At least 1 AE with fatal outcome	19 (0.9)[1]	28 (1.3)	35 (1.6)	29 (1.4)	111 (1.3)
Cardiovascular	10 (0.5)	11 (0.5)	22 (1.0)	10 (0.5)	53 (0.6)
Cancer	1 (0)	3 (0.1)	3 (0.1)	7 (0.3)	14 (0.2)
Respiratory	4 (0.2)	9 (0.4)	6 (0.3)	4 (0.2)	23 (0.3)
COPD	4 (0.2)	5 (0.2)	3 (0.1)	4 (0.2)	16 (0.1)
Pneumonia	0 (0)	2 (<0.1)	3 (0.1)	0 (0)	5 (<0.1)
Other Respiratory	0 (0)	2 (<0.1)	0 (0)	0 (0)	2 (0)
Other	4 (0.2)	5 (0.2)	4 (0.2)	8 (0.4)	21 (0.2)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
[1]This does not include one subject who was listed to have 3 AEs linked to the outcome of death, and the outcome was considered to be post-treatment.
Source: PT010005 CSR Edition 1; Table 68; Section 8, pg. 275; confirmed by Clinical Reviewer

The medical reviewer also reviewed deaths that occurred in the post-treatment period (i.e. deaths that occurred after the treatment emergent period) based on non-adjudicated and adjudicated results. The review of the additional post-treatment deaths was consistent with the on-treatment deaths.

Overall, in Trial 05, similar to the previously reviewed BGF trials, deaths were infrequent and consistent with the population studied. Causes of death were also similar. Analysis of on-treatment AEs with an outcome of death did not reveal differences between treatment groups and no new safety concerns were identified.

Serious Adverse Events

In Trial 05, there were 1744 (20.4%) patients who experienced at least one SAE. Subjects who experienced at least one SAE were numerically similar across treatment groups, with 426 (19.9%) in the BGF 320/14.4/9.6 µg group, 445 (21.0%) in the BGF 160/14.4/9.6 µg group, 433 (20.4%) in the GFF group, and 440 (20.6%) in the BFF group. SAEs were most commonly reported in the respiratory, thoracic and mediastinal disorders System Organ Class (SOC). COPD (i.e., COPD exacerbation) was the most common SAE Preferred Term (PT) across all treatment groups and rates of SAE for COPD were similar across all treatment groups. Similar SOC and PT findings were also seen in BGF Trial 06/08, BFF Trial 02, and BFF Trial 03. Pneumonia rates were higher in treatment groups containing ICS (BGF and BFF), which is a known safety concern of ICS. SAEs occurring in ≥0.5% patients in any treatment group are summarized in Table 33.

Table 33. Treatment-emergent SAEs Reported by ≥0.5% of Subjects in Any Treatment Group by Preferred Term (Safety Population)

Preferred Term	BGF 320/14.4/9.6 µg N=2144 n(%)	BGF 160/14.4/9.6 µg N=2124 n(%)	GFF 14.4/9.6 µg N=2125 n(%)	BFF 320/9.6 µg N=2136 n(%)	Totals N=8529 n(%)
At least 1 treatment emergent SAE	426 (19.9)	445 (21.0)	433 (20.4)	440 (20.6)	1744 (20.4)
Respiratory, thoracic, and mediastinal disorders	225 (10.5)	250 (11.8)	243 (11.4)	262 (12.3)	980 (11.5)
Chronic obstructive pulmonary disease	202 (9.4)	221 (10.4)	219 (10.3)	241 (11.3)	883 (10.4)
Acute respiratory failure	14 (0.7)	20 (0.9)	20 (0.9)	7 (0.3)	61 (0.7)
Respiratory failure	10 (0.5)	9 (0.4)	5 (0.2)	9 (0.4)	33 (0.4)
Cardiac disorders	43 (2.0%)	54 (2.5%)	81 (3.8%)	40 (1.9%)	218 (2.6%)
Acute myocardial infarction	7 (0.3)	10 (0.5)	17 (0.8)	7 (0.3)	41 (0.5)
Atrial fibrillation	9 (0.4)	8 (0.4)	14 (0.7)	3 (0.1)	34 (0.4)
Infections and infestations	100 (4.7%)	98 (4.6%)	74 (3.5%)	91 (4.3%)	363 (4.3%)
Pneumonia	61 (2.8)	59 (2.8)	35 (1.6)	55 (2.6)	210 (2.5)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 69; Section 8, pg. 277; confirmed by Clinical Reviewer

These data are consistent with the SAE data previously reviewed for Trial 06 and not unexpected given the patient population and drug class. Overall, analysis of SAEs did not raise any new safety concerns.

Dropouts and/or Discontinuations Due to Adverse Effects

In Trial 05, 517 (6.1%) of patients experienced a TEAE that lead to discontinuation of study drug, with the GFF and BFF treatment groups having slightly higher frequencies than both BGF groups. The most common TEAE SOC leading to discontinuation in all groups was respiratory,

thoracic, and mediastinal disorders SOC in Trial 05. This is consistent with the most common TEAE SOC seen in BGF Trial 06/08, BFF Trial 02, and BFF Trial 03. The most common PT associated with discontinuation in Trial 05 was COPD, which was highest in the BFF group (2.1%) and lowest in the BGF 320/14.4/9.6 µg (1.0%). COPD was also the most common TEAE leading to discontinuation in Trial 06/08. TEAEs leading to discontinuation of trial drug in Trial 05 are summarized in Table 34.

Table 34. TEAEs Leading to Discontinuation of Study Drug Reported by ≥0.5% of Subjects in Any Treatment Group by Preferred Term (Safety Population)

Preferred Term	BGF 320/14.4/9.6 µg n=2144 n(%)	BGF 160/14.4/9.6 µg n=2124 n(%)	GFF 14.4/9.6 µg n=2125 n(%)	BFF 320/9.6 µg n=2136 n(%)	Totals n=8529 n(%)
At least 1 TEAE leading to discontinuation of study drug	119 (5.6)	112 (5.3)	146 (6.9)	140 (6.6)	517 (6.1)
Respiratory, thoracic and mediastinal disorders	78 (3.6)	70 (3.3)	90 (4.2)	93 (4.4)	331 (3.9)
COPD	22 (1.0)	33 (1.6)	39 (1.8)	44 (2.1)	138 (1.6)
Dyspnea	7 (0.3)	8 (0.4)	9 (0.4)	11 (0.5)	35 (0.4)
Infections and infestations	58 (2.7)	59 (2.8)	67 (3.2)	73 (3.4)	257 (3.0)
Pneumonia	5 (0.2)	11 (0.5)	14 (0.7)	4 (0.2)	34 (0.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 70; Section 8, pg. 279; confirmed by Clinical Reviewer

Overall, dropouts and discontinuations due to AEs were uncommon, occurred numerically more frequently in double combinations versus triple combination group, and were generally consistent with BGF Trial 06. These data did not reveal new safety signals.

Significant Adverse Events

In Trial 05, a severe AE was defined as an event that resulted in the inability to carry out usual activities, marked discomfort, life-threatening, resulting in significant capacity or disability, or requiring therapeutic intervention.

The majority of TEAEs reported in Trial 05 were not severe (i.e., mild or moderate). The number of patients with TEAEs of severe intensity was comparable across trial groups. The most common PT of severe intensity in Trial 05 was COPD (5.4%) and the number of patients was comparable across groups. COPD was also the most common PT of severe intensity in BGF Trial 06/08, BFF Trial 02, and BFF Trial 03. Pneumonia rates were higher in treatment groups containing ICS (BGF and BFF), which is a known safety concern of ICS. Table 35 presents the severe AEs that occurred ≥0.5 patients in any trial group.

Table 35. Severe TEAEs Reported for ≥0.5% of Subjects in Any Treatment Group by Preferred Term (Safety Population)

Preferred Term	BGF 320/14.4/9.6 µg N=2144 n(%)	BGF 160/14.4/9.6 µg N=2124 n(%)	GFF 14.4/9.6 µg N=2125 n(%)	BFF 320/9.6 µg N=2136 n(%)	Total N=8529 n(%)
At least 1 severe TEAE	394 (18.4)	402 (18.9)	391 (18.4)	412 (19.3)	1599 (18.7)
COPD	201 (9.4)	216 (10.2)	213 (10.0)	242 (11.3)	872 (5.4)
Pneumonia	55 (2.6)	51 (2.4)	31 (1.5)	48 (2.2)	185 (1.2)
Acute respiratory failure	15 (0.7)	19 (0.9)	23 (1.1)	7 (0.3)	64 (0.4)
Acute myocardial infarction	6 (0.3)	9 (0.4	15 (0.7)	5 (0.2)	35 (0.2)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 66; Section 8, pg. 271; confirmed by Clinical Reviewer

Overall, analysis of severe TEAEs did not identify new safety concerns for the triple combination.

Treatment Emergent Adverse Events and Adverse Reactions

Table 36 summarizes TEAEs that occurred in at least 2% of patients in any treatment group in Trial 05. The proportion of patients with at least 1 TEAE was similar across treatment groups. The most common PTs were nasopharyngitis, COPD, upper respiratory tract infection (URTI), and pneumonia. COPD and URTIs were also among the most common PTs in BGF Trial 06/08, BFF Trial 02, and BFF Trial 03. In Trial 05, rates of pneumonia were higher in both BGF (4.6% in BGF 320/14.4/9.6 µg and 4.0% in BGF 160/14.4/9.6 µg) groups and BFF (5.0%) when compared to GFF (2.9%). This may reflect the known pneumonia safety concern with ICS.

Table 36. Treatment Emergent Adverse Events occurring in ≥2% of Subjects in Any Treatment Group by Preferred Term (Safety Population)

Preferred Term	BGF 320/14.4/9.6 µg N=2144 n(%)	BGF 160/14.4/9.6 µg N=2124 n(%)	GFF 14.4/9.6 µg N=2125 n(%)	BFF 320/9.6 µg N=2136 n(%)	Total N=8529 n(%)
At least 1 TEAE	1368 (63.8)	1356 (63.8)	1312 (61.7)	1377 (64.5)	5413 (63.5)
Nasopharyngitis	227 (10.6)	239 (11.3)	199 (9.4)	234 (11.0)	899 (5.6)
Chronic obstructive pulmonary disease	203 (9.5)	221 (10.4)	219 (10.3)	242 (11.3)	885 (5.5)
Upper respiratory tract infection	123 (5.7)	137 (6.5)	102 (4.8)	115 (5.4)	477 (3.0)
Pneumonia	98 (4.6)	85 (4.0)	61 (2.9)	107 (5.0)	351 (2.2)
Bronchitis	66 (3.1)	68 (3.2)	76 (3.6)	69 (3.2)	279 (1.7)

Back pain	67 (3.1)	65 (3.1)	55 (2.6)	64 (3.0)	251 (1.6)
Hypertension	59 (2.8)	54 (2.5)	62 (2.9)	76 (3.6)	251 (1.6)
Dyspnea	54 (2.5)	55 (2.6)	60 (2.8)	79 (3.7)	248 (1.5)
Headache	57 (2.7)	49 (2.3)	60 (2.8)	68 (3.2)	234 (1.5)
Sinusitis	56 (2.6)	61 (2.9)	47 (2.2)	55 (2.6)	219 (1.4)
Urinary tract infection	58 (2.7)	59 (2.8)	60 (2.8)	41 (1.9)	218 (1.4)
Influenza	63 (2.9)	52 (2.4)	42 (2.0)	61 (2.9)	218 (1.4)
Cough	58 (2.7)	48 (2.3)	50 (2.4)	51 (2.4)	207 (1.3)
Oral candidiasis	65 (3.0)	47 (2.2)	24 (1.1)	57 (2.7)	193 (1.2)
Muscle spasms	60 (2.8)	39 (1.8)	19 (0.9)	53 (2.5)	171 (1.1)
Diarrhea	44 (2.1)	28 (1.3)	37 (1.7)	38 (1.8)	147 (0.9)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 63; Section 8, pg. 266; confirmed by Clinical Reviewer

In Table 37, the TEAEs occurring in ≥2% of subjects in any treatment group by preferred term from 0 to ≤24 weeks and >24 weeks are presented for the Safety Population. The TEAEs that occurred most commonly in both time periods were nasopharyngitis, COPD, URTI, and pneumonia. Nasopharyngitis, URTI, dyspnea, and muscle spasms all had a higher frequency in the ≤24 weeks group versus the < 24 weeks group in all treatment groups. Of note, the incidence of pneumonia was higher in both BGF treatment groups and BFF when compared to GFF in both ≤24 and > 24 weeks groups.

Table 37. TEAEs Occurring in ≥2% of Subjects in Any Treatment Group from 0 to ≤24 Weeks and >24 Weeks by Preferred Term (Safety Population)

	≤24 weeks					> 24 weeks				
Preferred Term	BGF 320/14.4/9.6 µg (N=2144) n (%)	BGF 160/14.4/9.6 µg (N=2124) n (%)	GFF 14.4/9.6 µg (N=2125) n (%)	BFF 320/9.6 µg (N=2136) n (%)	All Subjects (N=8529) n (%)	BGF 320/14.4/9.6 µg (N=2144) n (%)	BGF 160/14.4/9.6 µg (N=2124) n (%)	GFF 14.4/9.6 µg (N=2125) n (%)	BFF 320/9.6 µg (N=2136) n (%)	All Subjects (N=8529) n (%)
	1101 (51.4)	1042 (49.1)	1043 (49.1)	1095 (51.3)	4281 (50.2)	822 (38.3)	840 (39.5)	741 (34.9)	836 (39.1)	3239 (38.0)
Nasopharyngitis	161 (7.5)	154 (7.3)	128 (6.0)	152 (7.1)	595 (7.0)	94 (4.4)	123 (5.8)	95 (4.5)	116 (5.4)	428 (5.0)
COPD	112 (5.2)	117 (5.5)	136 (6.4)	137 (6.4)	502 (5.9)	112 (5.2)	120 (5.6)	104 (4.9)	128 (6.0)	464 (5.4)
URTI	86 (4.0)	78 (3.7)	70 (3.3)	72 (3.4)	306 (3.6)	50 (2.3)	71 (3.3)	43 (2.0)	59 (2.8)	223 (2.6)
Pneumonia	46 (2.1)	46 (2.2)	36 (1.7)	54 (2.5)	182 (2.1)	52 (2.4)	44 (2.1)	28 (1.3)	60 (2.8)	184 (2.2)
Dyspnea	36 (1.7)	36 (1.7)	46 (2.2)	62 (2.9)	180 (2.1)	21 (1.0)	20 (0.9)	17 (0.8)	22 (1.0)	80 (0.9)
Muscle spasms	44 (2.1)	26 (1.2)	12 (0.6)	44 (2.1)	126 (1.5)	17 (0.8)	13 (0.6)	7 (0.3)	11 (0.5)	48 (0.6)
Headache	36 (1.7)	32 (1.5)	42 (2.0)	43 (2.0)	153 (1.8)	27 (1.3)	21 (1.0)	22 (1.0)	29 (1.4)	99 (1.2)
Hypertension	37 (1.7)	32 (1.5)	36 (1.7)	45 (2.1)	150 (1.8)	24 (1.1)	23 (1.1)	29 (1.4)	31 (1.5)	107 (1.3)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease; URTI = upper respiratory tract infection
Source: PT010005 CSR Edition 1; Table 64; Section 8, pg. 269; confirmed by Clinical Reviewer

Overall these TEAE data are consistent with the known safety profile of similar inhaled drugs, consistent with BGF Trial 06/08, and do not raise safety concerns.

Laboratory Findings

The Applicant conducted analyses of clinical laboratory results in BGF Trial 05. Analyses included changes in mean values over time, changes in individual subjects over time, and in potentially clinically significant (PCS) values.

Laboratory findings from Trial 05, did not demonstrate clinically meaningful trends or mean changes from baseline within or between treatment groups in terms of the parameters of hematology, clinical chemistry, kidney functions, and urinalysis. Shift table analysis showed that shifts were not common for hematology, clinical chemistry, and kidney function, and these occurrences were similar across groups. Post-baseline newly occurring or worsening potentially clinically significant values for clinical chemistry, hematology, kidney function, and urinalysis were infrequent and similar across groups. These findings were consistent with the findings in BGF Trial 06/08.

Overall, no new safety concerns were identified in the analysis of laboratory values in the BGF phase 3 studies.

Vital Signs

No clinically significant changes in vital signs were identified in BGF Trial 05. Similarly, no clinically significant changes in vital signs were identified in BGF Trial 06/08, BFF Trial 02, or BFF Trial 03. Time trend analysis, box plots, and waterfall plots (JMP Clinical 7.1) were used by the Clinical Reviewer to assess systolic and diastolic blood pressure, heart rate, temperature, and BMI. Overall, no new safety concerns were identified in the analysis of vital signs in the BGF phase 3 studies.

Electrocardiograms (ECGs)

No clinically significant ECG trends were identified in BGF Trial 05. Similarly, no clinically significant changes in ECG parameters were identified in the BGF Trial 06/08, BFF Trial 02, or BFF Trial 03. Time trend analysis, box plots, and waterfall plots (JMP Clinical 7.1) were used by the Clinical Reviewer to assess heart rate, PR interval, QRS interval, axis, and QTcF. Overall, no safety concerns were identified in the analysis of ECG parameters in the BGF phase 3 studies.

QT

See ECG section above. No TQT study was performed under this NDA submission. A TQT study was performed under NDA 208294 (GFF, Bevespi Aerosphere) and no significant QT prolongation was detected for GFF in that study.

Immunogenicity

Not Applicable

8.2.5. Analysis of Submission-Specific Safety Issues

Given specific safety concerns with products containing LABA, LAMA, and ICS components, the Applicant analyzed TEAEs of special interests (AESI). The AESIs were organized into medical concepts with the operational definition of each concept based on a group of MedDRA PTs. PT groupings were reviewed and are adequate to identify AESIs for each medical concept. The most frequently occurring AESIs are discussed in this section.

In BGF Trial 05, the most common AESIs by medical concept were cardiovascular conditions, pneumonia, lower respiratory tract infections (LRTIs) other than pneumonia, and hypertension. LRTIs were also the among the most common AESIs by medical concept in BGF Trial 06/08. An increased frequency of pneumonia, oral candidiasis, and dysphonia were observed in both BGF treatment groups and BFF over GFF. This is an expected effect from the inclusion of ICS. A summary of the most common AESIs in Trial 05 is shown in Table 38.

Table 38. AESIs Reported by ≥1% of Subjects in Any Treatment Group by Preferred Term (Safety Population)

Medical Concept Preferred Term	BGF 320/14.4/9.6 µg n=2144 n(%)	BGF 160/14.4/9.6 µg n=2124 n(%)	GFF 14.4/9.6 µg n=2125 n(%)	BFF 320/9.6 µg n=2136 n(%)	Totals n=8529 n(%)
Agitation or Anxiety	36 (1.7)	22 (1.0)	26 (1.2)	31 (1.5)	115 (1.3)
Anxiety	30 (1.4)	20 (0.9)	24 (1.1)	28 (1.3)	102 (1.2)
Candidiasis	69 (3.2)	54 (2.5)	25 (1.2)	66 (3.1)	214 (2.5)
Oral candidiasis	65 (3.0)	47 (2.2)	24 (1.1)	57 (2.7)	193 (2.3)
Cardiovascular condition	95 (4.4)	110 (5.2)	137 (6.4)	93 (4.4)	435 (5.1)
Atrial fibrillation	18 (0.8)	19 (0.9)	31 (1.5)	13 (0.6)	81 (0.9)
Diabetes mellitus	72 (3.4)	65 (3.1)	53 (2.5)	61 (2.9)	251 (2.9)
Hyperglycemia	26 (1.2)	15 (0.7)	20 (0.9)	21 (1.0)	82 (1.0)
Dysphonia or aphonia	39 (1.8)	27 (1.3)	7 (0.3)	31 (1.5)	104 (1.2)
Dysphonia	37 (1.7)	26 (1.2)	7 (0.3)	31 (1.5)	101 (1.2)
Headache	61 (2.8)	56 (2.6)	63 (3.0)	71 (3.3)	251 (2.9)
Headache	57 (2.7)	49 (2.3)	60 (2.8)	68 (3.2)	234 (2.7)
Hypertension	75 (3.5)	70 (3.3)	72 (3.4)	93 (4.4)	310 (3.6)
Hypertension	59 (2.8)	54 (2.5)	62 (2.9)	76 (3.6)	251 (2.9)
Hypokalemia	25 (1.2)	17 (0.8)	21 (1.0)	29 (1.4)	92 (1.1)
Hypokalemia	25 (1.2)	16 (0.8)	20 (0.9)	26 (1.2)	87 (1.0)
Lower Respiratory tract infections other than pneumonia	80 (3.7)	82 (3.9)	87 (4.1)	87 (4.1)	336 (3.9)
Bronchitis	66 (3.1)	68 (3.2)	76 (3.6)	69 (3.2)	279 (3.3)

Ocular effects	19 (0.9)	28 (1.3)	27 (1.3)	25 (1.2)	99 (1.2)
Cataract	15 (0.7)	22 (1.0)	21 (1.0)	16 (0.7)	74 (0.9)
Pneumonia	116 (5.4)	101 (4.8)	67 (3.2)	118 (5.5)	402 (4.7)
Pneumonia	98 (4.6)	85 (4.0)	61 (2.9)	107 (5.0)	351 (4.1)
Psychiatric effects	42 (2.0)	38 (1.8)	41 (1.9)	32 (1.5)	153 (1.8)
Insomnia	30 (1.4)	17 (0.8)	23 (1.1)	11 (0.5)	81 (0.9)
Depression	14 (0.7)	21 (1.0)	17 (0.8)	22 (1.0)	74 (0.9)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: PT010005 CSR Edition 1; Table 71; Section 8, pg. 281; confirmed by Clinical Reviewer

Overall, analysis of AESIs in the BGF program were consistent drugs of the similar class and did not identify any new safety concerns.

Pneumonia

The CEC reviewed and adjudicated TEAEs and SAEs with PTs that could relate to pneumonia and that occurred during the treatment period. In BGF Trial 05, the frequency of confirmed pneumonia events, as adjudicated by the CEC, were slightly higher in frequency in the BGF and BFF groups compared to GFF. This likely reflects the known pneumonia safety concerns for ICS. A summary of pneumonia events in Trial 05 is shown in Table 39.

Table 39. Adjudicated Pneumonia as Determined by CEC (Safety Population)

	BGF 320/14.4/9.6 µg n=2144 n(%)	BGF 160/14.4/9.6 µg n=2124 n(%)	GFF 14.4/9.6 µg n=2125 n(%)	BFF 320/9.6 µg n=2136 n(%)	Totals n=8529
# subjects Events Submitted to CEC	115 (5.4)	100 (4.7)	66 (3.1)	118 (5.5)	399 (4.7)
Events submitted to CEC	121	109	71	131	432
Subjects with confirmed pneumonia during Treatment Period as determined by CEC	90 (4.2)	75 (3.5)	48 (2.3)	96 (4.5)	309 (3.6)
0 to ≤ 24 weeks	43 (2.0)	40 (1.9)	29 (1.4)	43 (2.0)	155 (1.8)
>24 weeks	48 (2.2)	38 (1.8)	22 (1.0)	59 (2.8)	167 (2.0)
Subjects with serious confirmed pneumonia during Treatment Period as determined by CEC	64 (3.0)	54 (2.5)	28 (1.3)	51 (2.4)	197 (2.3)
0 to ≤ 24 weeks	31 (1.4)	33 (1.6)	17 (0.8)	26 (1.2)	107 (1.3)
>24 weeks	34 (1.6)	24 (1.1)	12 (0.6)	27 (1.3)	97 (1.1)

Abbreviations: CEC = Clinical Endpoint Committee; BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event;
Source: PT010005 CSR Edition 1; Table 72 Section 8, pg. 283; confirmed by Clinical Reviewer

Overall, no new pneumonia related safety issues were identified in the BGF program.

Cardiovascular Safety

MACE

The CEC reviewed and adjudicated serious cardiovascular and cerebrovascular events that occurred during the treatment period as MACE. MACE was defined as cardiovascular death, non-fatal MI, and non-fatal stroke. The frequency of MACE was similar across treatment groups. This was consistent with the MACE analyses from BGF Trial 06/08. A summary of MACE events in Trial 05 is shown in Table 40.

Table 40. Adjudicated MACE as Determined by CEC (Safety Population)

	BGF 320/14.4/9.6 µg n=2144	BGF 160/14.4/9.6 µg n=2124	GFF 14.4/9.6 µg n=2125	BFF 320/9.6 µg n=2136	Totals n=8529
Number of subjects with events submitted to the CEC, n(%)	54 (2.5)	55 (2.6)	64 (3.0)	53 (2.5)	226 (2.6)
Events submitted to the CEC	57	56	70	56	239
Subjects with MACE during the Treatment Period as determined (confirmed) by CEC	31 (1.4)	30 (1.4)	44 (2.1)	23 (1.1)	128 (1.5)
Timeframe in which confirmed MACE occurred					
<= 24 weeks	15 (0.7)	17 (0.8)	22 (1.0)	10 (0.5)	64 (0.8)
> 24 weeks	16 (0.7)	13 (0.6)	23 (1.1)	13 (0.6)	65 (0.8)
Type of MACE event					
Cardiovascular death	10 (0.5)	11 (0.5)	22 (1.0)	10 (0.5)	53 (0.6)
Non-fatal MI	9 (0.4)	13 (0.6)	17 (0.8)	8 (0.4)	47 (0.6)
Non-fatal stroke	12 (0.6)	6 (0.3)	6 (0.3)	6 (0.3)	30 (0.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event;
Source: PT010005 CSR Edition 1; Table 74; Section 8, pg. 285; confirmed by Clinical Reviewer

Overall, analysis of AESIs in the BGF program did not reveal any new safety concerns. MACE occurrence was similar across treatment groups. Adjudicated pneumonia was slightly higher in the treatment groups treated with an ICS component, and this is consistent with other ICS-containing products.

Holter Monitoring sub-study

A 24-hour Holter Monitoring sub-study was done to evaluate the effect of BGF relative to GFF and BFF on cardiac rhythm. A subset of 721 subjects had at least 18 hours of acceptable quality Holter monitoring data at both Visit 3 (Holter Baseline Visit) and Visit 8 (Week 16) and were included in the Holter Monitoring sub-study Population.

The primary Holter Monitoring endpoint was change from baseline in mean heart rate averaged over 24 hours at Week 16. The changes from baseline in 24-mean heart rate at Week 16 were small and similar across treatment groups. The LS mean differences from baseline in 24-hour mean heart rate at Week 16 across treatment groups were small and not clinically meaningful.

Secondary endpoints in the Holter Monitor study included: change from baseline in nighttime and daytime mean heart rate, change from baseline in the 24-hour maximum heart rate, change from the baseline in the 24-hour minimum heart rate, change from baseline in the frequency of isolated ventricular ectopic events, change from the baseline in frequency of ventricular couplets, change from the baseline in the frequency of isolated supraventricular ectopic events, change from the baseline in the frequency of supraventricular couplets, change from the baseline of supraventricular runs, incidence of atrial fibrillation with rapid ventricular response. No notable differences were seen in these parameters across treatment groups. No subject met any withdrawal criteria for the 24-hour Holter Monitoring sub-study.

Bone and Endocrine Safety

Corticosteroids, including ICS, are known to have effects on the HPA axis and bone health, and the labels of ICS-containing products have statements regarding these effects in the Warnings and Precautions section. These effects were specifically studied in BGF Trial 05. However, in BGF Trial 06/08, sub-studies were performed to assess these effects. In BGF Trial 06, this was assessed by measuring adrenocorticoid testing, and in BGF Trial 08 this was assessed by a bone mineral density (BMD) sub-study. In Trial 06, serum cortisol curves showed normal diurnal variation over the 24-hour period and were similar between groups at both baseline and Week 24. In the Trial 08 BMD sub-study (N=323) there was a small numerical decrease in BMD of the lumbar spine at Week 52 in the BGF group compared to the GFF group (-0.5% [-1.4, 0.5]) that was above the pre-specified non-inferiority margin of -2%. Similarly, BMD of the hip showed a small numerical decrease in the BGF group compared to the GFF group (-0.6% [-1.3, 0.2]). Frequencies of bone-related AEs, including osteoarthritis, osteoporosis, osteopenia, and bone fractures, were infrequent and similar across treatment groups. The results of the HPA axis and BMD results do not raise new safety concerns.

Overall, analysis of AESIs in the BGF program were consistent drugs of the similar class and did not identify any new safety concerns.

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 conducted demographic subgroup analyses on AEs in BGF Trial 05. Subgroup analyses were performed by age, gender, and race. Small numerical differences were identified between subgroups, but this is to be expected given the relatively small number of subjects within

subgroups. This finding is consistent with Trial 06/08. Overall, demographic subgroup analysis of Trial 05 did not reveal any safety concerns.

8.2.8. Specific Safety Studies/Clinical Trials

There were no specific safety studies submitted with this Application. A development safety update report (DSUR) under IND 118313 was submitted on 5/8/2020. Review of the safety data included in the DSUR does change the previous safety related conclusions regarding BGF 320/14.4/9.6 µg.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No human carcinogenicity studies have been conducted in this application.

Human Reproduction and Pregnancy

No studies in this application assessed pregnancy, lactation, or reproduction. No pregnancies were reported in BGF Trial 05. No pregnancies were reported in BGF Trial 06/08, or BFF Trials 02 and Trial 03.

Pediatrics and Assessment of Effects on Growth

BGF is not subject to PREA requirements due to the nature of COPD involving an older population group.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Given the nature of the drug components and delivery method, drug abuse, withdrawal, and rebound are not anticipated for this combination drug product. It is expected that overdose with BGF would produce typical class effects for LABA and anticholinergic agents. Theoretically, abrupt stoppage of excessive dosages of BGF may result in adrenal crisis. The product labels for other ICS-containing products contain warning language regarding this risk.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no post-market experience for BGF. No safety concerns have been identified through post-market experience with GFF (Bevespi Aerosphere).

Expectations on Safety in the Postmarket Setting

The BGF phase 3 program evaluated a moderate-severe COPD population already taking at least two maintenance therapies for COPD. Additionally, patients with certain respiratory

comorbidities, chronic oxygen use, or recent exacerbations or infections were excluded from the clinical trials. Demographically, the BGF phase 3 program had some differences from the overall COPD population in the United States. Therefore, the COPD population exposed to BGF after marketing may experience other reactions not observed in the clinical trials. However, there is extensive experience in the COPD population with this class of drugs and safety can be monitored for with standard post-marketing safety infrastructure.

8.2.11. **Integrated Assessment of Safety**

The safety data submitted with this application were sufficient for review. The safety data were derived primarily from two phase 3 trials (BGF Trial 05 and Trial 06). Supportive data was derived the BGF Trial 06 safety-extension (BGF Trial 08), and also from two phase 3 studies for the unapproved BFF combination product (24-week Trial 02 and variable-length Trial 03) and the known safety profile of GFF (Bevespi Aerosphere, NDA 208294.)

Overall, the safety assessment across the BGF phase 3 trials, which included an evaluation of deaths, SAEs, all TEAEs, dropouts, AESIs, MACE, pneumonia events, laboratory findings, vital signs, ECGs, BMD, HPA axis, and ocular safety, was consistent with other products containing LAMA, LABA, or ICS alone or in combination. No new safety signals were revealed in this application. Overall, deaths, SAEs, and TEAEs were generally similar across groups. BGF did show some numerical increases compared to GFF in pneumonia, URTIs, dysphonia, thrush, and cataracts, which is consistent with the known adverse effects of ICS. Analysis of AE-related study discontinuations did not raise safety related concerns. Laboratory testing, vital signs, and ECG analysis did not show trends of concern for BGF. When comparing between BGF doses 320/14.4/9.6µg and 160/14.4/9.6 µg safety was comparable.

In conclusion, BGF at either dose does not show significant safety concerns above the active comparators GFF and BFF. Identified numerical differences between BGF and GFF can be attributed to the ICS component and is already reflected in the Warnings and Precautions of other ICS-containing products. Overall, the BGF safety profile is consistent with other inhaled products containing drugs in these classes.

8.3. **Statistical Issues**

In the following, we will discuss statistical issues in five categories: combination rule, substantial evidence of effectiveness, overall type I error control, estimand, and missing data and sensitivity analysis. In this section, BGF refers to BGF 320/14.4/9.6 µg.

Combination Rule

First, BGF is a fixed dose triple combination product of ICS, LAMA and LABA. To assess the efficacy of this product, it is necessary to demonstrate the contribution of each mono

component to the triple. Due to lack of treatment regimen of ICS and LAMA combo, it is only necessary to show the contribution of ICS and contribution of LAMA to the triple.

Contribution of ICS to the triple was assessed by comparison of BGF versus GFF on moderate or severe exacerbation and co-primary endpoints of morning trough FEV_1 at Week 24 in the sub-study.

Contribution of LAMA to the triple was assessed by comparison of BGF versus BFF on moderate or severe exacerbation and co-primary endpoint of FEV_1 AUC_{0-4} at Week 24 in the sub-study.

Trial 05 demonstrated the contribution of ICS and LAMA to the triple. Thus, the combination rule was satisfied in the BGF Trial 05.

Second, BFF was a double combination of ICS and LABA. It was not an approved product. It is necessary to demonstrate the contribution of ICS and LABA to the double. The original submission included two phase 3 BFF trials: Trial 02 and Trial 03. Both served as supporting efficacy trials. Both trials won on all the co-primary endpoints or the primary endpoint and provided a qualification for BFF as an active comparator in Trial 05.

Overall, combination rule was satisfied in the primary BGF exacerbation Trial 05, and in the supporting BFF efficacy trials.

Substantial Evidence of Effectiveness

Effectiveness of BGF was studied in Trial 05 which served as a primary efficacy trial. Effectiveness of BGF was also studied in the original submission Trial 06.

The effectiveness of BGF were assessed mainly in three categories: exacerbation benefit, lung function benefit and SGRQ benefit.

1. Exacerbation Benefit
   For Trial 05, contribution of ICS and LAMA to the triple in exacerbation benefit was assessed on annual rate of moderate or severe COPD exacerbation over 52 weeks by comparing BGF to GFF and BGF to BFF, both results were statistically significant.

   For the original submission Trial 06, contribution of ICS to the triple in exacerbation benefit was assessed on annual rate of moderate or severe COPD exacerbation over 24 weeks. Comparison of BGF to BFF only showed numerically less exacerbation and did not reach nominal significance.

   Overall BGF demonstrated exacerbation benefit.

2. Lung Function Benefit

For Trial 05, lung function benefits were assessed by endpoints of trough FEV1 (BGF vs GFF) and FEV1 AUC_{0-4} (BGF vs BFF) at week 24 in the sub-study. Both results reached statistical significance.

For the original submission Trial 06, BGF won on the endpoint FEV1 AUC_{0-4} but failed on trough FEV1.

Overall BGF demonstrated lung function benefit.

3. SGRQ Benefit
   For Trial 05, contribution of ICS and LAMA to the triple in SGRQ benefit was assessed on responder rate in SGRQ total score at Week 24. Both results reached nominal significance.

   For the original submission Trial 06, contribution of ICS to the triple in SGRQ benefit was assessed on responder rate in SGRQ total score at Week 24. The result reached nominal significance. Contribution of LAMA to the triple in SGRQ benefit was assessed on responder rate in SGRQ total score, and the result only showed that BGF was numerically better than BFF but not nominally significant.

   Overall, BGF demonstrated some SGRQ benefit over GFF and BFF, but not statistically significant.

Overall, after considering important benefits including exacerbation, lung function and SGRQ, the substantial evidence of effectiveness of BGF was assessed. We conclude that overall the program demonstrated substantial evidence of effectiveness of the study drug BGF.

Overall Type I Error Control

For all the trials in the program, overall type I error was controlled by performing a hierarchical testing procedure among the primary endpoint(s) and secondary endpoints and among the two doses, combined with the Hochberg procedure. Please refer to multiplicity adjustment in the statistical analysis plan in Section 8.1.1.1 for the testing hierarchy. The testing results according to the hierarchy are summarized in Table 41.

Table 41: Summary of Testing Results (Trial 05)

Endpoint	BGF vs GFF	BGF vs BFF
Rate of moderate or severe COPD exacerbations (Efficacy estimand; mITT population)	S.S.	S.S.
Rate of moderate or severe COPD exacerbations	S.S.	S.S.

(Attributable estimand; mITT population		
FEV1 AUC_{0-4} in PFT Sub-study (Efficacy estimand; mITT population)	n/a	S.S.
CFB trough FEV1 (Efficacy estimand; mITT population)	S.S.	n/a
Rate of moderate or severe COPD exacerbations in subjects with ≥2 exacerbations in the year before Screening (Efficacy Estimand; mITT Population)	S.S.	Fail
Time to first moderate or severe COPD exacerbation	S.S.	S.S.
CBF in average daily rescue Ventolin Hydrofluoroalkane (HFA) use over 24 weeks	S.S.	S.S.
Percentage of subjects achieving a minimal clinically important difference (MCID) of 4 units or more in SGRQ total score at week 24	S.S.	S.S.
Rate of severe COPD exacerbations	Fail	Fail
Time to death (all cause)	Fail	Fail

Abbreviations: S.S = statistically significant; n/a = not applicable

Estimand

All the data collected after discontinuing study treatment while on study (retrieved data) were excluded in the analysis. A hypothetical estimand was used by the sponsor. It assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomized treatment had they remained on treatment. This estimand is not a regulatory preferred estimand. The regulatory preferred estimand is a treatment policy estimand; it targets the treatment effect over the study period regardless of whether randomized treatment is continued. When estimating a treatment policy estimand, all the retrieved data are included in the analysis.

This review focused on both analyses using different estimands. Although the results using the treatment policy estimand showed less effectiveness, the difference was minimal and lead to the same conclusion. Overall the program showed effectiveness of the study drug BGF.

Missing Data and Sensitivity Analyses

Table 42 presented number of subjects who completed study drug treatment and study for

each arm in Trial 05. Overall, the BGF arm has the highest rate of subjects who completed study drug treatment and study, 79.4% and 84.2%, respectively. The rate of missing data was higher in the GFF and BFF arms than in the BGF arm. This review focused on the analysis using both on-treatment data and on-study data. The on-study data included data collected after the discontinuation of the study treatment. The results are consistent. The sponsor also conducted sensitivity analysis using tipping point analysis. Tipping point analyses showed the conclusions for BGF relative to GFF and BFF were robust to missing data assumptions.

Table 42: Number of Subjects Completed Study Drug Treatment and Study (Trial 05)

	BGF 320/14.4/9.6 µg (N=2157) n (%)	BGF 160/14.4/9.6 µg (N=2137) n (%)	GFF 14.4/9.6 µg (N=2143) n (%)	BFF 320/9.6 µg (N=2151) n (%)
Completed 52 weeks of treatment with study drug	1711 (79.4)	1715 (80.4)	1584 (74.1)	1644 (76.6)
Completed Study	1815 (84.2)	1820 (85.4)	1764 (82.5)	1788 (83.3)

Source: CSR, Page 117; Table 20.

8.4. Conclusions and Recommendations

The recommended regulatory action for BGF 320/18/9.6 µg is Approval.

The support for efficacy is primarily derived from two phase 3 trials comparing BGF to BFF and GFF. In the initial NDA submission, the Applicant included data from a single phase 3, 24-week, randomized, placebo-controlled trial with the primary objective of assessing the effect of BGF compared to GFF and BFF on lung function (Trial 06). Results from this trial were insufficient to support the contribution of the ICS monocomponent to BGF, though contribution of the LAMA monocomponent was supported. As a result, a CR action was taken. To address the CR deficiencies and provide substantial evidence of efficacy and the contribution of the ICS and LAMA monocomponents, the Applicant submitted the results from a second phase 3, 52 week, randomized, placebo-controlled trial (Trial 05) with the primary objective of assessing the effect of BGF compared to GFF and BFF on exacerbation. This trial also included a PFT sub-study to support effects on lung function. Trial 05 demonstrated evidence of efficacy as determined by achieving a statistically significant reduction in rate of moderate or severe COPD exacerbations for BGF treated patients versus GFF and BFF treated patients. This also demonstrated the contribution of the ICS (BD) and LAMA (GP) monocomponents to the triple combination. The secondary exacerbation related endpoints were also consistent with the primary endpoint. BGF demonstrated statistically significant improvement over GFF and BFF for time to first moderate or severe COPD exacerbation. Results were similar for severe exacerbations, though not statistically significant for the BGF to BFF comparison. SGRQ results were also generally consistent with the exacerbation data. The PFT sub-study demonstrated statistically significant

improvements in lung function for BGF versus GFF and BFF, demonstrating both efficacy and the contribution of the LAMA and ICS monocomponents in terms of bronchodilation. Results from Trial 05, with additional support for the previously reviewed Trial 06 taken together represent substantial evidence of efficacy and the contribution of the relevant monocomponents to the triple combination. The deficiencies outlined in the CR letter have been sufficiently addressed to warrant Approval of BGF for the maintenance treatment of COPD.

Regarding safety, assessment of BGF safety focused on Trial 05, with supporting evidence from Trial 06 and its safety extension Trial 08. No large imbalances in terms of deaths, serious adverse events (SAE), adverse events (AE) leading to discontinuation, or common AEs were observed when comparing BGF to the active comparators. Observed events were generally consistent with drugs of the same classes. No safety concerns precluding Approval were identified.

In summary, the BGF development program provided substantial evidence of efficacy and safety. The overall risk-benefit assessment support approval of BGF. The recommendation is Approval.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was necessary as ICS, LAMA, and LABA are well-established classes of therapeutics for COPD. There were no controversial issues that required advisory committee discussion.

10 Pediatrics

Not applicable

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The key changes to the Applicant proposed label were as follows:

- Section 6 Table 1 (b) (4) was edited to include on Trial 05 data as that trial was longer and larger.
- Section 14 was reordered to present spirometric data prior to exacerbation data. (b) (4) This was edited for brevity.
- Other sections were edited for consistency with existing labels and based of best labeling practices.

12 Risk Evaluation and Mitigation Strategies (REMS)

None

13 Postmarketing Requirements and Commitment

None

14 Division Director (Clinical) (Designated Signatory Authority) Comments

This is a resubmission of a 505(b)(2) NDA for a new triple therapy (ICS/LABA/LAMA) fixed-dose combination (FDC) of budesonide (BD), glycopyrrolate (GP), and formoterol fumarate (FF) inhalation aerosol (BGF) proposed for the (b) (4) maintenance treatment of (b) (4) patients with COPD (b) (4). BGF is delivered by a pressurized MDI. Each inhalation contains budesonide 160 µg, glycopyrrolate (glycopyrronium bromide) 9 µg, and formoterol fumarate 4.8 µg. The proposed dose is 2 inhalations for a total dose of 320, 18, and 9.6 µg of each component, respectively, and it is taken twice daily. The proposed trade name is Breztri Aerosphere.

There is currently one approved triple therapy inhalation product for patients with COPD, Trelegy Ellipta, which contains fluticasone furoate (ICS), vilanterol (LABA), and umeclidinium (LAMA). The Trelegy Ellipta program was quite large and was supported by development programs for two combination products, Breo Ellipta (ICS/LABA) and Anoro Ellipta (LABA/LAMA) as well as the LAMA single ingredient (Incruse Ellipta), all of which were approved in the US.

The FDC of glycopyrrolate and formoterol fumarate (GFF) is approved in the United States under the tradename Bevespi Aerosphere using the same delivery device. The FDC of budesonide and formoterol fumarate (BFF) is not approved, nor are the mono-components, budesonide (BD), glycopyrrolate (GP), and formoterol fumarate (FF) in this delivery device.

The initial NDA for BGF was submitted on November 30, 2018. A Complete Response (CR) action was taken on September 30, 2019 as the results from the single phase 3 trial (Trial 06) meant as primary support for safety and efficacy did not demonstrate the contribution of the ICS monocomponent to the combination and did not provide substantial evidence of efficacy. To address the CR deficiency, the Applicant submitted results from a new single phase 3 study (Trial 05) on January 22, 2020.

In the original NDA, Astra Zeneca submitted the results of one pivotal phase 3 trial (Trial 06) comparing the BGF combination product to BFF and GFF. Since BFF is not an approved product, AZ also submitted the results of 2 additional supportive trials (Trial 02 and Trial 03) to support the efficacy and safety of BFF.

BFF Combination
Trial 02 was a 24 week, randomized, double-blind trial in 2361 patients with COPD. Patients were randomized to one of 2 doses of BFF (320/9.6 µg BID or 160/9.6 µg BID), FF 9.6 µg BID, or BD 320 µg BID. Co-primary endpoints were change from baseline trough FEV_1 at week 24 (BFF vs. FF) to show the contribution of BD and change from baseline FEV_1 AUC_{0-4} at week 24 (BFF 320/9.6 µg vs. BD 320 µg) to show the contribution of FF. Results showed a statistically significant improvement in both co-primary endpoints for the BFF 320/9.6 µg dose,

demonstrating a contribution of each component to the BFF combination.

Trial 03 was a randomized, double-blind trial in 1843 patients with COPD. This trial was initially designed as a 52-week exacerbation trial but was subsequently amended to a be a 12-week bronchodilator trial. As such, all patients received at least 12-weeks of treatment, but some received treatment for longer. Patients were randomized to one of 2 doses of BFF (320/9.6 µg BID or 160/9.6 µg BID) or FF 9.6 µg BID. The primary endpoint was the change from baseline in trough FEV_1 at 12 weeks (BFF 320/9.6 µg vs. FF) to show the contribution of BD. Results showed a statistically significant improvement in change from baseline in trough FEV_1 at Week 12 for BFF 320/9.6 µg compared to FF.

In both trials, statistically significant improvements in time to first exacerbation were shown for BFF 320/9.6 µg compared to FF. The results of Trials 02 and 03 demonstrate the contribution of BD and FF to the BFF combination and support the use of BFF as a comparator in the BGF program.

BGF Combination
Trial 06 was a 24 week, randomized, double-blind, trial in 1896 patients with COPD designed to show the benefit of BGF over the two double combinations (BFF and GFF). Patients were randomized to BGF 320/14.4/9.6 µg, GFF 14.4/9.6 µg, BFF 320/9.6 µg BID, or open label Symbicort Turbuhaler 400/12 µg BID. The co-primary endpoints were change from baseline in FEV_1 AUC_{0-4} (BGF vs. BFF) at week 24 to show the contribution of GP and change from baseline in trough FEV_1 (BGF vs. GFF) at week 24 to show the contribution of BD. The results of Trial 06 showed a statistically significant increase in FEV_1 AUC_{0-4} for BGF vs. BFF, but results did not show a statistically significant increase in trough FEV_1 for BGF vs. GFF. Thus, Trial 06 failed to demonstrate the contribution of BD in the BGF combination product based on the results of the co-primary endpoint. Because of the failure to achieve statistical significance in the co-primary endpoint, all secondary endpoints are considered not statistically significant, including exacerbation rate and SGRQ. Of note, the exacerbation rate for comparison of BGF vs. GFF (contribution of BD) was numerically favorable.

Trial 05 was a 52 week, randomized, double-blind, parallel-group trial in 8588 patients with COPD designed to show the benefit of BGF over the two double combinations (BFF and GFF). Patients were randomized to BGF 320/14.4/9.6 µg, BGF 160/14.4/9.6 µg, GFF 14.4/9.6 µg, or BFF 320/9.6 µg, each administered BID. The trial included the following 2 sub-studies: a PFT sub-study and a 24-hour Holter Monitoring sub-study. The primary endpoint was the rate of moderate or severe COPD exacerbations, with an acceptable definition for COPD exacerbations. The results of Trial 05 showed a stasticially significant difference in the rate of moderate or severe COPD exacerbations for BGF 320/14.4/9.6 µg compared to GFF and BFF, demonstrating the contribution of both the BD and GP components, respectively. Secondary endpoints were supportive, including SGRQ. In this trial, the lower dose of BGF (160/14.4/9.6 µg) was also statistically significant compared to GFF and BFF. However, some secondary endpoints (e.g. mortality) numerically favored the higher dose. In addition, Trial 06 only included the higher

dose of BGF (320/14.4/9.6 µg), providing more safety and efficacy data for the higher dose. (b) (4)

Review of the safety data from this development program did not identify a new safety signal. ICS, LABA, and LAMA are well-established therapeutic classes in patients with COPD. The safety findings were consistent with the known safety profile of these therapeutic classes.

With the submission of Trial 05, the Applicant has demonstrated substantial evidence of efficacy of BGF for the treatment of patients with COPD. The program showed that BGF demonstrates an improvement in lung function, reduces COPD exacerbations, and has a favorable impact on SGRQ. BGF will provide another treatment option for patients with COPD. The regulatory action is Approval.

15 Appendices

15.1. References

1. *An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. ISOLDE Study Group.* **Jarad NA, Wedzicha JA, Burge PS, Calverley PM.** 1999, Respir Med, Vol. 93, pp. 161-6.
2. *Effects of withdrawal of inhaled steroids in men with severe irreversible airflow obstruction.* **O'Brien A, Russo-Mago P, Karki A, et al.** 2001, Am J Respir Crit Care Med, Vol. 164, pp. 365-371.
3. *Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. .* **van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C.** 2002, Am J Respir Crit Care Med, Vol. 166, pp. 1358-63.
4. *Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. .* **Choudhury AB, Dawson CM, Kilvington HE, et al.** 2007, Respir Res, Vol. 8, p. 93.
5. *Probability and determinants of relapse after discontinuation of inhaled corticosteroids in patients with COPD treated in general practice.* **Schermer TR, Hendriks AJ, Chavannes NH, et al.** 2004, Prim Care Respir J, Vol. 13, pp. 48-55.
6. *Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. .* **Wouters EF, Postma DS, Fokkens B, et al.** 2005, Thorax, Vol. 60, pp. 480-7.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): PT001005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3829		
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): 1		
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: 1. Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The research site ((b) (6)) where (b) (6) was a subinvestigator received a grant of $589,488.68 USD from AstraZeneca to cover the salary of a research fellow. This was not exclusively for the clinical trial. This grant is unlikely to affect interpretation of the study due to the randomized, double-blind, active controlled study design, as well as the site randomizing 1 study subject out of a total of 8588 subjects.

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/s/

ROBERT H LIM
07/23/2020 11:10:56 AM

SALLY M SEYMOUR
07/23/2020 11:29:04 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

MEMORANDUM

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

DATE: June 30, 2020

TO: File for NDA 212122

FROM: Mingyu Xi, PhD

SUBJECT: Primary Statistical Review

APPLICATION/DRUG: Budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler (Breztri Aerosphere)

Executive Summary

Astra-Zeneca (AZ) originally submitted an NDA for the fixed dose combination of budesonide 320 mcg, glycopyrrolate 18 mcg, and formoterol fumarate 9.6 mcg (BGF) for the maintenance treatment of COPD on November 30, 2018. The initial NDA reviewed Trial 06, a single phase 3, 24-week lung function trial comparing BGF to glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg (GFF, approved under tradename Bevespi Aerosphere) and budesonide 320 mcg/formoterol fumarate 9.6 mcg (BFF, not approved). This submission received a Complete Response (CR) action on September 30, 2019 for failure to demonstrate substantial evidence of efficacy and the contribution of the budesonide to the triple combination based on results of Trial 06. While BGF demonstrated a statistically significant difference for one of the co-primary endpoints (FEV1 AUC 0-4 hours for BGF vs. BFF), for the other (trough FEV1 for the comparison of BGF vs. GFF) it failed. All secondary endpoints were not considered statistically significant due to the Type I error control strategy.

AZ submitted a complete response to CR for BGF on January 23, 2020, which included Trial 05, a single phase 3, 52-week exacerbation and lung function trial comparing BGF to GFF and BFF as primary support for efficacy and safety of BGF. Trial 05 demonstrated evidence of efficacy for exacerbation based on the results of the primary endpoint, rate of moderate or severe exacerbation. Compared to GFF, BGF showed a statistically significant improvement in the primary endpoint of rate of moderate or severe COPD exacerbation, with a treatment rate ratio of 0.76 (95% CI: 0.69, 0.83; $p<0.0001$). BGF also demonstrated a statistically significant improvement in the primary endpoint compared to unapproved BFF with a treatment rate ratio of 0.87 (95% CI: 0.79, 0.95; $p=0.0027$). Additionally, BGF showed statistically significant improvements in the PFT sub-study primary endpoints. Compared to BFF, BGF showed a statistically significant improvement in the primary PFT sub-study endpoint of FEV1 area under the curve from 0-4 hours (AUC0-4) at Week 24 (119ml; 95%CI 95, 143mL; $p<0.0001$). Compared to GFF, BGF showed a statistically significant change from the mean baseline in

morning predose trough FEV1 at Week 24 (35ml; 95%CI 12, 57; p=0.0025). Additional secondary endpoints did not all reach statistical significance, but trended in the direction of favoring BGF over GFF and BFF.

Trial 05 addressed the deficiencies that led to the CR of Trial 06 in the initial BGF review. Trial 05 demonstrated statistically significant results for its primary endpoint of rate of moderate or severe COPD exacerbation when comparing BGF to GFF and BFF. Trial 05 was able to support the overall efficacy of BGF, as well as demonstrate that budesonide and glycopyrrolate both contribute to the triple combination in terms of exacerbation and bronchodilation.

My primary statistical review is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly. The statistical reviewer recommends Approval, pending finalization of labeling language with the Applicant. Refer to the Multi-Disciplinary Review and Evaluation for details.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MINGYU XI
07/01/2020 03:29:00 PM

YONGMAN KIM
07/01/2020 03:31:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

MEMORANDUM

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

DATE: June 30, 2020
TO: File for NDA 212122
FROM: Aishah Ali, MD
SUBJECT: Primary Clinical Review
APPLICATION/DRUG: Budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler (Breztri Aerosphere)

Executive Summary

Astra-Zeneca (AZ) originally submitted an NDA for the fixed dose combination of budesonide 320 mcg, glycopyrrolate 18 mcg, and formoterol fumarate 9.6 mcg (BGF) for the maintenance treatment of COPD on November 30, 2018. The initial NDA reviewed Trial 06, a single phase 3, 24-week lung function trial comparing BGF to glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg (GFF, approved under tradename Bevespi Aerosphere) and budesonide 320 mcg/formoterol fumarate 9.6 mcg (BFF, not approved). This submission received a Complete Response (CR) action on September 30, 2019 for failure to demonstrate substantial evidence of efficacy and the contribution of the budesonide to the triple combination based on results of Trial 06. While BGF demonstrated a statistically significant difference for one of the co-primary endpoints (FEV1 AUC 0-4 hours for BGF vs. BFF), for the other (trough FEV1 for the comparison of BGF vs. GFF) it failed. All secondary endpoints were not considered statistically significant due to the Type I error control strategy.

AZ submitted a complete response to CR for BGF on January 23, 2020, which included Trial 05, a single phase 3, 52-week exacerbation and lung function trial comparing BGF to GFF and BFF as primary support for efficacy and safety of BGF. Trial 05 demonstrated evidence of efficacy for exacerbation based on the results of the primary endpoint, rate of moderate or severe exacerbation. Compared to GFF, BGF showed a statistically significant improvement in the primary endpoint of rate of moderate or severe COPD exacerbation, with a treatment rate ratio of 0.76 (95% CI: 0.69, 0.83; $p<0.0001$). BGF also demonstrated a statistically significant improvement in the primary endpoint compared to unapproved BFF with a treatment rate ratio of 0.87 (95% CI: 0.79, 0.95; $p=0.0027$). Additionally, BGF showed statistically significant improvements in the PFT sub-study primary endpoints. Compared to BFF, BGF showed a statistically significant improvement in the primary PFT sub-study endpoint of FEV1 area under the curve from 0-4 hours (AUC0-4) at Week 24 (119ml; 95%CI 95, 143mL; $p<0.0001$). Compared to GFF, BGF showed a statistically significant change from the mean baseline in morning predose trough FEV1 at Week 24 (35ml; 95%CI 12, 57; $p=0.0025$). Additional

secondary endpoints did not all reach statistical significance, but trended in the direction of favoring BGF over GFF and BFF.

Trial 05 addressed the deficiencies that led to the CR of Trial 06 in the initial BGF review. Trial 05 demonstrated statistically significant results for its primary endpoint of rate of moderate or severe COPD exacerbation when comparing BGF to GFF and BFF. Trial 05 was able to support the overall efficacy of BGF, as well as demonstrate that budesonide and glycopyrrolate both contribute to the triple combination in terms of exacerbation and bronchodilation. Safety findings for BGF were consistent with the known safety profile of other COPD products in the same classes. Taken together, the results of Trial 05, along with supportive results of Trials 06/08, Trial 02, and Trial 03, demonstrated substantial evidence of effectiveness on exacerbation and lung function and contribution of all mono-components.

The primary clinical review recommends Approval.

My primary clinical review is complete and has been added to the NDA Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly. The primary clinical reviewer recommends Approval of this NDA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

A'ISHAH ALI
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ROBERT H LIM
06/30/2020 05:16:45 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION OF LEACHABLES FROM THE CONTAINER CLOSURE SYSTEM

Application number:	212122 (BGF MDI); 208294 (GFF MDI)
Review number:	Click here to enter text.
Supporting document/s:	NDA 212122 (BGF MDI): SDN 1 ; NDA 208294 (GFF MDI) SDN1

Click here to enter a date.

CDER stamp date:	11/30/2018 and 06/25/2015
Product:	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
Indication:	Maintenance treatment (b) (4) chronic obstructive pulmonary disease (COPD) (b) (4)
Therapeutic area:	Pulmonary Disease
Sponsor:	AstraZeneca
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Reviewer:	Ijeoma Uzoma, PhD
Supervisor/Team Leader:	Timothy Robison, PhD, DABT
Division Director:	Sally Seymour, MD
Project Manager:	Linda Ebonine, PA

Template Version: July 13, 2017

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

The Applicant has submitted a marketing application for the inhaled triple-combination product composed of glycopyrrolate (G), budesonide (B), and formoterol fumarate (F or FF) as a treatment for COPD. The Applicant currently markets the combination of glycopyrrolate and formoterol under the tradename of BEVESPI AEROSPHERE™ (NDA 208294) as a treatment for COPD. The inhaled triple-combination product represents the addition of budesonide to the approved combination of glycopyrrolate and formoterol. The Sponsor reported that the BGF MDI uses essentially the same container closure system (CCS) and excipients as BEVESPI AEROSPHERE (GFF MDI, NDA 208294- approved 4/25/2016). The only difference between the two products is the addition of micronized budesonide. The nonclinical review for GFF MDI (NDA 208294) stated that there were no nonclinical safety concerns for leachable levels in the product (Dr. Luqi Pei, dated 3/10/2016). The present review provides more detailed information for the leachables identified in the drug product formulation for the GFF MDI and their daily dose levels as well as safety assessments of the identified leachables. Potential leachables in the BGF MDI would be expected to be very similar to those identified in the GFF MDI given that both products use the same CCS and the only difference was the addition of budesonide. The Sponsor has also conducted abbreviated stability studies with the BGF MDI product based on the conditions used for the GFF MDI product. Leachables identified with the BGF MDI are described and evaluated for safety in the present review.

1.2 Brief Discussion of Nonclinical Findings

Controlled extraction studies and leachables testing within the stability studies were conducted with three unique registration stability batches of BEVESPI AEROSPHERE (GFF MDI) under NDA 208294. Additional analyses were also conducted for (b) (4) and foreign particulates. Abbreviated leachables testing within the stability studies was conducted with four drug product batches of BGF MDI under NDA 212122.

For the three registrational batches of GFF MDI, observed leachables were non-genotoxic and below the TTC of 5 µg/day. No (b) (4) were identified. Levels of (b) (4) were less than the TTC of 5 µg/day. Foreign particles were within acceptable levels.

For the four registrational batches of BGF MDI, observed leachables were non-genotoxic and below the TTC of 5 µg/day.

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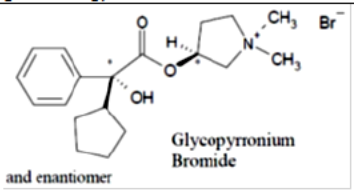
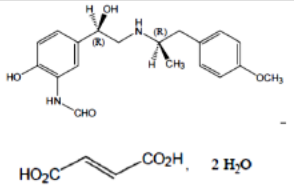
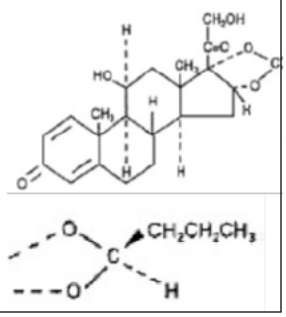
2 Drug Information

2.1 Drug

Table 1: Information for APIs used in GFF MDI (NDA 208294) and BGF MDI (NDA 212122)

	Glycopyrronium Bromide (GP)	Formoterol Fumarate (F or FF)	Budesonide (B)
CAS Registry Number	596-51-0	43229-80-7	51333-22-3
Generic Name	Glycopyrronium Bromide (GP)	Formoterol Fumarate	Budesonide
Chemical Name	Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, Bromide or 3-Hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate	(R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide,(E)-2-butendioate (2:1), dihydrate	(RS)-11b, 16a, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde
Molecular Weight/Formula	$C_{19}H_{28}BrNO_3$/ 398.33 g/mol	$(C_{19}H_{24}N_2O_4)2.C_4H_4O_4.2H_2O$/ 840.91 g/mol	$C_{25}H_{34}O_6$ / 430.5 g/mol
Pharmacologic Class	Anticholinergic (long acting muscarinic antagonist [LAMA])	Long-acting β2-adrenergic agonist [LABA]	Corticosteroid
Structures	 Glycopyrronium Bromide and enantiomer		

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2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 208294 BEVESPI AEROSPHERE® (Glycopyrronium/Formoterol Fumarate MDI)

IND 118313 (AstraZeneca, Budesonide/Glycopyrronium/Formoterol Fumarate MDI)

2.3 Drug Formulation

The BGF MDI 160 product delivers 160 µg budesonide, 7.2 µg glycopyrronium, and 4.8 µg formoterol fumarate per actuation. One dose is two actuations from the MDI. It is noted that 7.2 µg of glycopyrronium is equivalent to 9.0 µg glycopyrronium bromide or glycopyrrolate (quaternary ammonium bromide salt form of the drug substance). Throughout the review, the drug substance will be referred to as glycopyrrolate and concentrations of the drug substance also reflect the glycopyrrolate form. The MDI is manufactured at 120, (b) (4) and 28 actuations. The quantity of the drug substances per cannister varies based on the number of actuations per MDI, but the metered and delivered dose per actuation are identical between the different MDIs.

Table 2. Composition of BGF MDI 120/(b) (4)/28 Inhalations, 160/9/4.8 µg Per Actuation

Component	Quantity Per Canister (120 (b) (4)/28 Inhalations)[a]	Metered Dose (Ex-Valve)	Delivered Dose (Ex-Actuator)	Function	Reference to Standard
Budesonide, micronised	(b) (4)	(b) (4)	160 µg	Active ingredient	USP / AstraZeneca
Glycopyrrolate, micronised			9 µg[b]	Active ingredient	USP / AstraZeneca
Formoterol fumarate, micronised			4.8 µg	Active ingredient	USP / AstraZeneca
Porous particles					(b) (4)
HFA-134a					

Abbreviations: MDI = metered dose inhaler; BGF = budesonide/glycopyrrolate/formoterol fumarate; USP = United States Pharmacopeia; HFA = hydrofluoroalkane

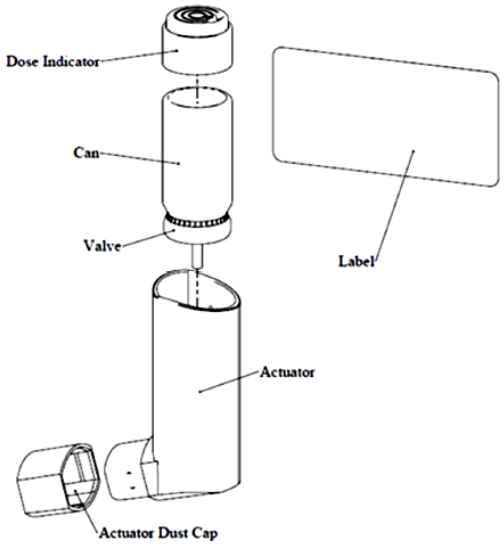
(b) (4)

Container Closure System

The primary CCS for both the BGF MDI (NDA 212122, BREZTRI AEROSPHERE) and the GFF MDI (NDA 208294, BEVESPI AEROSPHERE) consists of a (b) (4)

(b) (4) aluminum can sealed with a retention type metering valve, collectively referred to as the canister. The system delivers a (b) (4) metered dose per actuation. Each MDI is individually wrapped in a foil laminate pouch containing desiccant for moisture protection. The container closure system has multiple plastic and elastomeric components from which monomer/additives could leach into the drug product formulation.

Figure 1: Schematic Drawing of BGF MDI Container Closure System



An overview of the container closure system used in Phase III development and in the commercial product is summarised in Table 1 with the changes bolded.

Below is a side-by-side comparison of the To-Be-Marketed BGF-MDI and the approved GFF MDI noting the minor differences between the two CCS. The main changes of the to-be-marketed device and device approved under NDA 208294 are:

- Color changes of actuator dust cap (orange to grey)
- Tightening of the SOD (from (b) (4))

Table 3: Container Closure Comparison of the To-Be-Marketed BGF MDI and the

Component	NDA 208294 product	BGF MDI
Can	14 mL aluminium can (b) (4)	14 mL aluminium can (b) (4)
Valve	(b) (4) retention valve with (b) (4)	(b) (4) retention valve with (b) (4)
Actuator body	(b) (4)	(b) (4)
Actuator dust cap	Orange (b) (4)	**Grey** (b) (4)
Dose indicator	For 120 inhalation product: (b) (4) or For 28 inhalation product: (b) (4)	For 120 inhalation product: (b) (4) or (b) (4) For 28 inhalation product: (b) (4)
Canister label	(b) (4)	
Secondary pack	(b) (4)	

Abbreviations: (b) (4) MDI = metered dose inhaler; BGF = budesonide, glycopyrrolate, and formoterol; NDA = new drug application (b) (4)

Source: Response to clinical pharmacology IR dated January 14 2019.pdf, page 2-3, Table 1.

(Excerpted from CMC Section of the Unireview for NDA 212122)

2.4 Comments on Novel Excipients

NDA 212122 BGF MDI: This product contains no novel excipients. BGF contains HFA-134a as the propellant and porous particles as an excipient. The same propellant and excipients are present in the marketed product, BEVESPI AEROSPHERE (NDA 208294). Porous particles are comprised of (b) (4) DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and (b) (4) $CaCl_2$ (calcium chloride). The Applicant has rights of reference to DMF (b) (4) from (b) (4) for safety data with HFA-134a.

Porous particles have the same chemical composition as (b) (4). The estimated daily dose of porous particles from BEVESPI AEROSPHERE is (b) (4).

2.5 Comments on Impurities/Degradants, Extractables, and Leachables of Concern

Extractable and leachable studies were conducted with the GFF MDI under NDA 208294 for BEVESPI AEROSPHERE, which contains two active ingredients, glycopyrronium bromide (GP) and formoterol fumarate (FF), porous particles (b) (4), and HFA 134a (propellant) (Table 4). The DP formulation for BGF MDI contains the same active and inactive ingredients in equivalent amounts as GFF MDI with the exception of the addition of budesonide as third active ingredient (Table 2).

Table 4: Composition of BEVESPI AEROSPHERE (NDA 208294), GFF MDI

Component	Concentration (% w/w)	Quality per actuation [a]		Function
		Metered dose	Delivered dose	
Glycopyrronium bromide (GP)	(b) (4)	8.3 (b) (4) µg	7.2 µg	Active ingredient
Formoterol fumarate (FF)		5.5 µg	4.8 µg	Active ingredient
Porous particle (PP)[b]				(b) (4)
HFA 134a			(b) (4)	Propellant

a. Metered and delivered dose are expressed as the active moiety (or free base, i.e. glycopyrronium). Each actuation releases 9.0-µg glycopyrrolate.
b. See Section 2.4 Comments on Novel Excipients for the composition of the porous particles.

(Excerpted from Sponsor's submission)

2.6 Proposed Clinical Population and Dosing Regimen

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The proposed dosing regimen is two inhalations (budesonide 320 µg, glycopyrrolate 18 µg, and formoterol fumarate 9.6 µg) twice daily for (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD), (b) (4).

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2.8 Regulatory Background

Per discussions with the Review Chemist, potential leachables from the BGF MDI were not considered significant safety concerns given similarities of the CCS and drug

formulation to the approved GFF MDI (NDA 208294). The PharmTox reviewer for the GFF MDI product (NDA 208294), Dr. Luqi Pei, was also consulted. Dr. Pei stated that there is little safety concern for extractables and leachables from the BGF MDI product given the device and excipients are the same as the marketed GFF MDI product (emailed dated 3/21/2018).

3 Studies Submitted

3.1 Studies Reviewed

NDA 212122:
3.2.P.2. Pharmaceutical Development Attachment 3
P.8.1A Stability Summary for Drug Product – BGF MDI 160, 120 Inhalations

NDA 208294:
3.2.P.2. Pharmaceutical Development Attachment 4- Controlled Extraction Studies
3.2.P.2. Pharmaceutical Development Attachment 5- Characterization of Foreign Particles
3.2.P.8.3.1 Stability Data
3.2.P.8.3 Stability Data – GFF MDI, 28 Inhalations
3.2.P.8.1 Stability Summary and Conclusions

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of NDA 208294 for BEVESPI AEROSPHERE (Combination of formoterol and glycopyrrolate) by Dr. Luqi Pei dated March 10, 2016.

11 Integrated Summary and Safety Evaluation

Controlled extraction studies and leachables testing within the stability studies were conducted with three unique registration stability batches of BEVESPI AEROSPHERE (GFF MDI) under NDA 208294. Additional analyses were also conducted for (b) (4), and foreign particulates. Abbreviated leachables testing within the stability studies was conducted with four drug product batches of BGF MDI under NDA 212122.

Extractable Studies with the GFF MDI

Controlled extraction studies with CCS components (b) (4)

(b) (4)

The canister consists of a (b) (4) aluminum can and a pharmaceutical metering valve. A schematic diagram of the container closure system, showing the relevant individual component names and materials, is provided below. (b) (4)

(b) (4)

Figure 1. Schematic Drawing of the Valve Crimped Onto the Can Showing Individual Components and Component Materials

(Excerpted from the Sponsor's submission)

Table 5: Summary of CCS material and extractable species

Component	Component material	Target potential extractables
(b) (4)		(b) (4)
(b) (4) can Actuator		

(Excerpted from the Sponsor's submission)

Sponsor's Assessment of Controlled Extraction Studies:

(b) (4)

2. Levels of all compounds observed in the controlled extraction studies were below the specification limits established by the vendor.

3. Component suppliers were judged to be adequately controlling and monitoring the quality of the components.

Target leachables identified from controlled extraction studies are shown in the table below.

Table 6: Potential product leachables (identified from controlled extraction studies)

Leachable compound	Valve component	Source
(b) (4)		

(Excerpted from the Sponsor's submission)

Leachables Studies with GFF MDI (NDA 208294):

Based on the data from the controlled extraction studies specific, sensitive, analytical methods were developed and validated to determine whether any of the extractable species were present as leachables in the drug product after storage under long-term and accelerated storage conditions.

BEVESPI AEROSPHERE three NDA stability batches (lots 3H015A, 3H023A, and 3H024A) were manufactured (b) (4) commercial scale (b) (4) at (b) (4) the commercial manufacturing site. All three batches were 120 inhalation, 7.2/4.8 µg actuation Glycopyrronium/Formoterol fumarate (GFF) HFA inhalation products. (b) (4) (b) (4)

Each of the three NDA stability batches were placed in stability conditions of 25ºC/60%RH (long term), 30ºC/65%RH (intermediate) and 40ºC/75%RH (accelerated). The GFF MDIs are affixed with dose indicator, are placed into actuators along with a (b) (4) desiccant sachet, and stored foil overwrapped in valve down and valve up orientations for the long term and accelerated storage conditions and in the worst-case valve down orientation for the intermediate storage condition.

Leachables testing was initiated three months after the main stability was launched. Stability testing was conducted through 15 months for lots 3H015A, 3H023A, and 3H024A at the long-term stability condition and through 6 months for the accelerated storage condition.

Table 7: Conditions for GFF MDI NDA Stability Testing

Storage Configuration	Batch number		
	3H015A	3H023A	3H024A
25°C/60%RH, Protected VD	0 – 15 months	0 – 15 months	0 – 15 months
25°C/60%RH, Protected VU	0, 6, 12, and 15 months	0, 6, 12, and 15 months	0, 6, 12, and 15 months
40°C/75%RH, Protected VD	0 – 6 months	0 – 6 months	0 – 6 months
40°C/75%RH, Protected VU	0 and 6 months	0 and 6 months	0 and 6 months
30°C/75%RH, Protected VD	0 – 12 months	0 – 12 months	0 – 12 months

(Excerpted from the Sponsor's submission)

Leachables were identified and quantified by validated GC-MS and HPLC analytical procedures. Validated analytical procedures were also available for the identification and measurement of [redacted] (b) (4) testing procedures and the corresponding validation summaries.

Table 8: Stability testing for GFF MDI NDA

Testing Groups	Tests	Method Reference
A	Leachables by GC-MS	ATM-0038
	Leachables by HPLC	ATM-0039
B	[redacted] (b) (4)	ATM-0040
		ATM-0041
C		ATM-0054

(Excerpted from the Sponsor's submission)

Results:

HPLC Leachables [redacted] (b) (4) were detected in the drug formulation for GFF MDI (NDA 208294) during stability studies, levels below the acceptance criterion of [redacted] (b) (4) canister. [redacted] (b) (4) was observed in all three registration lots at similar levels and similar increase under accelerated conditions (40°C/75% RH) up to 6 months, but remain within acceptable limits. The potential daily exposure of [redacted] (b) (4) was

(b) (4) day, which was considered acceptable based upon the Product Quality Research Institute (PQRI) qualification threshold of 5 µg/day for non-genotoxic chemicals.

In the BGF (NDA 212122) stability study, (b) (4) were detected at (b) (4) day, under accelerated conditions (40°C/75% RH) up to 6 months, resulting in a potential daily exposure of (b) (4) at (b) (4) day, which was also considered acceptable based upon the PQRI qualification threshold of 5 µg/day for non-genotoxic leachables (see below for a more detailed assessment).

(b) (4) was identified as a leachable in the GFF MDI NDA 208294 registration stability study at levels below the acceptance criterion of 10 µg/canister. With these lots, clinical use of GFF MDI, the potential daily exposure of (b) (4) was (b) (4) day, which was considered acceptable based upon the Product Quality Research Institute (PQRI) qualification threshold of 5 µg/day for non-genotoxic chemicals. The Sponsor stated that the source of the (b) (4) was determined to be (b) (4), which contained (b) (4), and was inadvertently used by the clinical manufacturer. The Sponsor has specified that only (b) (4) should be used on their products, therefore (b) (4) should be eliminated from the container closure system and was not expected to be present as a leachable in the commercial product.

(b) (4) was not detected in the BGF MDI NDA 212122 stability study. In the BGF MDI NDA 212122 stability study, an unknown compound detected at (b) (4) (b) (4) was detected in batch E15-215 at a level of (b) (4) canister under accelerated storage conditions (40°C/75%RH) at 6 months. The sponsor was unable to identify the compound. However, the daily patient exposure was calculated to be (b) (4) day, which was below PQRI thresholds.

GC-MS Leachables

In the NDA 208294 GFF MDI registration stability study (b) (4) was observed in one of the three canisters tested for lot 3H024A of GFF MDI, at a level of (b) (4) canister, under accelerated conditions (40°C/75% RH) at 6 months. The daily patient exposure of (b) (4) was approximately (b) (4) day, which was considered acceptable based upon the Product Quality Research Institute (PQRI) qualification threshold of 5 µg/day for non-genotoxic chemicals.

Table 9: Summary Leachables Reported in Stability Studies with GFF MDI

Compound	Method	Daily Patient Exposure (µg/day)	Condition
(b) (4)	HPLC	(b) (4)	6 months- Batch 3H023A, 40°C/75%RH - Valve-Down

(b) (4)	HPLC	(b) (4)	12 months- Batch 3H024A, 30°C/75%RH - Valve-Down
	GC-MS		6 months- Batch 3H023A, 40°C/75%RH - Valve-Down

(b) (4)

Foreign particulates

Particles found from GFF MDIs, after actuation and subsequent dissolution of formulation, were characterized using Raman and Scanning Electron Microscopy (SEM) with Energy Dispersive X-Ray Spectroscopy (EDS). The main types of particles identified in this investigation originated from the valve (b) (4) . Other identified particles have traced back to the dose indicator, process equipment and materials handling

procedures, or the sample preparation materials or environment. Particles characterization was conducted on particles down to a minimum diameter of (b) (4).

The Sponsor determined for the GFF MDI that there were (b) (4) particles/actuation or (b) (4) particles/day in the respirable range with diameter (b) (4). The majority of the particles were determined to be (b) (4).

For this safety assessment, only particles in the size range up to (b) (4) were considered as these are the particles were most likely to be inhaled and deposited in the lower respiratory tract. To determine the weight of the daily exposure to foreign particle, it was assumed that the respirable particle size was (b) (4) and particles were spherical. The volume of one particle was determined using the formula (b) (4). The diameter was assumed to be (b) (4) and density was assumed to be (b) (4).

(b) (4)

Since quantitative data was not provided, a conservative approach was used whereby the total number of particles was to be composed of 100% of each of the following substances shown in the table below.

The safety of exposure to each substance was determined by comparing the daily exposure level with that derived from 8 hr Threshold Limits Values (TLV). These TLVs were recommended by the American Conference of Governmental Industrial Hygienists (2004). A safety factor of 14 has been incorporated to account for differences in population sensitivity (factor of 10) and exposure frequency (factor of 4).

Table 10: 8-hr TLV values (mg/m^3) for (b) (4)

(b) (4)

(b) (4)

Daily exposure to foreign particles (b) (4) from GFF pMDI represents from (b) (4) of the 8-hr TLV. This was determined from the total weight of the particles (b) (4) the 8-hr TLV, the respiratory volume of (b) (4) over an 8-hr period for a 70-kg adult, and the density assuming that particles were (b) (4) .

The EPA has health based national air quality standards for particulate matter (PM). For PM-2.5 (particulate matter ≤2.5 µm), the standards were set at 15 µg/m^3 (measured as an annual mean concentration) and 65 µg/m^3 (measured as a daily concentration). For PM-10 (particulate material ≤10 µm), the standards were at set at 50 µg/m^3 (measured as an annual mean concentration) and 150 µg/m^3 (measured as a daily concentration).

EPA

Table 11: EPA Acceptable mass (µg) of particulate matter for a respirable volume of (b) (4) over a 24 hr period based PM-2.5 and PM-10 Standards

EPA Acceptable mass (µg) of particulate matter for a respirable volume of (b) (4) over a 24 hr period based PM-2.5 and PM-10 Standards	
PM-2.5	PM-10
(b) (4)	

a. 24-hr respirable volume for a 50 kg adult based on the 24-hr respiratory volume of (b) (4) (b) (4) for a 70 kg adult.

Based on the EPA's standards for acceptable levels of particles over a 24-hr period, the exposure to (b) (4) particle with the highest density) of particulate matter from the GFF pMDI formulation was determined relative to the EPA standards. Results are presented in the following table.

Table 12: Comparison of foreign particle levels emitted by the GFF MDI to EPA standards for particulate exposure

Weight of particulate over 24-hr µg	% of EPA 24-hr Acceptable Particulate Material Set by the PM-2.5 and PM-10 Standard	
	PM-2.5	PM-10
(b) (4)	(b) (4)	

Assuming a density of (b) (4) the mass of particulate material ranged from (b) (4) of acceptable levels by the PM-2.5 standard and (b) (4) of acceptable levels by the PM-10 standard. Assuming a density of (b) (4), the mass of particulate material ranged from (b) (4) of acceptable levels by the PM-2.5 standard and from (b) (4) of acceptable levels by the PM-10 standard.

Daily exposures to foreign particles (b) from GFF pMDI were considered safe relative to the 8-hr threshold limit values for selected individual components and 24-hr particulate concentrations set by the PM-2.5 and PM-10 standards. For the calculations of the volume and weight of the particles, it was assumed that all the particles were (b) (4) in diameter. The total weight of the particles only included the number of particles (b). In determining the exposure to individual components, calculations were made on the assumption that particles were (b) (4) although there was actually a mixture of particles. For the GFF pMDI, daily exposure to (b) (4) foreign particles (b) was considered acceptable.

Leachables Studies with BGF MDI (NDA 212122):

The Sponsor provided a summary of the Leachables Stability study methods and results in section P.8 Stability of Drug Product Document

The Sponsor notes that the CCS components selected for the BGF MDI were based upon prior knowledge gained during the development of BEVESPI AEROSPHERE. BEVESPI AEROSPHERE leachable testing was conducted with three registration batches provided in the initial NDA submission and an additional 3 batches provided in Supplement #2 (only batches provided in the initial NDA submission are discussed in this review).

Methods:

Leachables were identified and quantified by validated GC-MS and HPLC analytical procedures. Resulting leachables from the CCS were quantitated on a µg/canister basis.

Test Article (Bulk Batch numbers): E15-185, E15-195, E15-160, E15-202

A total of four drug product batches were selected to represent two product strengths (160/7.2/4.8 µg or 80/7.2/4.8 µg) and two fill weights/number of inhalations (10.8 g/120 inhalations or 6.0 g/28 inhalations). The four batches were placed on stability testing according to ICH Q1A (R2), Stability Testing of New Drug Substances and Products. The four stability batches and their associated strength and fill weights along with the primary CCS component lot numbers are shown below in **Table 13**.

The stability conditions tested were 25ºC/60% RH (Zone II; long term), and 40ºC/75% RH (accelerated). Stability testing was conducted through 24 months for the "long term" stability condition and through 6 months for the "accelerated" storage condition (**Table 14**).

Table 13: BGF MDI drug product description for lots used on stability

Bulk (packaged) batch number	Strength	Fill weight (# of inhalations)	Valve lot	Can lot
E15-185 (E15-205)	160/7.2/4.8 µg per actuation	10.8 g (120 inhalations)	BK0556653	PPM0001535
E15-195 (E15-215)	80/7.2/4.8 µg per actuation	10.8 g (120 inhalations)	BK0574843	PPM0001503
E15-160 (E15-170)	160/7.2/4.8 µg per actuation	6.0 g (28 inhalations)	BK0555253/ BK0556653	PPM0001393
E15-202 (E15-224)	80/7.2/4.8 µg per actuation	6.0 g (28 inhalations)	BK0575098	PPM0001535

(Excerpted from the Sponsor's submission)

Table 14: BGF MDI drug product stability data

Storage configuration	Bulk batch number (packaged batch number)			
	E15-160 (E15-170)	E15-185 (E15-205)	E15-195 (E15-215)	E15-202 (E15-224)
25ºC/60% RH, protected VD	0–24 months	0–24 months	0–24 months	0–24 months
40ºC/75% RH, protected VD	0–6 months	0–6 months	0–6 months	0–6 months

(Excerpted from the Sponsor's submission)

Results:

Leachables by GC-MS:

Total Unspecified Leachables:

Total unspecified leachables (sum of all unknowns) detected at or above the PQRI determined analytical evaluation threshold (AET) of (b) (4)/canister (formula shown below) as well as any unspecified identified compounds were evaluated. The potential daily exposure of total unspecified leachables was (b) (4)/day, which was considered acceptable based upon the Product Quality Research Institute (PQRI) qualification threshold of 5 µg/day for non-genotoxic chemicals.

(b) (4)

(The Sponsor used 8 actuations/day vs. the intended 4 actuations/day for BGF MDI)

Where total unspecified leachables exceeded the AET, the unknown compounds were identified by NIST library match, in conjunction with analysis of the appropriate reference materials, to be small (b) (4)

The highest concentration of an (b) (4) species ((b) (4)) was observed in both batches E15-205 and E15-224 at the 6-month time point for the 40°C/75%RH condition at a concentration of (b) (4) canister. The highest concentration of (b) (4), was observed in batch E15-205 at the 18-month time point for the 25°C/65%RH (long term) condition at a concentration of (b) (4) canister. The potential daily exposure of the (b) (4) was (b) (4) /day, which was considered acceptable based upon the Product Quality Research Institute (PQRI) qualification threshold of 5 µg/day for non-genotoxic chemicals.

Leachables by HPLC

The (b) (4) (predominantly (b) (4)) were observed in all four registration batches at similar levels and similar increase with temperature and time. The leachables stability data showed a peak concentration of approximately (b) (4) /canister for (b) (4) (b) (4) at the 6-month time point in batch E15-215 under accelerated (40ºC/75% RH) storage condition, resulting in a potential daily exposure of (b) (4) at (b) (4) (b) (4) /day, which was considered acceptable based upon the PQRI qualification threshold of 5 µg/day for non-genotoxic chemicals.

Total unspecified leachables by HPLC (sum of all unknowns or unspecified) included the sum of all unknowns or unspecified identified compounds detected at or above the Sponsor's method reporting threshold of (b) (4) /canister was evaluated. An unknown at (b) (4) was observed in two of three canisters tested for lot E15-215 at the 6-month time point for a 40ºC/75%RH stability condition. The unknown at (b) (4) was observed just above the method reporting threshold at a level of (b) (4) canister and (b) (4) (b) (4) /canister for replicate 1 and replicate 2, respectively. An investigation failed to identify the unknown leachable.

Table 15: Summary Leachables Reported in Stability Studies with BGF MDI with the CCS

Compound	Method	Daily Patient Exposure (µg/day)	Condition
(b) (4)	HPLC	(b) (4)	6 months- Batch E15-215, 40°C/75%RH - Valve-Down
	GC-MS		18 months- Batch E15-205, 25°C/65%RH - Valve-Down
	HPLC		6 months- Batch E15-215, 40°C/75%RH - Valve-Down
	GC-MS		6 months- batches E15-205 and E15-224, 40°C/75%RH Valve-Down

Table 16: Leachables by HPLC total unspecified leachables – (b) (4)

Leachable[a]	Batch	Time point (months)	Condition/orientation	Replicate	Result (µg/canister)
(b) (4)	E15-215	6	40°C/75%RH / VD	1	(b) (4)
	E15-215	6	40°C/75%RH / VD	2	
	E15-215	6	40°C/75%RH / VD	3	

[a] (b) (4) was the only unspecified leachable detected by HPLC.

Foreign particulate

The Sponsor determined for the BGF MDI that there were (b) (4) particles/actuation or (b) (4) particles/day in the respirable range with diameter (b) (4), which was comparable to GFF MDI. See the evaluation of foreign particles for GFF MDI above.

Conclusions

For the three registrational batches of GFF MDI, observed leachables were non-genotoxic and below the TTC of 5 µg/day. No (b) (4) were identified. Levels of (b) (4) were less than the TTC of 5 µg/day. Foreign particles were within acceptable levels.

For the four registrational batches of BGF MDI, observed leachables were non-genotoxic and below the TTC of 5 µg/day.

Overall, there appear to be no nonclinical safety concerns for the BGF MDI related to leachables, (b) (4), or foreign particles based upon studies with the GFF MDI (NDA 208294) or BGF MDI (NDA 212122). No new safety concerns would be expected with the addition of budesonide to the formulation or the minor changes to the CCS for BGF MDI (NDA 212122).

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/s/

IJEOMA K UZOMA
11/12/2019 11:19:06 AM

TIMOTHY W ROBISON
11/12/2019 05:15:33 PM
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212122
Supporting document/s:	SND #1
Applicant's letter date:	November 30, 2018
CDER stamp date:	November 30, 2018
Product:	Budesonide, Formoterol Fumarate, Glycopyrrolate (BGF) pMDI
Indication:	COPD
Applicant:	AstraZeneca
Review Division:	Division of Pulmonary Allergy and Rheumatology Products
Reviewer:	Ijeoma Uzoma, PhD
Supervisor/Team Leader:	Timothy Robison, PhD, DABT
Division Director:	Sally Seymour, MD
Project Manager:	Linda Ebonine, PA

Template Version: September 1, 2010

Disclaimer

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TABLE OF CONTENTS

Table of Tables

Table of Figures

No table of figures entries found.

1 Executive Summary

1.1 Introduction

The Applicant has submitted a marketing application for the inhaled triple-combination product composed of glycopyrrolate (G), budesonide (B), and formoterol fumarate (F or FF) as a treatment for COPD. The Applicant currently markets the combination of glycopyrrolate and formoterol under the tradename of Bevespi Aerosphere™ (NDA 208294) as a treatment for COPD. The inhaled triple-combination product represents the addition of budesonide to the approved combination of glycopyrrolate and formoterol. The Applicant also markets the combination of formoterol and budesonide under the tradename of Symbicort (NDA 21929) for the treatment of asthma and COPD. The Applicant has complete nonclinical programs for formoterol and budesonide, which were reviewed under the NDA 21929 for Symbicort (Budesonide and Formoterol Fumarate) and NDA 20929 for Pulmicort Respules (Budesonide). NDA 212122 is a 505(b)(2) application where ROBINUL Injection (NDA 17558) and CUVPOSA (NDA 022571) are reference listed drugs to support the glycopyrrolate program.

The Sponsor, AstraZeneca, has provided proposed product labeling for TRADENAME AEROSPHERE BGF MDI (NDA 212122) in the present application for marketing. This review evaluated the Applicant's proposed product labeling for Established Pharmacologic Classification (EPC) (under Highlights of Prescribing Information), Use in Specific Populations (under Highlights of Prescribing Information), Section 8.1 (Pregnancy), Section 8.2 (Lactation), Section 12.1 (Mechanism of Action), Section 13.1 (Nonclinical Toxicology), and Section 13.2 (Animal Toxicology and/or Pharmacology).

1.2 Brief Discussion of Nonclinical Findings

The nonclinical review of the proposed product label was limited to Established Pharmacologic Classification (EPC) under Highlights of Prescribing Information, Use in Specific Populations (under Highlights of Prescribing Information), Section 8.1 (Pregnancy), Section 8.2 (Lactation), Section 12.1 (Mechanism of Action), Section 13.1 (Nonclinical Toxicology), and Section 13.2 (Animal Toxicology and/or Pharmacology).

Symbicort (NDA 21929) was used as reference for labeling for the individual components, budesonide and formoterol fumarate. Bevespi Aerosphere™ (NDA 208294) was referenced for the mechanism of action of glycopyrrolate. CUVPOSA, an approved oral glycopyrrolate product (NDA 022571), was referenced to support glycopyrrolate labeling in Section 13.1 for carcinogenicity.

1.3 Recommendations

1.3.1 Approvability

Recommended changes for labeling that describes the results and risk assessment of nonclinical studies in Established Pharmacologic Classification (EPC) (under Highlights of Prescribing Information), Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism

of Action), 13.1 (Nonclinical Toxicology), and 13.2 (Animal Toxicology and/or Pharmacology) are described in this review.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Provided below is the Reviewer's recommended labeling for nonclinical sections of the proposed product label. The Sponsor's proposed labeling for nonclinical sections and a description of the Reviewer's recommended edits are shown in Section 11.

TRADENAME AEROSPHERE is combination of budesonide, an inhaled corticosteroid (ICS); glycopyrrolate, an anticholinergic; and formoterol fumarate, a long-acting beta$_2$-adrenergic agonist (LABA), indicated for:

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

(b) (4)

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with TRADENAME AEROSPHERE or two of its individual components, glycopyrrolate or formoterol fumarate, in pregnant women to inform a drug associated risk; however, studies are available for the other component, budesonide.

In animal reproduction studies, budesonide alone, administered by the subcutaneous route, caused structural abnormalities, was embryocidal, and reduced fetal weights in rats and rabbits at 0.3 and 0.75 times the maximum recommended human daily inhalation dose (MRHDID), but these effects were not seen in rats that received inhaled doses up to 4 times the MRHDID. Studies of pregnant women (b) (4) inhaled budesonide alone (b) (4) during pregnancy. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

Formoterol fumarate alone, administered by the oral route, caused structural abnormalities in rats and rabbits at 1500 and 61,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats at 110 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 structural abnormalities, embryocidal (b) (4), or developmental effects were seen in rats that received inhalation doses up to 350 times the MRHDID.

Glycopyrrolate alone, administered by the subcutaneous route, did not cause structural abnormalities or affect fetal survival, in rats or rabbits at exposures approximately (b) (4)

(b) (4) times the MRHDID, respectively. Glycopyrrolate had no effects on the physical, functional, and behavioral development of rat pups with exposures up to (b) (4) times the MRHDID

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

Clinical Considerations

Labor and Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of TRADENAME AEROSPHERE during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Data

Human Data
Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Animal Data

Budesonide

In a fertility and reproduction study, male rats were subcutaneously dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were dosed up until weaning of their offspring. Budesonide caused a decrease in

prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body weight gain, at a dose 0.3 times the MRHDID (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and above). No such effects were noted at a dose 0.08 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 5 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to 18, budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at doses 0.75 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 25 mcg/kg/day). In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, budesonide produced similar adverse fetal effects at doses approximately 8 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 500 mcg/kg/day). In another embryo-fetal development study in pregnant rats, no structural abnormalities or embryocidal effects were seen at doses up to 4 times the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 250 mcg/kg/day).

In a peri-and post-natal development study, rats dosed from gestation day 15 to postpartum day 21, budesonide had no effects on delivery, but did affect growth and development of offspring. Offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation at doses 0.3 times the MRHDID and higher (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred 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 1500 times and greater than the MRHDID (on a mcg/m^2 basis at maternal oral doses of 3000 mcg/kg/day and higher). Brachygnathia was observed in rat fetuses at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Pregnancy was prolonged at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Pregnancy was prolonged at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Fetal and pup deaths occurred at doses approximately 1500 times the MRHDID and higher (on a mcg/m^2 basis at oral doses of 3000 mcg/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 to 15, no structural abnormalities, embryocidal effects, or developmental effects were seen at doses up to 350 times the MRHDID (on a mcg/m^2 basis with maternal inhalation doses up to 690 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to 18, subcapsular cysts on the liver were

observed in the fetuses at a dose 61,000 times the MRHDID (on a mcg/m2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed at doses up to 3500 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 3500 mcg/kg/day).

In a pre- and post-natal development study, pregnant female rats received (b) (4) formoterol at oral doses of 0, 210, 840, and 3400 mcg/kg/day from GD 6 through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 110 times the MRHDID and higher (on a mcg/m^2 basis at maternal oral doses of 210 mcg/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.

Glycopyrrolate
In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 17, glycopyrrolate produced no structural abnormalities or effects on fetal survival; however, slight reductions of fetal body weight in the presence of maternal toxicity at the highest tested dose that was (b) (4) times the MRHDID (on a (b) (4) basis at a maternal subcutaneous dose of 10,000 mcg/kg/day). Fetal body weights were unaffected with doses up to (b) (4) times the MRHDID (on a (b) (4) (b) (4) basis with maternal subcutaneous doses up to 1000 mcg/kg/day). Maternal toxicity was observed with doses (b) (4) times the MRHDID and higher (on a (b) (4) basis with maternal subcutaneous doses of 1000 mcg/kg/day and higher).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from GDs 6 to 18, glycopyrrolate produced no structural abnormalities or effects on fetal survival; however, slight reductions of fetal body weight in the presence of maternal toxicity at the highest tested dose that was (b) (4) times the MRHDID (on a (b) (4) basis at a maternal subcutaneous dose of 10,000 mcg/kg/day). Fetal body weights were unaffected with doses up to (b) (4) times the MRHDID (on a (b) (4) basis with maternal subcutaneous doses up to 1000 mcg/kg/day). Maternal toxicity was observed with doses (b) (4) times the MRHDID and higher (on a (b) (4) basis with maternal subcutaneous doses of 1000 mcg/kg/day and higher).

In a pre- and post-natal development study, pregnant female rats received glycopyrrolate at doses of 100, 1000, and 10,000 mcg/kg/day from gestation day 6 through the lactation period. Pup body weight gain was slightly reduced from birth through the lactation period at a dose (b) (4) times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 10,000 mcg/kg/day); however, pup body weight gain was unaffected after weaning. There were no treatment-related effects on the physical, functional, and behavioral development of pups with doses up to (b) (4) times the MRHDID (on a mcg/m^2 basis with maternal subcutaneous doses up to 10,000 mcg/kg/day). Maternal toxicity was observed from gestation days 6 to 18 with doses (b) (4) times the MRHDID and higher (on an AUC basis with maternal subcutaneous doses of 1000 mcg/kg/day and higher).

8.2 Lactation

Risk Summary

There are no available data on the effects of TRADENAME AEROSPHERE, budesonide, glycopyrrolate, or formoterol fumarate on the breastfed child or on milk production. Budesonide, like other inhaled corticosteroids, is present in human milk [see Data]. There are no available data on the presence of glycopyrrolate or formoterol fumarate in human milk. Formoterol fumarate and glycopyrrolate have been detected in the plasma of undosed rat pups suckling from exposed dams (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME AEROSPHERE and any potential adverse effects on the breast-fed child from TRADENAME AEROSPHERE or from the underlying maternal condition.

Data

Human Data

Human data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother (b) (4). For TRADENAME AEROSPHERE, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

There is no available human data for formoterol or glycopyrrolate.

Animal Data

In the fertility and reproduction study in rats, plasma levels of formoterol were measured in pups on postnatal 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).

In the (b) (4) in rats, plasma levels of glycopyrrolate were measured in pups on post-natal day 4. The maximum concentration in the pups was 6% of the maternal dose of 10 mg/kg/day (pup plasma concentration of 96 ng/mL at 1 hour after dosing corresponded with 1610 ng/mL in the dam at 0.5 hours after dosing).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRADENAME AEROSPHERE

TRADENAME AEROSPHERE contains budesonide, glycopyrrolate, and formoterol fumarate. The mechanisms of action described below for the individual components

applies to TRADENAME AEROSPHERE. These drugs represent three different classes of medications (a synthetic corticosteroid, an anticholinergic, and a long-acting selective beta$_2$-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of COPD.

Budesonide
Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. In vitro studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of COPD. Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non–allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.

(b) (4)

Glycopyrrolate
Glycopyrrolate 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 the 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 vitro as well as in vivo studies, prevention of methylcholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted more than 12 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of glycopyrrolate is predominantly a site-specific effect.

Formoterol Fumarate
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 beta1receptors. The in vitro binding selectivity to beta$_2$- over beta$_1$-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta$_2$-selectivity ratio than formoterol.

Although beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$ receptors are the predominant receptors in the heart, there are also beta$_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta$_2$-agonists may have cardiac effects.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including formoterol fumarate, 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.

(b) (4)

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with TRADENAME AEROSPHERE; however, separate studies of budesonide, glycopyrrolate, and formoterol fumarate are described below.

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

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID (b) (4) on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equivalent to the MRHDID (b) (4) on a mcg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused (b) (4) at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID (b) (4) on a mcg/m^2 basis). (b) (4)

(b) (4) The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide (b) (4) no treatment-related (b) (4) at oral doses up to 200 mcg/kg (approximately 2 times the MRHDID (b) (4) on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in (b) (4) Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster, and DNA repair analysis in rat hepatocyte culture.

Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg (approximately equal to the MRHDID on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (0.3 times the MRHDID on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (0.08 times the MRHDID on a mcg/m^2 basis).

Glycopyrrolate

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

In a 24-month inhalation carcinogenicity study in B6C3F1 mice, glycopyrrolate produced no evidence of tumorigenicity when administered to males or females at doses up to 705 and 335 mcg/kg/day, respectively (approximately 95 and 45 times the MRHDID of glycopyrrolate on a mcg/m^2 basis, respectively).

In a 24-month carcinogenicity study in rats, glycopyrrolate produced no evidence of tumorigenicity when administered to males or females by oral gavage at dosages up to 40,000 mcg/kg/day (approximately 11,000 times the MRHDID of glycopyrrolate on a mcg/m^2 basis).

Glycopyrrolate was not mutagenic or clastogenic in the Ames Salmonella/microsome plate test, in vitro mammalian cell micronucleus assay in TK6 cells, or in vivo micronucleus assay in rats.

Fertility and reproductive performance indices were unaffected in male and female rats that received glycopyrrolate by the subcutaneous route at doses up to 10,000 µg/kg/day (approximately (b) (4) times, respectively, the MRHDID on a (b) (4) basis).

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 100 mcg/kg and above (approximately 25 times MRHDID on a mcg/m2 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 130 mcg/kg (approximately 65 times the MRHDID on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the MRHDID on a mcg/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, or rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15,000 mcg/kg, (approximately (b) (4) times the MRHDID on an AUC basis). No such effect was seen at 3,000 mcg/kg (approximately (b) (4) times the MRHDID on a mcg/m^2 basis). In a separate study with male rats treated with an oral dose of 15,000 mcg/kg (approximately 8000 times the MRHDID on a mcg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No effect on fertility was detected in female rats at doses up to 15,000 mcg/kg (approximately (b) (4) times the MRHDID on an AUC basis).

(b) (4)

2 Drug Information

2.1 Drug

Generic Name: Budesonide, Glycopyrrolate, and Formoterol Fumarate Inhalation Aerosol, 120 Inhalations for Budesonide, Glycopyrrolate, and Formoterol Fumarate metered dose inhaler, 120 Inhalations (BGF MDI)

Individual Components

Budesonide

CAS Registry Number: 51333-22-3

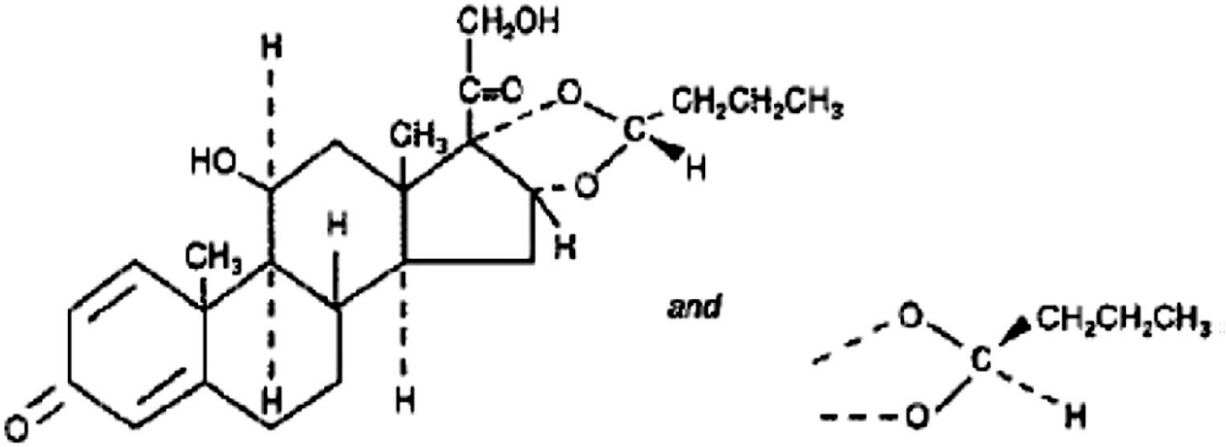
Generic Name: Budesonide

Code Name: NA

Chemical Name: (RS)-11b, 16a, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde

Molecular Formula/Molecular Weight: $C_{25}H_{34}O_6$ / 430.5 g/mol

Structure or Biochemical Description: Budesonide is provided as a mixture of two epimers (22R and 22S).



Pharmacologic Class: Corticosteroid

Glycopyrrolate

CAS Registry Number (Optional): 596-51-0

Generic Name: Glycopyrrolate (or Glycopyrronium Bromide)

Code Name: NA

Chemical Name: Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, Bromide or 3-Hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate

Molecular Formula/Molecular Weight: $C_{19}H_{28}BrNO_3$/ 398.33 g/mol

Structure or Biochemical Description: There are two asymmetric carbons in the molecule (denoted by * in structural formula). The product is a 50/50% mixture of three enantiomers i.e., racemate of the (R,S) and (S,R) enantiomeric pair. The product is not optically active.

Pharmacologic Class: Anticholinergic

Formoterol Fumarate

CAS Registry Number: 43229-80-7

Generic Name: Formoterol Fumarate

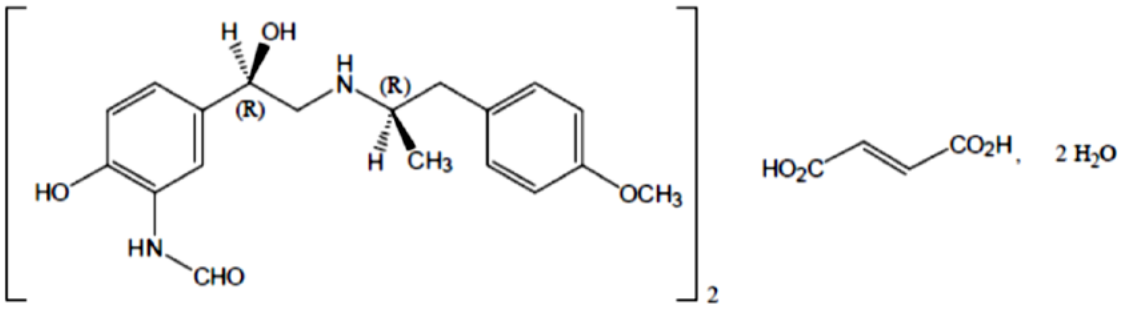
Code Name: NA

Chemical Name: N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino] ethyl]phenyl] formamide, (E)-2-butenedioate dihydrate

Molecular Formula/Molecular Weight: $(C_{19}H_{24}N_2O_4)2.C_4H_4O_4.2H_2O$/ 840.91 g/mol

Structure or Biochemical Description: Formoterol fumarate (FF) has two chiral centers. The active ingredient is an equimolar mixture of (R,R) and (S,S) enantiomers as shown below. (b) (4)

ENANTIOMER (R,R)



Pharmacologic Class: Long-acting β_2-adrenergic agonist [LABA]

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 21929: Symbicort® MDI (budesonide/formoterol) Inhalation Aerosol

NDA 208294: Bevespi Aerospheres® (formoterol fumarate/glycopyrrolate)

IND 118313: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI)

IND 101,985: Glycopyrrolate Inhalation Aerosol (GP MDI) as a monoproduct

IND 105,586: Formoterol Fumarate Inhalation Aerosol (FF MDI) as a monoproduct

IND 107,739: Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol (GFF MDI) as a dual combination product

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Adult COPD patients will use BGF pMDI twice daily. Each dose consists of two actuations. Each actuation of Bevespi releases 9 µg glycopyrrolate, 4.8 µg formoterol fumarate, and 160 µg budesonide. This dosing regimen corresponds to the maximum recommended human daily inhalation dose (MRHDID) of 36 µg glycopyrrolate, 19.2 µg formoterol fumarate, and 640 µg budesonide, respectively. These inhaled doses correspond to nominal doses of 0.6 µg/kg/day glycopyrrolate, 0.32 µg/kg/day formoterol fumarate, and 10.7 µg/kg/day budesonide on a unit bodyweight basis for a 60-kg patient.

11 Integrated Summary and Safety Evaluation

The nonclinical review of the proposed product label recommended changes for labeling that describe the results and risk assessment of nonclinical studies in Established Pharmacologic Classification (EPC) (under Highlights of Prescribing Information), Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), 13.1 (Nonclinical Toxicology), and 13.2 (Animal Toxicology and/or Pharmacology) are described in this review.

The Symbicort (NDA 21929) product label that contains descriptions of nonclinical studies with budesonide and formoterol served as the basic template for these sections of the label. Data from nonclinical reproductive toxicity, genetic toxicity, and carcinogenicity studies with glycopyrrolate provided in the current application or NDA 208294 for Bevespi Aerosphere was inserted into the label.

The Symbicort (NDA 21929) product label that contains descriptions of nonclinical studies with budesonide and formoterol served as the basic template for these sections of the label. Data from nonclinical reproductive toxicity, genetic toxicity, and carcinogenicity studies with glycopyrrolate provided in the current application or NDA 208294 for Bevespi Aerosphere was inserted into the label.

Table 1: Established Pharmacologic Classification (under Highlights of Prescribing Information)

Sponsor's Proposed Labeling	Nonclinical Labeling
TRADENAME AEROSPHERE is combination of budesonide, an inhaled corticosteroid (ICS); glycopyrrolate, an anticholinergic; and formoterol fumarate, a long-acting beta$_2$-adrenergic agonist (LABA), indicated for: • the (b) (4), maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD). (b) (4)	TRADENAME AEROSPHERE is combination of budesonide, an inhaled corticosteroid (ICS); glycopyrrolate, an anticholinergic; and formoterol fumarate, a long-acting beta$_2$-adrenergic agonist (LABA), indicated for: • the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD). (b) (4)

Nonclinical Comments: Established Pharmacologic Classification

Established Pharmacologic Classifications have been updated using labeling from the Symbicort product label for the individual drug components, budesonide and formoterol

fumarate. Labeling for Glycopyrrolate was identical that found in Bevespi Aerosphere (NDA 208294)

Table 2: Proposed Labeling Changes for Sections 8.1 (Pregnancy) and 8.2 (lactation)

Sponsor's Proposed Labeling	Nonclinical Labeling
8 USE IN SPECIFIC POPULATIONS	**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy Risk Summary There are no adequate and well-controlled studies with TRADENAME AEROSPHERE (b) (4) two of its individual components, glycopyrrolate or formoterol fumarate, in pregnant women to inform a drug-associated risk; however, studies are available for the other component, budesonide. Budesonide alone, administered by the subcutaneous route, caused structural abnormalities, was embryocidal, and reduced fetal weights in rats and rabbits (b) (4) maximum recommended human daily inhaled dose (MRHDID), but these effects were not seen in rats that received inhaled doses up to 4 times the MRHDID. Studies of pregnant women (b) (4) inhaled budesonide alone (b) (4) during pregnancy. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.	**8.1 Pregnancy** Risk Summary There are no adequate and well-controlled studies with TRADENAME AEROSPHERE or two of its individual components, glycopyrrolate or formoterol fumarate, in pregnant women to inform a drug associated risk; however, studies are available for the other component, budesonide. In animal reproduction studies, budesonide alone, administered by the subcutaneous route, caused structural abnormalities, was embryocidal, and reduced fetal weights in rats and rabbits at 0.3 and 0.75 times (b) (4) maximum recommended human daily inha (b) (4) dose (MRHDID), but these effects were not seen in rats that received inhaled doses up to 4 times the MRHDID. Studies of pregnant women (b) (4) inhaled budesonide alone increases (b) (4) risk of abnormalities (b) (4) Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

Formoterol fumarate alone, administered by the oral route, caused structural abnormalities in rats and rabbits at 1500 and 61,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats at 110 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 structural abnormalities, embryocidal, or developmental effects were seen in rats that received inhalation doses up to (b) (4) times the MRHDID.	Formoterol fumarate alone, administered by the oral route, caused structural abnormalities in rats and rabbits at 1500 and 61,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats at 110 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 structural abnormalities, embryocidal (b) (4) or developmental effects were seen in rats that received inhalation doses up to 350 times the MRHDID.
Glycopyrrolate alone, administered by the subcutaneous route, (b) (4) in rats or rabbits (b) (4) approximately ~~2700~~ and ~~5400~~ times the MRHDID, respectively.	Glycopyrrolate alone, administered by the subcutaneous route, did not cause structural abnormalities or affect fetal survival, in rats or rabbits at exposures approximately 1400 and 3000 times the MRHDID, respectively. Glycopyrrolate had no effects on the physical, functional, and behavioral development of rat pups with exposures up to 24,000 times the MRHDID.
(b) (4) The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.	The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Clinical Considerations *Labor and Delivery:* Because of the potential for beta-agonist interference with uterine contractility, use	Clinical Considerations *Labor and Delivery:* Because of the potential for beta-agonist interference with uterine contractility, use of

of TRADENAME AEROSPHERE during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.	TRADENAME AEROSPHERE during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.
Human Data	Data *Human Data*
Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).	Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).
These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among	These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among

infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).	infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).
Animal Data	*Animal Data*
Budesonide	Budesonide
In a fertility and reproduction study, (b) (4) No such effects were noted at a dose (b) (4) the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 5 mcg/kg/day).	In a fertility and reproduction study, male rats were subcutaneously dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were dosed up until weaning of their offspring. Budesonide caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body weight gain, at a dose 0.3 times the MRHDID (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and above). No such effects were noted at a dose 0.08 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 5 mcg/kg/day).
In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at dose (b) (4) the MRHDID (on a mcg/m2 basis at a maternal subcutaneous dose of 25 mcg/kg/day).	In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to GD 18, budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at doses 0.75 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 25 mcg/kg/day).
In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, budesonide produced similar adverse fetal effects at doses approximately 8 times the MRHDID (on a mcg/m2 basis at a maternal subcutaneous dose of 500 mcg/kg/day). In another embryo-fetal	In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, budesonide produced similar adverse fetal effects at doses approximately 8 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 500 mcg/kg/day). In another embryo-fetal development study in pregnant rats, no

development study in pregnant rats, no (b) (4) or embryocidal effects were seen at doses up to 4 times the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 250 mcg/kg/day).	structural abnormalities or embryocidal effects were seen at doses up to 4 times the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 250 mcg/kg/day).
In a peri-and post-natal development study, rats dosed from gestation day 15 to postpartum day 21, budesonide had no effects on delivery, but did affect growth and development of offspring. Offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation at doses (b) (4) the MRHDID and higher (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.	In a peri-and post-natal development study, rats dosed from gestation day 15 to postpartum day 21, budesonide had no effects on delivery, but did affect growth and development of offspring. Offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation at doses 0.3 times the MRHDID and higher (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.
Formoterol Fumarate In a fertility and reproduction study, rats were orally dosed prior to pairing and throughout the mating period. Females were either dosed up to gestation day 19 or up until weaning of their offspring. Umbilical hernia was observed in rat fetuses at oral doses 1500 times the MRHDID (on a mcg/m^2 basis at maternal oral doses of 3000 mcg/kg/day and higher). (b) (4) etal and pup deaths occurred at doses approximately 1500 times the MRHDID and higher (on a mcg/m2 basis at oral doses of 3000 mcg/kg/day and higher) during gestation.	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 1500 times and greater than the MRHDID (on a mcg/m^2 basis at maternal oral doses of 3000 mcg/kg/day and higher). Brachygnathia was observed in rat fetuses at a dose 8000 times the MRHDID (on a mcg/m2 basis at a maternal oral dose of 15,000 mcg/kg/day). Pregnancy was prolonged at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Fetal and pup deaths occurred at doses approximately 1500 times the MRHDID and higher (on a

	mcg/m^2 basis at oral doses of 3000 mcg/kg/day and higher) during gestation.
In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis, no (b) (4) or developmental effects were seen at doses up to (b) (4) times the MRHDID (on a mcg/m^2 basis with maternal inhalation doses up to (b) (4) mcg/kg/day).	In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 15, no structural abnormalities, embryocidal effects, or developmental effects were seen at doses up to 350 times the MRHDID (on a mcg/m^2 basis with maternal inhalation doses up to 690 mcg/kg/day).
In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis, subcapsular cysts on the liver were observed in the fetuses at a dose 61,000 times the MRHDID (on a mcg/m2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed at doses up to 3500 times the MRHDID (on a mcg/m2 basis at maternal oral doses up to 3500 mcg/kg/day).	In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to 18, subcapsular cysts on the liver were observed in the fetuses at a dose 61,000 times the MRHDID (on a mcg/m^2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed at doses up to 3500 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 3500 mcg/kg/day).
In a pre- and post-natal development study, pregnant female rats received (b) (4) formoterol (b) (4) through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 110 times the MRHDID and higher (on a mcg/m^2 basis at maternal oral doses of 210 mcg/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.	In a pre- and post-natal development study, pregnant female rats received (b) (4) formoterol at oral doses of 0, 210, 840, and 3400 mcg/kg/day from GD 6 through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 110 times the MRHDID and higher (on a mcg/m^2 basis at maternal oral doses of 210 mcg/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.
Glycopyrrolate	Glycopyrrolate

(b) (4)	In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 17, glycopyrrolate produced no structural abnormalities or effects on fetal survival; however, slight reductions of fetal body weight in the presence of maternal toxicity at the highest tested dose that was 24,000 times the MRHDID (on an AUC basis at a maternal subcutaneous dose of 10,000 mcg/kg/day). Fetal body weights were unaffected with doses up to 1400 times the MRHDID (on an AUC basis with maternal subcutaneous doses up to 1000 mcg/kg/day). Maternal toxicity was observed with doses 1400 times the MRHDID and higher (on an AUC basis with maternal subcutaneous doses of 1000 mcg/kg/day and higher). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation day 6 to 18, glycopyrrolate produced no structural abnormalities or effects on fetal survival; however, slight reductions of fetal body weight in the presence of maternal toxicity at the highest tested dose that was 39,000 times the MRHDID (on an AUC basis at a maternal subcutaneous dose of 10,000 mcg/kg/day). Fetal body weights were unaffected with doses up to 3000 times the MRHDID (on an AUC basis with maternal subcutaneous doses up to 1000 mcg/kg/day). Maternal toxicity was observed with doses 3000 times the MRHDID

	and higher (on an AUC basis with maternal subcutaneous doses of 1000 mcg/kg/day and higher).
In a pre- and post-natal development study, pregnant female rats received (b) (4) through the lactation period. Pup body weight gain (b) (4) was slightly reduced at 2700 times the MRHDID (on a mcg/m2 basis at maternal dose~~s~~ of 10,000 mcg/kg/day) however there were no treatment-related effects on the physical, functional, or behavioral development. (b) (4) ose 270 times the MRHDID (on a mcg/m2 basis at a maternal dose of 1000 mcg/kg/day).	In a pre- and post-natal development study, pregnant female rats received glycopyrrolate at doses of 100, 1000, and 10,000 mcg/kg/day from gestation day 6 through the lactation period. Pup body weight gain was slightly reduced from birth through the lactation period at a dose (b) (4) times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 10,000 mcg/kg/day); however, pup body weight gain was unaffected after weaning. There were no treatment-related effects on the physical, functional, and behavioral development of pups with doses up to (b) (4) times the MRHDID (on a mcg/m^2 basis with maternal subcutaneous doses up to 10,000 mcg/kg/day). Maternal toxicity was observed from gestation days 6 to 18 with doses (b) (4) times the MRHDID and higher (on an AUC basis with maternal subcutaneous doses of 1000 mcg/kg/day and higher).
8.2 Lactation **Risk Summary** There are no available data on the effects of TRADENAME AEROSPHERE, budesonide, glycopyrrolate, or formoterol fumarate on the breastfed child or on milk production. Budesonide, like other inhaled corticosteroids, is present in human milk *[see Data]*. There are no available data on the presence of glycopyrrolate or formoterol fumarate in human milk. Formoterol fumarate and glycopyrrolate have been detected in the plasma of undosed rat pups suckling from exposed dams *[see Data]*. The developmental and health benefits of breastfeeding should be considered along	**8.2 Lactation** **Risk Summary** There are no available data on the effects of TRADENAME AEROSPHERE, budesonide, glycopyrrolate, or formoterol fumarate on the breastfed child or on milk production. Budesonide, like other inhaled corticosteroids, is present in human milk *(see Data)*. There are no available data on the presence of glycopyrrolate or formoterol fumarate in human milk. Formoterol fumarate and glycopyrrolate have been detected in the plasma of undosed rat pups suckling from exposed dams *(see Data)*. The developmental and health benefits of breastfeeding should be considered

with the mother's clinical need for TRADENAME AEROSPHERE and any potential adverse effects on the breast-fed child from TRADENAME AEROSPHERE or from the underlying maternal condition. Data *Human Data* Human data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. For TRADENAME AEROSPHERE, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar. There is no available human data for formoterol or glycopyrrolate. *Animal Data* In the fertility and reproduction study in rats, plasma levels of formoterol were measured in pups on postnatal day 15. 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). In the ~~reproductive/developmental toxicity~~ study in rats, plasma levels of glycopyrrolate were measured in pups on post-natal day 4. The maximum concentration in the pups was 6% of the maternal dose of 10 mg/kg/day (pup plasma concentration of 96 ng/mL at 1	along with the mother's clinical need for TRADENAME AEROSPHERE and any potential adverse effects on the breast-fed child from TRADENAME AEROSPHERE or from the underlying maternal condition. Data *Human Data* Human data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother (b) (4) (b) (4). For TRADENAME AEROSPHERE, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar. There is no available human data for formoterol or glycopyrrolate. *Animal Data* In the fertility and reproduction study in rats, plasma levels of formoterol were measured in pups on postnatal 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). In the (b) (4) study in rats, plasma levels of glycopyrrolate were measured in pups on post-natal day 4. The maximum concentration in the pups was 6% of the maternal dose of 10 mg/kg/day (pup plasma concentration of 96 ng/mL at 1 hour after dosing corresponded with 1610

hour after dosing corresponded with 1610 ng/mL in the dam at 0.5 hours after dosing).	ng/mL in the dam at 0.5 hours after dosing).

Nonclinical Comments **Section 8.1 (Pregnancy) and 8.2 (Lactation)**

Risk Summary changes (Section 8.1):
To comply with the PLLR, additional detail was added to the Risk Summary regarding the relevancy of findings in nonclinical reproductive toxicity studies to a pregnant woman and the fetus as well as additional details of the nonclinical reproductive toxicity studies (e.g., days of drug administration during gestation and/or lactation, results of the pre- and post-natal development study).

The numerical dose (mg/m^2) or exposure (AUC) multiples for findings with budesonide, glycopyrrolate, and formoterol fumarate in nonclinical reproductive toxicology studies with rats and rabbits were reported relative to the MRHDID. Corrections to multiples were made as detailed in the labeling and tables (spreadsheets).

Animal Data (Section 8.1):
Budesonide:
The description of nonclinical reproductive toxicity studies as well as clinical studies with budesonide from the Symbicort label were incorporated into the recommended label.

The numerical values for dose margins were added in cases where previously there was a notation that the nonclinical dose was less than MRHDID.

Formoterol Fumarate:
The description of nonclinical reproductive toxicity studies with formoterol fumarate from the Symbicort label were incorporated into the recommended label.

The numerical values for dose margins were recalculated.

Glycopyrrolate:
The description of the fertility study in rats was moved to Section 13.1.

Descriptions of the Sponsor's nonclinical reproductive toxicity (EFD and PPND) studies with glycopyrrolate, provided in the current submission, were added to the label.

Exposure margins were changed from a mcg/m^2 basis to AUC basis for the EFD studies with glycopyrrolate in rats and rabbits.

Exposure margins were recalculated for the PPND study in rats on an AUC basis using data from the embryofetal development study with rats where comparable doses were used.

Table 3: Proposed Labeling Changes for Section 12.1 Mechanism of Action

Sponsor's Proposed Labeling	**Nonclinical Proposed Labeling**

12.1 Mechanism of Action TRADENAME AEROSPHERE TRADENAME AEROSPHERE contains budesonide, glycopyrrolate, and formoterol fumarate. The mechanism of action described below for the individual components applies to TRADENAME AEROSPHERE. These drugs represent three different classes of medications (b) (4) [redacted] Budesonide Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. Inflammation is an important component in the pathogenesis of COPD. Corticosteroids have a wide range of	**12.1 Mechanism of Action** TRADENAME AEROSPHERE TRADENAME AEROSPHERE contains budesonide, glycopyrrolate, and formoterol fumarate. The mechanisms of action described below for the individual components applies to TRADENAME AEROSPHERE. These drugs represent three different classes of medications (a synthetic corticosteroid, an anticholinergic, and a long-acting selective beta2-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of COPD. Budesonide Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. In vitro studies indicated that the two forms of budesonide do not interconvert. Inflammation is an important component in the pathogenesis of COPD. Corticosteroids have a wide range of

inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non–allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.	inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non–allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.
	(b) (4) 
<u>Glycopyrrolate</u> Glycopyrrolate 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 the 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 vitro as well as in vivo studies, prevention of methylcholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted more than 12 hours. The clinical relevance of these findings is unknown. The bronchodilation	Glycopyrrolate Glycopyrrolate 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 the 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 vitro* as well as *in vivo* studies, prevention of methylcholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted more than 12 hours. The clinical relevance of these findings is unknown. The bronchodilation

following inhalation of glycopyrrolate is predominantly a site-specific effect. Formoterol Fumarate 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- old greater agonist activity at beta2-receptors than at beta1-receptors. The *in vitro* binding selectivity to beta2- over beta1-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta$_2$-selectivity ratio than formoterol. Although beta2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-receptors are the predominant receptors in the heart, there are also beta2-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta2-agonists may have cardiac effects. The pharmacologic effects of beta2-adrenoceptor agonist drugs, including formoterol fumarate, 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	following inhalation of glycopyrrolate is predominantly a site-specific effect. Formoterol Fumarate 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 *in vitro* binding selectivity to beta$_2$- over beta$_1$-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta$_2$-selectivity ratio than formoterol. Although beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$receptors are the predominant receptors in the heart, there are also beta$_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta$_2$-agonists may have cardiac effects. The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including formoterol fumarate, 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

relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.	muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. (b) (4) 

Nonclinical Comments **Section 12.1 Mechanism of Action:**

The labeling from the Symbicort product label was incorporated into the description of "TRADENAME AEROSPHERE" and for the individual drug components, budesonide and formoterol fumarate.

Labeling for Glycopyrrolate was identical that found in Bevespi Aerosphere (NDA 208294)

Table 4: Proposed Labeling Changes for Section 13.1 Nonclinical Toxicology

Sponsor's Proposed Label	**Nonclinical Proposed labeling**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
(b) (4)	No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with TRADENAME AEROSPHERE; however, separate studies of budesonide, glycopyrrolate, and formoterol fumarate are described below.
Budesonide	Budesonide Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide. In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID in adults and children on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equivalent to the MRHDID in adults and children on a mcg/m^2 basis).
(b) (4)	In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately

(b) (4)	equivalent to the MRHDID in adults and children on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID in adults and children on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.
In a 91-week ~~carcinogenicity~~ study in mice, budesonide ~~produced~~ no treatment-related ~~increases in the incidence of tumors~~ at oral doses up to 200 mcg/kg (approximately 2 times the MRHDID on a mcg/m2 basis).	In a 91-week study in mice, budesonide (b) (4) no treatment-related (b) (4) at oral doses up to 200 mcg/kg (approximately 2 times the MRHDID (b) (4) on a mcg/m^2 basis).
Budesonide was not mutagenic or clastogenic in Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster, and DNA repair analysis in rat hepatocyte culture.	Budesonide was not mutagenic or clastogenic in (b) (4) (b) (4): Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.
Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg (approximately equal to the MRHDID on a mcg/m^2 basis).	Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg (approximately equal to the MRHDID on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at

	subcutaneous doses of 20 mcg/kg and above (0.3 times the MRHDID on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (0.08 times the MRHDID on a mcg/m^2 basis).
Glycopyrrolate	Glycopyrrolate Long-term studies were conducted in mice using inhalation administration and rats using oral administration to evaluate the carcinogenic potential of glycopyrrolate.
(b) (4)	In a 24-month inhalation carcinogenicity study in B6C3F1 mice, glycopyrrolate produced no evidence of tumorigenicity when administered to males or females at doses up to 705 and 335 mcg/kg/day, respectively (approximately 95 and 45 times the MRHDID of glycopyrrolate on a mcg/m^2 basis, respectively).
	In a 24-month carcinogenicity study in rats, glycopyrrolate produced no evidence of tumorigenicity when administered to males or females by oral gavage at dosages up to 40,000 mcg/kg/day (approximately 11,000 times the MRHDID of glycopyrrolate on a mcg/m^2 basis).
Glycopyrrolate was not mutagenic in the (b) (4) in vitro mammalian cell micronucleus assay in TK6 cells or (b) (4) in vivo micronucleus assay in rats.	Glycopyrrolate was not mutagenic or clastogenic in the Ames Salmonella/microsome plate test, *in vitro* mammalian cell micronucleus assay in TK6 cells, or *in vivo* micronucleus assay in rats.
(b) (4)	Fertility and reproductive performance indices were unaffected in male and female rats that received glycopyrrolate by the subcutaneous route at doses up to 10,000 µg/kg/day (approximately (b) (4)

	(b) (4) times, respectively, the MRHDID on an AUC basis).
Formoterol Fumarate	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 mice, formoterol fumarate at oral doses of 100 mcg/kg and above (approximately 25 times MRHDID on a mcg/m2 basis) caused a dose-related increase in the incidence of uterine leiomyomas.	In a 24-month carcinogenicity study in CD-1 mice, formoterol fumarate at oral doses of 100 mcg/kg and above (approximately 25 times MRHDID on a mcg/m^2 basis) caused a dose-related increase in the incidence of uterine leiomyomas.
In a 24-month carcinogenicity study in rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 65 times the MRHDID on a mcg/m2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the MRHDID on a mcg/m2 basis).	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 130 mcg/kg (approximately 65 times the MRHDID on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the MRHDID on a mcg/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.	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, or rat micronucleus test.	Formoterol fumarate was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, or rat micronucleus test.

A reduction in fertility and/or reproductive performance (b) (4) in male rats treated with formoterol at oral doses of 15,000 mcg/kg (approximately (b) (4) times the MRHDID on a mcg/m2 basis.) No such effect was seen at 3,000 mcg/kg (approximately ~~1500~~ times the MRHDID on a mcg/m2 basis). No effect on fertility was detected in female rats at doses up to 15,000 mcg/kg (approximately (b) (4) times the MRHDID on a (b) (4) basis).	A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15,000 mcg/kg (approximately (b) (4) times the MRHDID on a AUC basis.) No such effect was seen at 3,000 mcg/kg (approximately (b) (4) times the MRHDID on a mcg/m^2 basis). In a separate study with male rats treated with an oral dose of 15,000 mcg/kg (approximately 8000 times the MRHDID on a mcg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No effect on fertility was detected in female rats at doses up to 15,000 mcg/kg (approximately (b) (4) times the MRHDID on an AUC basis).
(b) (4)	

Nonclinical Comments **Section 13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility:**

Budesonide:
The descriptions of the 2-year carcinogenicity studies with budesonide in rats and mice from the Symbicort product label was incorporated into the label.
For the description of the fertility study, the nominal exposure multiples for budesonide relative to the MRHDID for decrease in prenatal/pub viability and no effect were added.

Glycopyrrolate:
The descriptions of the carcinogenicity studies with glycopyrrolate were changed. (b) (4) The 2-year oral study in rats from the CUVPOSA (NDA 022571) product label was added.

Additional details for the 24-month inhalation study in B6C3F1 mice were added and the exposure multiples were recalculated based on the NOAELs determined following FDA review of the study (See review of carcinogenicity studies).

Additional details for the fertility study in rats were added. Exposure multiples were recalculated from mcg/m^2 to an AUC basis.

Formoterol Fumarate:
The species name (CD-1) for the 24-month carcinogenicity study in mice was added.

For the fertility study in rats, the exposure multiple for effect on reproductive performance in male rats was changed to an AUC basis as described in the Symbicort label; however, it was recalculated using the clinical AUC for formoterol fumarate from the BGF product. The exposure multiple based upon the NOAEL relative to the clinical exposure was adjusted (b) (4) to 1600 due to rounding.

An additional "separate" study from the Symbicort label was added to Section 13.1.

The exposure multiple for the NOAEL in the fertility study with females rats relative to the clinical exposure was changed to an AUC basis.

(b) (4)

Drug: **Formoterol Fumarate- Breztri (BGF pMDI)**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric				0	18	0.0000	25	0.00
Adult	>12	0.0096	2	0.019	60	0.0003	37	0.01

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	oral	0.1	3	0.3	25.34	---	25	---
rat			6	0	---	---	---	---
hamster			4	0	---	---	---	---
rat	inhaled	0.022	6	0.132	11.15	---	10	---
rat	inhaled	0.13	6	0.78	65.88	---	65	---
Reproduction and Fertility:								
mouse			3	0	---	N/A	---	N/A
rat	oral	3	6	18	1520.27	N/A	1500	N/A
rat	oral	15	6	90	7601.35	N/A	7600	N/A
rat			6	0	---	N/A	---	N/A
Teratogenicity:								
mouse			3	0	---	N/A	---	N/A
mouse			3	0	---	N/A	---	N/A
rat	inhalation	0.69	6	4.14	349.66		350	
rat	oral	0.21	6	1.26	106.42		110	
rat	oral	3	6	18	1520.27	N/A	1500	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rabbit	oral	3.5	12	42	3547.30		3500	
rabbit	oral	60	12	720	60810.81		61000	
rabbit			12	0	---	N/A	---	N/A
mouse	udies here)		3	0	---	N/A	---	N/A
Overdosage:								
mouse			3	0	---	---	---	---
mouse			3	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
Other:	(Describe studies here)							
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

Drug: **Glycopyrrolate Breztri (BGF pMDI)**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric				0	18	0.0000	25	0.00
Adult	>12	0.018	2	0.036	60	0.0006	37	0.02

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	inhalation	0.705	3	2.115	95.27	---	95	---
mouse	inhalation	0.335	3	1.005	45.27	---	45	---
rat	oral	40	6	240	10810.81	---	11000	---
hamster			4	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
Reproduction and Fertility:								
mouse			3	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
Teratogenicity:								
mouse			3	0	---	N/A	---	N/A
mouse			3	0	---	N/A	---	N/A
rat			6	0	---		---	
rat			6	0	---		---	
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---		---	
rabbit			12	0	---		---	
rabbit			12	0	---	N/A	---	N/A
mouse	udies here)		3	0	---	N/A	---	N/A
Overdosage:								
mouse			3	0	---	---	---	---
mouse			3	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
Other:	(Describe studies here)							
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

Drug: **Budesonide Breztri (BGF pMDI)**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric				0	18	0.0000	25	0.00
Adult	>12	0.32	2	0.64	60	0.0107	37	0.39

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	oral	0.2	3	0.6	1.52	---	2	---
rat			6	0	---	---	---	---
hamster			4	0	---	---	---	---
rat	oral	0.025	6	0.15	0.38	---	1/3	---
rat	oral	0.05	6	0.3	0.76	---	1/1	---
Reproduction and Fertility:								
mouse			3	0	---	N/A	---	N/A
rat	s.c.	0.02	6	0.12	0.30	N/A	1/3	N/A
rat	s.c.	0.08	6	0.48	1.22	N/A	1	N/A
rat	s.c.	0.005	6	0.03	0.08	N/A	1/13	N/A
Teratogenicity:								
mouse			3	0	---	N/A	---	N/A
mouse			3	0	---	N/A	---	N/A
rat	inhalation	0.25	6	1.5	3.80		4	
rat	s.c.	0.5	6	3	7.60		8	
rat	s.c.	0.025	6	0.15	0.38	N/A	1/3	N/A
rat	s.c.	0.02	6	0.12	0.30	N/A	1/3	N/A
rat			6	0	---	N/A	---	N/A
rabbit	s.c.	0.025	12	0.3	0.76		1/1	
rabbit			12	0	---		---	
rabbit			12	0	---	N/A	---	N/A
mouse	udies here)		3	0	---	N/A	---	N/A
Overdosage:								
mouse			3	0	---	---	---	---
mouse			3	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
Other:	(Describe studies here)							
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

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/s/

IJEOMA K UZOMA
11/06/2019 03:22:57 PM

TIMOTHY W ROBISON
11/06/2019 04:54:54 PM
I concur

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212122
Priority or Standard	Standard
Submit Date(s)	November 30, 2018
Received Date(s)	November 30, 2018
PDUFA Goal Date	September 30, 2019
Division/Office	Division of Pulmonary, Allergy, and Rheumatology Products/ODEII
Review Completion Date	September 30, 2019
Established/Proper Name	Budesonide, glycopyrrolate, and formoterol fumarate
(Proposed) Trade Name	Breztri Aerosphere
Pharmacologic Class	Inhaled corticosteroid, LAMA, LABA combination
Code name	PT010
Applicant	AstraZeneca AB
Dosage form	Inhalation aerosol
Applicant proposed Dosing Regimen	Two inhalations (budesonide 320 µg, glycopyrrolate 18 µg, and formoterol fumarate 9.6 µg) 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	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Linda Ebonine, PA-C
Nonclinical Reviewer	Ijeoma Uzoma, PhD
Nonclinical Team Leader	Timothy Robison, PhD
Office of Clinical Pharmacology Reviewer(s)	Yunzhao Ren, MD, PhD
Office of Clinical Pharmacology Team Leader(s)	Jingyu Yu, PhD, Bhawana Saluja, PhD
Clinical Reviewer	Andrew Clerman, MD, PhD
Clinical Team Leader	Robert Lim, MD
Statistical Reviewer	Mingyu Xi, PhD
Statistical Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Robert Lim, MD
Division Director (DPARP)	Sally Seymour, MD
Office Director (or designated signatory authority)	Sally Seymour, MD

Additional Reviewers of Application

OPQ RBPM	Bamidele (Florence) Aisida
Microbiology	Ramesh Dandu
OPDP	Taylor Burnett
OSI	Jean Mulinde / Min Lu
OSE/DMEPA	Lissa Pringle-Owens / Sarah Vee
OSE/PM	Michael Sinks / Nichelle Rashid
Patient Labeling	Marcia Williams / Sharon Williams

DHOT = Division of Hematology Oncology Toxicology
OCP = Office of Clinical Pharmacology
OB = Office of Bioequivalence
OHOP = Office of Hematology and Oncology Products
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

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ijeoma Uzoma, PhD	OND/ODEII/DPARP	Sections: 5	Select one: _X_ Authored ___ Approved
	Signature: Ijeoma K. Uzoma -S Digitally signed by Ijeoma K. Uzoma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002231243, cn=Ijeoma K. Uzoma -S Date: 2019.09.25 09:06:55 -04'00'			
Nonclinical Supervisor	Timothy W. Robison, PhD, DABT	OND/ODEII/DPARP	Sections: 5	Select one: _X_ Authored _X_ Approved
	Signature: Timothy W. Robison -S Digitally signed by Timothy W. Robison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300110610, cn=Timothy W. Robison -S Date: 2019.09.25 09:18:38 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Yunzhao Ren MD, PhD	OTS/OCP/DCPII	Sections: 6	Select one: _X_ Authored ___ Approved
	Signature: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yunzhao Ren -S, 0.9.2342.19200300.100.1.1=2000971048 Date: 2019.09.25 10:04:49 -04'00'			
Clinical Pharmacology Team Leader	Bhawana Saluja, PhD	OTS/OCP/DCPII	Section: 6	Select one: _X_ Authored ___ Approved
	Signature: Bhawana Saluja -S Digitally signed by Bhawana Saluja -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bhawana Saluja -S, 0.9.2342.19200300.100.1.1=2000559312 Date: 2019.09.25 10:43:33 -04'00'			
Pharmacometrics Reviewer	Yunzhao Ren MD, PhD	OTS/OCP/DCPII	Sections: 6	Select one: _X_ Authored ___ Approved
	Signature: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yunzhao Ren -S, 0.9.2342.19200300.100.1.1=2000971048 Date: 2019.09.25 10:05:33 -04'00'			
Pharmacometrics Team Leader	Jingyu Yu PhD	OTS/OCP/DPM	Section: 6	Select one: _X_ Authored ___ Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2019.09.25 10:35:22 -04'00'			
Clinical Reviewer	Andrew Clerman, MD, PhD	OND/ODEII/DPARP	Sections:1-4, 7-13	Select one: _X_ Authored ___ Approved
	Signature: Andrew M. Clerman -S Digitally signed by Andrew M. Clerman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002363517, cn=Andrew M. Clerman -S Date: 2019.09.26 09:37:58 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Robert Lim, MD	OND/ODEII/DPARP	Sections: All	Select one: ___ Authored _X_ Approved
	Signature: Robert H. Lim -S Digitally signed by Robert H. Lim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Robert H. Lim -S, 0.9.2342.19200300.100.1.1=2000596695 Date: 2019.09 26 10:19:13 -04'00'			
Division Director (Clinical, designated signatory authority)	Sally Seymour, MD	OND/ODEII/DPARP	Sections: All	Select one: ___ Authored _X_ Approved
	Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour -S Date: 2019.09.26 11:19:29 -04'00'			
Statistical Reviewer	Mingyu Xi, PhD	OB/DBII	Sections: 8.1 & 8.3	Select one: __X__ Authored ___ Approved
	Signature: Mingyu Xi -S Digitally signed by Mingyu Xi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mingyu Xi -S, 0.9.2342.19200300.100.1.1=2001034850 Date: 2019.09.26 09:20:31 -04'00'			
Statistical Team Leader	Yongman Kim, PhD	OB/DBII	Sections: 8.1 & 8.3	Select one: ___ Authored __x__ Approved
	Signature: Yongman Kim -S Digitally signed by Yongman Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yongman Kim -S, 0.9.2342.19200300.100.1.1=1300218531 Date: 2019.09.26 09:29:02 -04'00'			

Glossary

AE	adverse event
AESI	adverse event of special interest
API	active pharmaceutical ingredient
AUC	area under the curve
BD	budesonide
BFF	budesonide and formoterol fumarate
BGF	budesonide, glycopyrrolate, and formoterol fumarate
BMD	bone mineral density
BWG	body weight gain
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
DMF	drug master file
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
EFD	embryofetal development
FDC	fixed-dose combination
FF	formoterol fumarate
FEV1	forced expiratory volume in 1 second
GD	gestation day
GFF	glycopyrrolate and formoterol fumarate
GP	glycopyrrolate
HD	high dose
HFA	hydrofluoroalkane
HPA	hypothalamic-pituitary-adrenal
ICS	inhaled corticosteroid
ICF	informed consent form
IND	investigational new drug
ITT	intent to treat
LABA	long-acting β2-adrenergic receptor agonist
LAMA	long-acting muscarinic antagonist
LD	low dose
MACE	major adverse cardiovascular event
MCID	minimal clinically important difference
MDI	metered dose inhaler
MD	mid dose
mITT	modified-intent-to-treat
MRHDID	maximum recommended human daily intranasal dose
NDA	new drug application
NOAEL	no observable adverse effect level

PFT	pulmonary function test
PK	pharmacokinetic
PND	postnatal days
popPK	population pharmacokinetic
PP	per protocol
PPND	pre- and postnatal development
PT	preferred term
SAE	serious adverse event
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SOD	spray orifice diameters
TBH	Turbuhaler
TEAE	treatment emergent adverse event
TK	toxicokinetic
URTI	upper respiratory tract infection

1. Executive Summary

1.1. Product Introduction

The Applicant, AstraZeneca (AZ), submitted a 505(b)(2) New Drug Application (NDA) for the fixed-dose combination (FDC) of budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol (BGF) for the (b) (4), maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4) BGF is an FDC of the inhaled corticosteroid (ICS) budesonide, the long-acting muscarinic antagonist (LAMA) glycopyrrolate, and the long-acting β2-adrenergic receptor agonist (LABA) formoterol fumarate delivered by a pressurized metered dose inhaler (MDI).

BGF is to be administered as two inhalations twice daily. Each inhalation contains budesonide 160 µg, glycopyrrolate (glycopyrronium bromide) 9 µg, and formoterol fumarate 4.8 µg for a total dose of 320, 18, and 9.6 µg of each component, respectively, twice daily. The FDC of glycopyrrolate and formoterol fumarate (GFF) is approved in the United States under the tradename Bevespi Aerosphere at the same dose for the glycopyrrolate and formoterol fumarate components using the same delivery device. The FDC of budesonide and formoterol fumarate (BFF) is not approved, nor are the mono-components, budesonide (BD), glycopyrrolate (GP), and formoterol fumarate (FF) in this delivery device. However, they are approved alone and in combination in other delivery devices for inhalation.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Complete Response for BGF for the indication of the (b) (4)(b) (4), maintenance treatment of (b) (4) patients with COPD (b) (4)

To support the application for BGF, the Applicant submitted results from a single phase 3, 24-week, active-controlled trial (PT010006, referred to as Trial 06) as the primary evidence of efficacy in terms of bronchodilation and exacerbation reduction. Trial 06 was designed to show the added benefit of the triple-combination (BGF) over the two double combinations (BFF and GFF). As supportive evidence, two phase 3 trials of unapproved BFF were submitted [24-week trial PT009002 (Trial 02) and a 12-week lung function trial, PT009003 (Trial 03)], as BFF is not currently approved.

BGF Trial 06 did not demonstrate evidence of efficacy for bronchodilation based on the results of the co-primary endpoint. Compared to GFF, the approved LAMA/LABA combination, BGF did not show a statistically significant improvement in the co-primary endpoint of morning pre-dose trough forced expiratory volume in 1 second (FEV1) at Week 24 (Table 62). As such, there was no demonstration that BD contributed to the bronchodilatory effect of BGF. For the other co-primary endpoint of Trial 06, BGF did show a statistically significant improvement in FEV1

area under the curve from 0 to 4 hours (AUC_{0-4}) at Week 24 compared to BFF (Table 63), showing the contribution of GP to BGF. Because of the failure to achieve statistical significance for both components of the co-primary endpoint, all secondary endpoints are considered not statistically significant, including exacerbation rate and St. George's Respiratory Questionnaire (SGRQ). As such, results from the secondary endpoints could not be used to support efficacy or the contribution of BD to BGF. Therefore, Trial 06 is insufficient to support the efficacy of BGF in terms of bronchodilation, exacerbation, and contribution of the BD component to the combination. Furthermore, there is no replicate evidence of efficacy as the Applicant submitted only one phase 3 trial for BGF.

The BFF program (Trial 02 and Trial 03) did demonstrate effectiveness in lung function and exacerbation. In the 24-week lung function trial, Trial 02, a statistically significant improvement was shown in both co-primary endpoints, which included change from baseline in morning pre-dose trough FEV1 at Week 24 for the BFF 320/9.6 µg versus FF comparison and change from baseline in FEV1 AUC_{0-4} at Week 24 for the BFF 320/9.6 µg versus BD comparison. In Trial 03, the BFF 12-week lung function trial, a statistically significant improvement in primary endpoint of change from baseline in morning pre-dose trough FEV1 at Week 12 was shown for BFF 320/9.6 µg compared to FF. In both trials, statistically significant improvements in time to first exacerbation were shown for BFF 320/9.6 µg compared to FF. The results of the BFF program demonstrate the contribution of BD and FF to the BFF combination and support the use of BFF as a comparator in the BGF program. Results for the BFF trials support the efficacy of BFF 320/9.6 and its use as an active comparator in the BGF program.

Overall, the Applicant's application for BGF was dependent on a single trial for efficacy (Trial 06) and this trial failed to show a statistically significant improvement in morning pre-dose trough FEV1 and exacerbation rate and did not demonstrate a contribution of the BD to BGF. Though there was evidence for efficacy from the BFF program for BFF, substantial evidence of effectiveness has not been established for BGF in this application.

To address this deficiency and to meet the level of substantial evidence of effectiveness for BGF, the Applicant should submit additional clinical data from at least one trial supporting the efficacy of BGF and the contribution of the BD component to the combination.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Chronic obstructive pulmonary disease (COPD) is a debilitating respiratory condition that has significant morbidity and mortality; it is the third leading cause of death in the US. Substantial healthcare resources are utilized in managing long-term COPD and in treating acute exacerbations. It is often associated with active or prior cigarette smoking (typically >10 pack-years), but other environmental and genetic factors have been found to contribute to its etiology. Multiple long-acting muscarinic antagonist (LAMA)/long-acting β2-adrenergic receptor agonist (LABA) fixed-dose combination (FDC) inhalers exist, and this product potentially provides another alternative treatment for patients with COPD.

The Applicant submitted a new drug application (NDA) for Breztri Aerosphere [budesonide, glycopyrrolate, and formoterol fumarate (BGF) 320/18/9.6 µg inhalation aerosol), a fixed-dose combination LAMA/LABA/inhaled corticosteroid (ICS), for the (b) (4) (b) (4), maintenance treatment of (b) (4) patients with COPD (b) (4) To support this application, a single 24-week trial comparing BGF to its LAMA/LABA and ICS/LABA components was conducted with a safety extension to 52-weeks in a subset of patients. Based upon review of this trial and the supporting evidence, Complete Response is the recommended action due to lack of substantial evidence of effectiveness.

The 24-week trial (Trial 06) failed on one of its co-primary endpoints; BGF did not show a statistically or clinically significant improvement in pre-dose trough forced expiratory volume in 1 second (FEV1) at Week 24 compared to the LAMA/LABA combination glycopyrrolate/formoterol fumarate (GFF). Therefore, there was no demonstration of the contribution of the budesonide (BD) component to the BGF combination. For the other co-primary endpoint, BGF did show a statistically significant improvement in FEV1 area under the curve from 0 to 4 hours (AUC_{0-4}) at Week 24 compared to the ICA/LABA combination, BD/formoterol fumarate (BFF), demonstrating the contribution of glycopyrrolate (GP) to BGF. Because statistical significance was not achieved in the co-primary endpoint, all secondary endpoints were considered non-statistically significant due to hierarchical test procedures, including exacerbation rate. As such, results from the secondary endpoints could not be used to support efficacy or the contribution of BD to BGF. Therefore, Trial 06 is insufficient to support the efficacy of BGF in terms of bronchodilation, exacerbation, and contribution of the components to the combination. Safety findings for BGF were consistent with other products in this class.

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 is a common debilitating respiratory condition causing significant morbidity and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 <0.7 is used for diagnosis of COPD in the 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.	mortality. The diagnostic and symptom assessment instruments used by the Applicant are reasonable to assess COPD.
Current Treatment Options	Several classes of inhaled medications exist for the long-term maintenance treatment of COPD: Anticholinergics, LABA, and ICS (ICS is only available in combination products).	Multiple inhaled medications including LAMA/LABA/ICS fixed-dose combination inhalers exist, and this product provides another alternative treatment for patients with COPD.
Benefit	The Applicant has not demonstrated substantial evidence of efficacy for BGF in COPD patients based on submission of only a single trial that failed in its co-primary endpoint of pre-dose trough FEV1 of BGF compared to GFF. BGF also did not show a statistically significant improvement in exacerbation rate against any active comparator due to hierarchical test procedures.	There is insufficient evidence to conclude that BGF is effective in terms of bronchodilation or exacerbation or that the BD component contributes to BGF. BGF does not provide a statistically significant improvement in pre-dose trough FEV1 compared to GFF. BGF also did not show a statistically significant benefit in exacerbation rate compared to GFF. Overall, BGF was not shown to be superior to the approved product GFF, and the contribution of the ICS component to the combination was not demonstrated.
Risk and Risk Management	The safety program for BGF demonstrated no new concerning safety signals compared to the BFF and GFF treatment arms. REMS is not applicable given a Complete Response action.	The safety profile was similar to other medications in its class.

1.4. Patient Experience Data

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

☑	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☑	Clinical outcome assessment (COA) data, such as		
		☑	Patient reported outcome (PRO)	Section 8.1 (SGRQ)
		□	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

Chronic obstructive pulmonary disease is a common respiratory condition that results in significant morbidity and mortality; it is the third leading cause of death in the United States. Given its high prevalence and disease burden, maintenance therapy requirements and management of acute exacerbations result in a significant societal and economic burden. Cigarette smoking is most often associated with the disease, but it is increasingly understood that alternative noxious exposures, as well as a variety of host-specific factors, contribute to COPD pathogenesis.

Chronic obstructive pulmonary disease is characterized by persistent respiratory symptoms and airflow limitation. Chronic inflammation resulting from inhaled irritants causes structural changes, small airways narrowing, mucociliary dysfunction, and destruction of lung parenchyma. Common symptoms include dyspnea, fatigue, and cough, which often impact a patient's quality of life and ability to perform activities of daily living. Physical exam findings include wheezing, prolonged expiration, diminished breath sounds, and increased chest diameter. Spirometry is used to diagnose COPD. A FEV1/FVC ratio below 0.7 establishes the diagnosis, and percent of predicted FEV1 determines the severity of airflow obstruction. COPD exacerbation history and dyspnea scoring provide an additional layer of formal disease assessment. [1] Other diagnostic considerations are increases in lung volume measurements, decreased diffusing capacity, decreased pulse oximetry, and evidence of chronic hypercapnia. Radiographic studies may reveal changes such as vascular tapering, radiolucency, flattened diaphragms, bullous disease, emphysema, thickened airways, and prominent hilar vascularity.

In conclusion, COPD is a serious disease with societal and individual impacts. It is a leading cause of death globally, and its increasing prevalence and associated morbidity result in utilization of healthcare resources and loss of productivity. It also has significant impact on afflicted individuals, leading to reduced quality of life and difficulty performing regular activities. 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 the table below.

[1] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 at http://goldcopd.org

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
		Aclidinium bromide	Tudorza Pressair	2012
		Umeclidinium bromide	Incruse Ellipta	2014
		Glycopyrrolate	Seebri Neohaler	2015
			Lonhala Magnair	2017
		Revefenacin	Yupelri	2018
	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
		Aclidinium/formoterol	Duaklir Pressair	2019
	LAMA/LABA/ICS	Fluticasone/Umeclidinium/ Vilanterol	Trelegy	2017
Xanthines		Theophylline	Multiple	1992
Phosphodiesterase inhibitors	PDE4 Inhibitors	Roflumilast	Daliresp	2011

Abbreviations: LABA = long-acting β2-adrenergic receptor agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; SABA = short-acting beta agonist; HFA = hydrofluoroalkane; PDE = Phosphodiesterase; COPD = chronic obstructive pulmonary disease
*General bronchodilator claim, not specifically indicated for COPD
** No longer marketed

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BGF is not marketed or approved in the United States. GFF, which contains the same LAMA/LABA at the same dose and delivery platform as BGF, was approved on April 25, 2016 under NDA 208294 with the tradename Bevespi Aerosphere. GFF is approved for the (b) (4) (b) (4), maintenance treatment of airflow obstruction in patients with COPD, and it does not carry an exacerbation indication. Under this delivery platform, BFF, which contains the same ICS/LABA at the same dose as BGF, is not approved, nor are the mono-components BD and FF. However, these drug combinations have been approved for COPD in other delivery devices. This includes Symbicort (budesonide/formoterol fumarate), Foradil Aerolizer (formoterol fumarate, no longer marketed), Perforomist (formoterol), Seebri Neohaler (glycopyrrolate), and Lonhala Neohaler (glycopyrrolate). Additionally, Pulmicort (budesonide) is approved for asthma but not COPD.

3.2. Summary of Presubmission/Submission Regulatory Activity

BGF was studied under investigational new drug (IND) 118313, opened on October 11, 2013. Relevant regulatory interactions are summarized below:

<u>Pre-IND Meeting on July 17, 2013</u>

(b) (4)

<u>Written Responses on April 11, 2014</u>

- Advised that a single trial may be adequate for approval of the triple combination if both dual combination products demonstrate an added benefit in lung function over their respective mono-products and the trial demonstrates robust, clinically meaningful efficacy for reduction in exacerbation or other relevant endpoints such as mortality

Written Responses on May 18, 2015

- Advised that moderate and severe exacerbations are the events of clinical significance to regulatory decision-making
- All exacerbations should also be reported as AEs

Teleconference on September 9, 2016

- The FDA advised that developing fixed-dose triple-combination products based solely on a lung function claim will ultimately be a review issue

EOP2 meeting on November 7, 2016

- The FDA agreed with the dose of BD and FF selected for the Phase 3 program
- The Applicant agreed to proceed to Phase 3 with the GP dose that was approved for COPD at the time.

Pre-NDA Meeting on March 31, 2017

- The FDA agreed with the Applicant's proposal to include full study reports and data for both BFF and BGF (b) (4)
- The FDA advised that if the BFF development program demonstrates an exacerbation benefit, then a lung function benefit for the BGF product may be a viable path to registration but would be a review issue
- The FDA did not agree with the 'efficacy' estimand as the primary estimand and recommend that the primary analyses should target the 'treatment policy' estimand

BFF was studied under IND (b) (4), opened on July 18, 2014. Relevant regulatory interactions are summarized below:

EOP2 Meeting on October 15, 2015

- The proposed budesonide doses of 320 and 160 µg were considered acceptable by FDA
- The FDA recommended removal of the placebo group in study PT009002

(b) (4)

Teleconference on September 9, 2016

- The FDA agreed with an alternative development plan in which the BFF program would only pursue a lung function indication in order to qualify as the appropriate ICS/LABA comparator in the BGF program
- The FDA stated that development of a fixed-dose triple-combination products solely on a lung function claim was a review issue

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

4.1. Office of Scientific Investigations

An Office of Scientific Investigation consult evaluated three trial sites from the phase 3 program based upon participation in multiple studies, high enrollment, efficacy outcome, and safety. The sites chosen for inspection are shown in Table 2. No evidence of analysis-altering misconduct was identified at these sites.

Table 2. OSI Inspection Sites

Principal Investigator	Fakih, Faisal	Pearle, James	Spangenthal, Selwyn
Address	1788 W. Fairbanks Avenue, Suite B Winter Park, FL 32789	301 W Bastanchury Rd, Suite 220 Fullerton, CA 92835	1918 Randolph Road, Suite 440 Charlotte, NC 28207
Protocol Site # Number of subjects	PT010006 #6014 N=23	PT010006 #6057 N=46	PT010006 #6068 N=14
	PT009002 #2016 N=30	PT009003 #3052 N=17	PT009002 #2086 N=22
	PT009003 #3104 N=20		

Abbreviations: OSI = Office of Scientific Investigations
Source: Clinical Reviewer

4.2. Product Quality

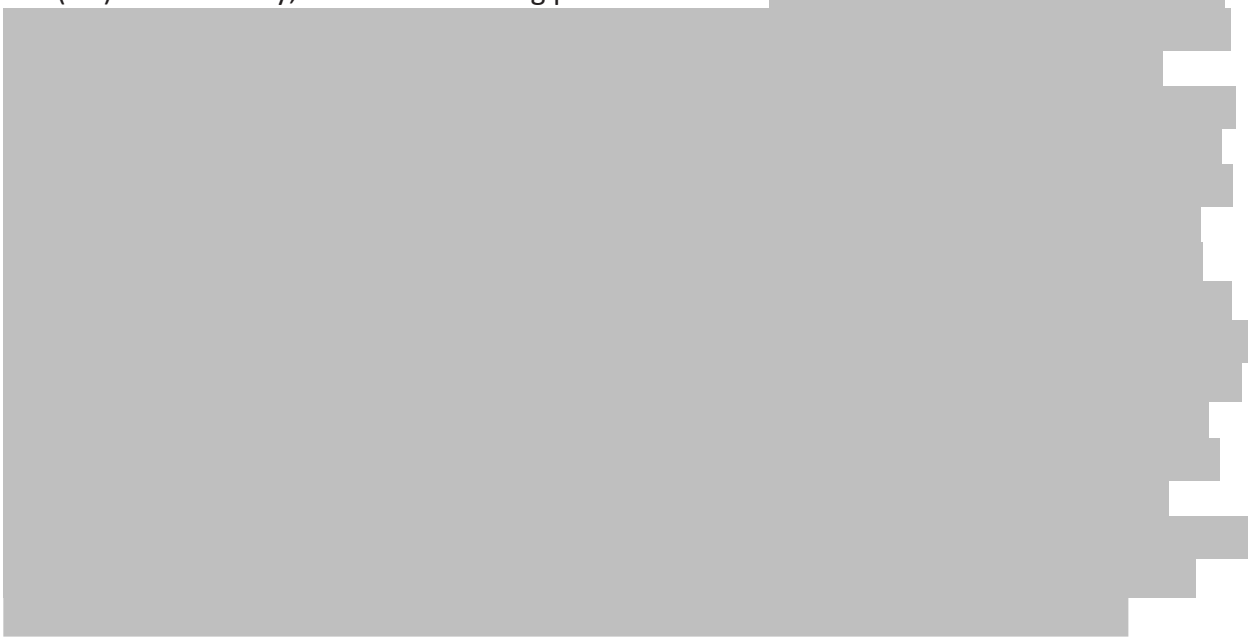
The application is recommended for Approval from the CMC/quality perspective.

The triple fixed-combination (21 Code of Federal Regulations) CFR 300.50) and combination product [21 CFR 3.2(e)] from AZ inhalation aerosol is formulated as a suspension of BD, GP, and FF, none of which are new molecular entities. The Applicant provides most of the information for BD, GP, and FF via references to supplier drug master files (DMFs). Note that the Applicant amended the application on August 15, 2019, to include the specification they apply when accepting FF from their supplier, as this was erroneously missing from the original application. Whereas the information supporting the FF and GP are now equivalent to what was approved for the Applicant's previously approved double combination Bevespi Aerosphere of NDA 208294 [both applications reference the same DMFs for these active pharmaceutical ingredients (APIs)], this triple combination inhalation aerosol adds BD, which is provided by two sources with 3 manufacturing sites (note that both GP and FF each have single sources). The drug substance review team confirms that BD from both sources have comparable quality and are adequate for use in formulating the drug product. A retest period of (b) (4) for the BD

is currently proposed and supported by stability data, however the Applicant will continue the stability studies to potentially extend this period to (b) (4).

The application has provided the results of multiple product development studies to demonstrate chemical and physical stability, and robustness of Breztri Aerosphere, and have provided information to support labeling statements and patient instructions for use. The Applicant has provided 24 months of long-term, 12 months intermediate, and 6 months of accelerated stability data for three primary stability batches each of 120 and 28 actuations configuration, along with the supportive in-use and leachables stability data. The primary stability batches of the 120-actuation configuration were also used in the Phase III clinical trials. Overall, the stability data submitted by the Applicant supports the proposed shelf-life of 24 months for all product configurations. The Applicant has adequately demonstrated *in vitro* comparability of the proposed triple API combination product with the respective dual-therapy products used in the clinical studies (GFF and BFF). Phase 3 clinical studies were conducted using drug product with actuator spray orifice diameters (SODs) centered in the range of (b) (4) (b) (4). However, afterwards, the Applicant narrowed the SOD acceptance criterion to a range of (b) (4). The narrower range results in a lower propensity for drug/excipient deposition in the orifice, which can lead to drug product performance issues if patients fail to follow the instructions for weekly cleaning. The Applicant has adequately bridged the change in the SOD acceptance criterion with *in vitro* performance data. During the review cycle, three information requests were sent to the Applicant, mainly for stability data summaries, specification justification, and for modification of the proposed comparability protocols. The Applicant responded adequately, and all drug product-related issues are resolved.

The manufacturing process for the triple combination inhalation aerosol is analogous to what was approved for Bevespi Aerosphere under NDA 208294, with the exception of the additional API (BD). In summary, the manufacturing process involves (b) (4)



(b) (4)

There are twelve manufacturing/testing sites supporting the application. No pre-approval inspections were considered necessary and all sites are found to be acceptable based on previous compliance histories.

4.3. Clinical Microbiology

None

4.4. Devices and Companion Diagnostic Issues

None.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Introduction

The Applicant has submitted a marketing application for the inhaled triple-combination product composed of glycopyrrolate (G), budesonide (B), and formoterol fumarate (F or FF) as a treatment for COPD. The Applicant currently markets the combination of glycopyrrolate and formoterol under the tradename of Bevespi Aerosphere™ (NDA 208294) as a treatment for COPD. The inhaled triple-combination product represents the addition of budesonide to the approved combination of glycopyrrolate and formoterol. The Applicant also markets the combination of formoterol and budesonide under the tradename of Symbicort (NDA 21929) for the treatment of asthma and COPD.

During the IND development phase for the inhaled triple-combination products, the Applicant was requested to conduct only one nonclinical study, a 90-day inhalation toxicology study in dogs with the combination of BGF.

The Applicant has complete nonclinical programs for formoterol and budesonide, which were reviewed under the NDA 21929 for Symbicort (Budesonide and Formoterol Fumarate) and NDA 20929 for Pulmicort Respules (Budesonide).

In an attempt to support a 505(b)(1) application for the inhaled triple combination, the Applicant provided a complete nonclinical program for glycopyrrolate. In the current

application, the Applicant provided a 90-day inhalation toxicology study with BGF in dogs, complete reproductive toxicity studies with glycopyrrolate, and 2-year inhalation carcinogenicity studies with glycopyrrolate in Sprague-Dawley rats and B6C3F1 mice. The Applicant had previously submitted 6-month inhalation toxicology studies with glycopyrrolate in rats and dogs, a 90-day inhalation toxicology study in dogs with the combination of glycopyrrolate and formoterol, and a complete battery of genetic toxicity studies with glycopyrrolate that were reviewed under NDA 208294 for Bevespi Aerosphere. The Applicant never conducted their own pharmacology studies with glycopyrrolate, but rather relied on the published literature. It is noted that NDA 208294 for Bevespi Aerosphere used the 505(b)(2) pathway, which relied on reproductive toxicity studies conducted with glycopyrrolate that are described in the label for the reference listed drug, ROBINUL Injection (NDA 17558) as well as published literature for the pharmacology of glycopyrrolate.

This review evaluated the reproductive toxicity studies and 2-year inhalation carcinogenicity studies in rats and mouse with glycopyrrolate. As described below, the Applicant's 505(b)(1) approach was determined to not be viable given that 2-year inhalation carcinogenicity study in rats was considered invalid. As a path forward to avoid repeating the 2-year carcinogenicity study with rats, the Applicant administratively changed the application to the 505(b)(2) pathway in order to rely on the Agency's previous findings of safety for glycopyrrolate with the reference listed drug, ROBINUL Injection (NDA 17558) and published literature on the pharmacology of glycopyrrolate. NDA 212122 is recommended for approval from the nonclinical perspective. There are no outstanding nonclinical issues.

Discussion of Nonclinical Findings

Established pharmacological classifications for glycopyrrolate, budesonide, and formoterol fumarate are anticholinergic, corticosteroid, and long-acting beta2-adrenergic agonist, respectively.

In the 90-day BGF-triple combination and BFF-dual combination inhalation toxicology study, beagle dogs were dosed via face mask inhalation daily for 90 days to assess potential toxicological interactions between the three drugs. Females receiving higher doses of G or FF were observed with increased heart rate; however, the addition of G to FF (i.e., BGF) did not result in any further increases of heart rate observed with either agent alone. The most notable histopathology findings were cortical atrophy in the adrenal gland, lymphocyte decrease in the tracheobronchial lymph nodes, and hepatocellular alteration in the liver. The observed histopathological findings were generally consistent with known corticosteroid class effects of budesonide with the exception of the findings in the liver that could be attributed to class effects for β-adrenergic agonists. There was no evidence of additive or synergistic toxic effects when adding budesonide to the approved combination of glycopyrrolate and formoterol (i.e., Bevespi Aerosphere).

In a 2-year inhalation carcinogenicity study in mice, treatment with glycopyrrolate had no effects on survival of male or female mice up to 104 weeks. Excessive decreases of body weight

gain (BWG) were evident for high-dose (HD) males and mid- and HD females that led to the exclusion of these groups from the assessment of drug-induced carcinogenicity. The Executive Carcinogenicity Assessment Committee (ECAC) determined that there were no statistically significant test article-related tumor findings in male mice from the low- and mid-dose groups and female mice in the low-dose (LD) group.

The 2-year inhalation carcinogenicity study with Sprague Dawley rats was judged to be inadequate by the ECAC due premature termination of all male and female control and drug-treated groups at 82-weeks. The label will report a description of the 2-year carcinogenicity study with glycopyrrolate administered by oral gavage to rats that described in the label for the referenced listed drug, CUVPOSA®.

In a fertility and early embryonic development study, glycopyrrolate at subcutaneous doses up to 10 mg/kg/day did not affect fertility or reproductive performance (mating and fertility indices) in male or female rats. The no observable adverse effect level (NOAEL) for male and female mating and fertility was the HD (10 mg/kg/day).

In an embryofetal development (EFD) study in rabbits, treatment with glycopyrrolate by the subcutaneous route caused reduced fetal body weights in the HD group (10 mg/kg/day), attributable to maternal toxicity. Glycopyrrolate did not cause any structural abnormalities and did not affect fetal survival at maternal doses up to 10 mg/kg/day. The NOAEL for EFD toxicity was the mid-dose (1 mg/kg/day).

In an EFD study in rats, treatment with glycopyrrolate by the subcutaneous route caused reduced fetal body weights in fetuses in the HD group (10 mg/kg/day), attributable to maternal toxicity. Glycopyrrolate did not cause any structural abnormalities and did not affect fetal survival at maternal doses up to 10 mg/kg/day. The NOAEL for EFD toxicity was the mid-dose (1 mg/kg/day).

In a rat pre- and postnatal development (PPND) study, mated female rats (F0 generation) were treated by the subcutaneous route with glycopyrrolate at doses up to 10 mg/kg/day. Absolute body weights of F1 pups in the HD group from birth throughout the lactation period were approximately 10% lower relative to the control group but were comparable between control and drug-treated groups from postnatal days (PND) 28 to 70. There were no effects on physical or neurological development in F1 generation pups. Development of F2 pups from PND 0 to 21 was unaffected by drug treatment of F0 dams. The NOAEL for F1 pup development was the HD (10 mg/kg/day).

Nonclinical programs for budesonide and formoterol fumarate, owned by the Applicant, include pharmacology, ADME, general toxicology, genetic toxicity, carcinogenicity, and reproductive toxicity studies.

5.2. Referenced NDAs, BLAs, DMFs

NDA 208294: Bevespi Aerosphere™ (formoterol fumarate/glycopyrrolate)

NDA 21929: Symbicort® MDI (budesonide/formoterol) Inhalation Aerosol

IND 118313: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI)

IND 101,985: Glycopyrrolate Inhalation Aerosol (GP MDI) as a monoproduct

IND 105,586: Formoterol Fumarate Inhalation Aerosol (FF MDI) as a monoproduct

IND 107,739: Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol (GFF MDI) as a dual combination product

(b) (4)

5.3. Drug Formulation

BGF MDI 160 product is 160 µg budesonide, 7.2 µg glycopyrronium, and 4.8 µg formoterol fumarate per actuation. One dose is two actuations from the MDI. It is noted that 7.2 µg of glycopyrronium is equivalent to 9.0 µg glycopyrronium bromide or glycopyrrolate (quaternary ammonium bromide salt form of the drug substance). Throughout the review, the drug substance will be referred to as glycopyrrolate and concentrations of the drug substance also reflect the glycopyrrolate form. The MDI is manufactured at 120, (b) (4) and 28 inhalations. The quantity of the drug substances varies based on the number of inhalations per MDI, but the metered and delivered dose per actuation are identical across all MDIs.

Table 3. Composition of BGF MDI 120/ (b) (4) 28 Inhalations, 160/9/4.8 µg Per Actuation

Component	Quantity Per Canister (120/ (b) (4) 28 Inhalations)[a]	Metered Dose (Ex-Valve)	Delivered Dose (Ex-Actuator)	Function	Reference to Standard
Budesonide, micronised	(b) (4)	(b) (4)	160 µg	Active ingredient	USP / AstraZeneca
Glycopyrrolate, micronised			9 µg[b]	Active ingredient	USP / AstraZeneca
Formoterol fumarate, micronised			4.8 µg	Active ingredient	USP / AstraZeneca
Porous particles			(b) (4)		
HFA-134a					

Abbreviations: MDI = metered dose inhaler; BGF = budesonide/glycopyrrolate/formoterol fumarate; USP = United States Pharmacopeia; HFA = hydrofluoroa kane

(b) (4)

5.4. Excipients

This product contains no novel excipients. BGF contains HFA-134a as the propellant and porous particles as an excipient. Both materials are present in approved and currently marketed products including Bevespi Aerosphere (NDA 208294). Porous particles are comprised of (b) (4) . The Applicant has rights of reference to DMF (b) (4) from (b) (4) for safety data with HFA-134a.

5.5. Impurities

There are no impurities or degradants of concern.

5.6. Pharmacology

The Applicant did not conduct any pharmacology studies with glycopyrrolate, but rather relied on the published literature. The Applicant conducted pharmacology studies with formoterol fumarate under NDA 21929 for Symbicort and budesonide under NDA 20929 for Pulmicort Respules. The mechanisms of action for glycopyrrolate, formoterol fumarate, and budesonide (described in Section 12.1 of the labels for Bevespi Aerosphere and Symbicort) are listed below:

BREZTRI AEROSPHERE contains glycopyrrolate, formoterol fumarate, and budesonide. The mechanism of action described below for the individual components apply to BREZTRI AEROSPHERE. These drugs represent three different classes of medications (a long-acting muscarinic antagonist, a long-acting selective beta$_2$-adrenoceptor agonist, and a corticosteroid) that have different effects on clinical and physiological indices.

Glycopyrrolate 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 the 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 vitro as well as in vivo studies, prevention of methylcholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted more than 12 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of glycopyrrolate is predominantly a site-specific effect.

Formoterol fumarate is a long-acting selective beta2-adrenergic agonist (beta2-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 beta2-receptors than at beta1receptors. The in vitro binding selectivity to beta2-over beta1-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta2-selectivity ratio than formoterol.

Although beta2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1receptors are the predominant receptors in the heart, there are also beta2-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta2-agonists may have cardiac effects.

The pharmacologic effects of beta2-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 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.

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. In vitro studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of COPD. Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non–allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in COPD and asthma.

(b) (4)

5.7. ADME/PK

The Applicant conducted limited ADME studies with glycopyrrolate. The Applicant conducted ADME studies with formoterol fumarate under NDA 21929 for Symbicort and with budesonide under NDA 20929 for Pulmicort Respules.

5.8. Toxicology

5.8.1. General Toxicology

Study Title: Budesonide: Glycopyrronium: Formoterol Fumarate: pMDI and Budesonide: Formoterol Fumarate pMDI: 90-Day Face Mask Inhalation Exposure Study in Male and Female Beagle Dogs	
Study no.:	FY14-148A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 26, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Glycopyrrolate, lot# 9-ABY-76-1, chemical purity 98%, Formoterol D6, lot# 5-CGJ-61-1, purity 96% Budesonide D8, lot# 7-JWA-141-2, chemical purity 98%,

Test Article 1 Budesonide, glycopyrronium, formoterol fumarate pMDI (BGF)
184.97 µg budesonide, 8.32 µg glycopyrronium, and 5.5 µg formoterol fumarate ex valve, pressurized metered dose inhaler; (7.2 µg glycopyrronium =9.0 µg glycopyrrolate)
Lot: 4H033A10

Test Article 2 Budesonide, formoterol fumarate pMDI (BFF)
184.97 µg budesonide and 5.5 µg formoterol fumarate ex valve, pressurized metered dose inhaler
Lot: 4H032A09

Placebo Calcium Chloride Dihydrate (CaCl2) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC)
Lot: 3H046A

Key Study Findings

Beagle dogs (4/sex/group) were dosed with budesonide (B), glycopyrrolate (GP), and formoterol fumarate (FF) as a triple combination (BGF) and budesonide and formoterol fumarate (BFF) as a double combination at low, mid, or high doses, via face mask inhalation daily for 90 days. Doses are listed below:

- Budesonide low, mid, and high doses were 3.02-3.35, 13.48-17.55, and 58.39-71.34 µg/kg/day, respectively
- Glycopyrrolate low, mid, and high doses were 0.20-0.21, 1.06-1.11, and 3.39-3.56 µg/kg/day, respectively
- Formoterol low, mid, and high doses were 0.10-0.11, 0.47-0.63, 1.94-2.4 µg/kg/day, respectively.

All animals survived to scheduled euthanasia on Day 91.

Increased GGT activities were noted in mid dose (MD) (38.5%) and HD (115%) BGF males and HD (284.6%) BFF males, relative to the vehicle control groups. In females, increased GGT activities were noted in MD (92.3%) and HD (130.8%) BGF groups, and in the HD (361.5%) BFF group. Elevations of GGT activity may correlate to histopathological finding in the liver of hepatocyte alteration.

Heart rates were increased for BGF HD and BFF HD females on Day 1 relative to air-control and vehicle-control groups. The addition of glycopyrrolate (BGF) did not result in any further enhancement of the increased heart rate observed with formoterol (BFF).

Treatment related gross pathology findings were noted in the thymus. Red discoloration in the thymus was noted at all doses in BFF treated males, in MD and HD BFF treated females, and HD BGF treated females. These findings correlated with histopathological findings of hemorrhage and decreased lymphocytes.

Reduced organ weights were noted in the adrenal gland at all doses in BGF and BFF treated males and females, which correlated with histopathology findings of cortical atrophy. Increased liver weights were noted in HD BFF males and females. Increased liver weights were noted in MD and HD BGF treated females. Increased liver weights correlated with histopathological findings of hepatocellular alteration. Decreased thymus weights were noted in MD and HD BGF and BFF treated males. Decreased thymus weights were noted at all doses in BGF and BFF treated females at higher magnitudes than in males. Decreased thymus weights correlated with histopathological findings of hemorrhage and decreased lymphocytes.

Treatment related microscopic findings were noted in the adrenal glands, lymph nodes, liver, and thymus. Findings in the adrenal glands, lymph nodes, and thymus could be attributed to effects of budesonide. Findings in the liver could be attributed to effects of formoterol fumarate.

Cortical atrophy was observed in the adrenal glands in males and females in the BGF and BFF treatment groups.

Decreased lymphocytes in the tracheobronchial LN were observed in MD and HD BGF males and HD BFF males.

Hepatocellular alteration in the liver was observed at all doses in BGF males, at the MD and HD in BFF males, and at all doses in BGF and BFF treated females. These findings in the liver were accompanied by increases of GGT activity. Hemorrhage was noted at all doses in BFF treated males, at the MD and HD in BFF treated females, and at the HD in BGF treated females. Decreased lymphocytes were observed in all doses in BFF and BGF treated males, at the MD and HD in BGF-treated females, and at all doses in BFF treated females.
The observed histopathological findings were generally consistent with known corticosteroid class effects of budesonide with the exception of the findings in the liver that could be attributed to formoterol fumarate. There was no evidence of additive or synergistic toxic effects when adding glycopyrrolate to the approved combination of budesonide and formoterol.

It was not possible to discern if there were any toxicokinetic (TK) interactions on the basis of how the study was designed.

Table 4. Toxicology Study Parameters, Study No. F14-148A

Methods	Details
Doses:	Respective doses of Budesonide (B), Formoterol fumarate (F or FF), and Glycopyrrolate (G) in the LD, MD, HD groups for the BGF and BFF combination products in µg/kg/day (See **Table 5**) Budesonide (BGF): LD (M/F): 3.16/3.35 MD (M/F):16.73/17.55 HD (M/F): 58.39/61.37 Budesonide (BFF): LD (M/F): 3.02/3.16 MD (M/F):13.48/14.08 HD (M/F): 67.73/71.34 Formoterol Fumarate (BGF): LD (M/F): 0.10/0.11 MD (M/F): 0.60/0.63 HD (M/F): 1.94/2.03 Formoterol Fumarate (BFF): LD (M/F): 0.10/0.11 MD (M/F): 0.47/0.49 HD (M/F): 2.28/2.4 Glycopyrrolate (BGF) LD (M/F): 0.20/0.21 MD (M/F): 1.06/1.11 HD (M/F): 3.39/3.56
Frequency of dosing:	Daily
Route of administration:	Nose-only inhalation
Dose volume:	Air control: 60 min Placebo control: 60 min Low Dose: 10 min (BGF and BFF) Mid Dose: 30 min (BGF and BFF) High Dose: 60 min (BGF and BFF)
Formulation/vehicle:	Calcium Chloride Dihydrate ($CaCl_2$) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC)
Species/strain:	Dog/Beagle
Number/sex/group:	4/sex/group
Age:	5-7 months
Weight:	Males- 8.15-12 kg; females- 6.25-9.45 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were no deviations that impacted interpretation of the results of the study

Abbreviations: LD = low dose; MD = mid dose; HD = high dose; M = male; F = female; BGF = budesonide, glycopyrrolate and formoterol fumarate; BFF = budesonide and formoterol fumarate

Exposure System

Figure 1. Schematic Example Diagram of the Test Article and Placebo Exposure Chambers

(b) (4)

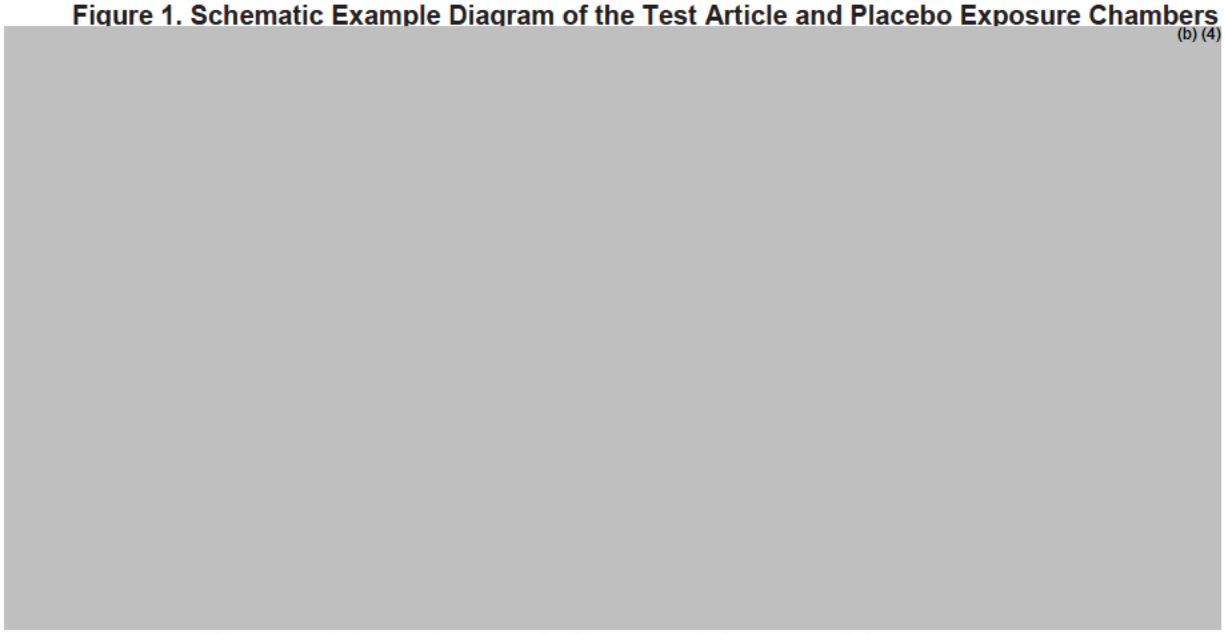


Figure 1. Schematic example diagram of the test article and placebo exposure chambers.

(b) (4)

Source: Excerpted from the Applicant's submission

(b) (4)

Table 5. Average Budesonide, Glycopyrrolate, and Formoterol Fumarate Pulmonary Doses

	Budesonide Aerosol Concentration (µg/kg/day)		Glycopyrrolate Aerosol Concentration (µg/kg/day)		Formoterol Fumarate Aerosol Concentration (µg/kg/day)	
Group	Male	Female	Male	Female	Male	Female
Air	N/A	N/A	N/A	N/A	N/A	N/A
Placebo	N/A	N/A	N/A	N/A	N/A	N/A
Low Dose BGF	3.16	3.35	0.20	0.21	0.10	0.11
Mid Dose BGF	16.73	17.55	1.06	1.11	0.60	0.63
High Dose BGF	58.39	61.37	3.39	3.56	1.94	2.03
Low Dose BFF	3.02	3.16	N/A	N/A	0.10	0.11
Mid Dose BFF	13.48	14.08	N/A	N/A	0.47	0.49
High Dose BFF	67.73	71.34	N/A	N/A	2.28	2.40

Abbreviations: BGF = budesonide, glycopyrrolate, and formoterol fumarate; BFF = budesonide and formoterol fumarate; N/A = not applicable
Source: Excerpted from the Applicant's submission

Doses of glycopyrrolate represent the salt form (i.e., quaternary ammonium bromide) of the drug substance (7.2 µg glycopyrronium =9.0 µg glycopyrrolate)

The particle size for placebo, BGF and BFF in the exposure systems was determined to be in the respirable range (b) (4)

Observations and Results

See Key Study Findings (above) for descriptions of study results. Study results not reported in Key Study Findings and/or more detailed descriptions of results will be discussed below.

ECG

Electrocardiograms (ECGs) were performed on all animals prior to assignment to treatment groups. In addition, ECGs were collected after the first exposure (Day 1) and on Day 90 after the last exposure.

Table 6. Mean Heart Rate in 90-Day BGF and BFF Study in Dogs

Males	Air Control	Vehicle	BGF Low	BGF Mid	BGF High	BFF Low	BFF Mid	BFF High
Pre-Study Mean	75	93	102	93	90	99	93	84
Range	(72-84)	(60-144)	(84-132)	(72-108)	(72-108)	(72-144)	(84-96)	(84-84)
Day 1 Mean	90	66	87	99	111	87	90	108
Range	(72-120)	(48-84)	(84-96)	(84-108)	(108-120)	(60-108)	(72-108)	(96-120)
Day 90 Mean	81	63	84	81	99	84	72	93
Range	(60-96)	(48-72)	(72-108)	(60-96)	(84-120)	(72-108)	(60-96)	(60-132)
Females								
Pre-Study Mean	84	90	90	87	108	99	102	93
Range	(72-96)	(72-108)	(60-120)	(60-120)	(84-144)	(96-108)	(84-120)	(60-108)
Day 1 Mean	87	93	114	87	144	93	105	135
Range	(60-120)	(72-120)	(72-180)	(72-108)	(120-216)	(72-120)	(84-132)	(108-156)
Day 90 Mean	87	105	78	75	105	78	84	120
Range	(84-96)	(72-132)	(60-108)	(60-96)	(72-132)	(72-84)	(60-108)	(108-132)

Abbreviations: BGF = budesonide, glycopyrrolate, and formoterol fumarate; BFF = budesonide and formoterol fumarate

No treatment-related effects on PR interval, QRS duration, QT interval, or QTc interval were observed for BGF and BFF treated animals at any dose level. Heart rates were increased for HD BGF and HD BFF females on Day 1 relative to air-control and vehicle-control groups. The addition of glycopyrrolate (BGF) did not result in any further enhancement of the increased heart rate observed with formoterol (BFF). Increased heart rates were not evident on Day 90, possibly due to rapid development of tachyphylaxis.

Hematology

All study animals had baseline (prior to randomization) and terminal blood samples collected. Whole blood was collected from the jugular vein into K3EDTA vacutainers and evaluated using an automated hematology analyzer for Complete Blood Count.

There were potentially treatment related reductions in eosinophils in MD (42.5%) and HD (60%) BGF males and LD (42.5%), MD (52.5%), and HD (80%) BFF females relative to the vehicle control group. Reductions in eosinophils were also noted in MD (52.2%) and HD (56.5%) BGF females and MD (30.4%) and HD (69.6%) BFF females.

Clinical Chemistry

All study animals had baseline (prior to randomization) and terminal whole blood samples collected from the jugular vein into serum tubes and evaluated using an automated chemistry analyzer.

Increased GGT was noted in MD (38.5%) and HD (115%) BGF males and HD (284.6%) BFF males, relative to the vehicle control groups. In females, increases in GGT were noted in MD (92.3%) and HD (130.8%) BGF groups, and in the HD (361.5%) BFF group. Elevated GGT activities might correlate with histopathological findings of hepatocellular alteration.

Histopathology

Histopathologic examination was conducted in a "read down" fashion: i.e. all tissues and gross lesions were examined for Groups 1-Air Control, 2-Placebo Control, 5-BGF High, and 8- BFF High, whereas respiratory and related tissues plus gross lesions were initially examined for remaining groups (3-BGF Low, 4-BGF Mid, 6-BFF Low and 7-BFF Mid). Additional tissues were examined in Low and Mid groups for tissues found demonstrating apparent treatment effects in HD groups (adrenal gland, liver, and thymus).

Treatment related microscopic findings were noted in the adrenal glands, lymph nodes, liver, and thymus. The observed histopathological findings were generally consistent with known corticosteroid class effects of budesonide with the exception of the findings in the liver that could be attributed to formoterol fumarate.

Cortical atrophy (zona fasciculata/reticularis) in the adrenal gland was noted in MD and HD males and females in the BGF and BFF treatment groups. This finding was noted in all MD and HD BGF males and all MD and HD BFF males with increased severity (minimal to moderate) with respect to the dose. This finding was also noted in 4 of 4 MD and HD BGF females with increased severity (minimal to moderate) with respect to the dose and MD and all HD BFF females with moderate severity. These findings could be attributed to the effects of budesonide.

In the tracheobronchial lymph node, lymphocytes decreased was noted in MD and HD BGF males and HD BFF males. These findings could be attributed to the effects of budesonide.

Hepatocellular alteration in the liver was noted at all doses in BGF males, at the MD and HD in BFF males, and at all doses in BGF and BFF treated females. Hepatocellular alteration in periportal regions of the liver was consistent with glycogen accumulation and or increased metabolic activity (an adaptive response) and could be attributed to the pharmacologic action of formoterol fumarate. These findings were accompanied by elevations of GGT activities.

In the thymus, hemorrhage was noted at all doses in BFF treated males, at the MD and HD in BFF treated females, and at the HD in BGF treated females. Decreased lymphocytes were

observed in all doses in BFF and BGF treated males, MD and HD BGF-treated females, and at all doses in BFF treated females.

Table 7. Histopathology Findings in 90-Day BGF and BFF Study in Dogs

Target Organs	Males								Females							
	Air Control	Vehicle	BGF Low Dose	BGF Mid Dose	BGF High Dose	BFF Low Dose	BFF Mid Dose	BFF High Dose	Air Control	Vehicle	BGF Low Dose	BGF Mid Dose	BGF High Dose	BFF Low Dose	BFF Mid Dose	BFF High Dose
Adrenal Gland																
number examined	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Atrophy, Cortical (Zona fasciculata/reticularis)																
Minimal	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0
Mild	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0
Moderate	0	0	0	2	4	0	3	4	0	0	0	2	3	0	1	4
Lymph Node, tracheobronchial																
number examined	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Lymphocyte decrease																
minimal	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0
mild	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Liver																
number examined	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Alteration, hepatocellular																
Minimal	0	0	1	4	2	0	2	0	0	0	2	1	0	2	1	0
Mild	0	0	0	0	0	0	0	0	0	0	0	2	2	0	1	1
Moderate	0	0	0	0	0	0	0	4	0	0	0	1	0	0	0	3
Thymus																
number examined	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Hemorrhage																
Minimal	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
Mild	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
Lymphocyte decrease																
Minimal	0	0	3	1	0	2	0	0	0	0	0	0	0	4	0	0
Mild	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Moderate	0	0	1	2	0	0	0	0	0	0	0	1	0	0	1	0
Severe	0	0	0	1	4	0	4	4	0	0	0	3	4	0	2	4

Abbreviations: BGF = budesonide, glycopyrrolate, and formoterol fumarate; BFF = budesonide and formoterol fumarate

Toxicokinetics

Blood samples for plasma toxicokinetic analysis were collected in K3EDTA tubes from the jugular, cephalic or saphenous veins from all study animals at pre-exposure, immediately after the first exposure, and 0.083, 0.5, and 1, 3, 6, and 24 hours post exposure on Day 1 and at the same time points for the last exposure on Day 90. Blood collections were as close as possible to the target times as practical; however, actual times were used in the analyses. Blood was centrifuged (1300 g, 2-8ºC, ≥10 minutes), and plasma was separated and stored frozen at -70 to -90°C in an appropriately labeled vial.

Plasma glycopyrronium bromide (glycopyrrolate), formoterol fumarate, and budesonide concentrations at nominal sampling times were used for all calculations.

After inhalation of BGF, glycopyrrolate and formoterol were not detectable in the plasma at the LDs on Day 1 or Day 90. Increases of AUC were approximately dose proportional or slightly greater than dose proportional for budesonide treated males and females on Days 1 and 90.

The exposures for glycopyrrolate and formoterol fumarate showed approximately dose proportional or greater than dose proportional increases for both males and females on Days 1 and 90. Drug accumulation for budesonide, glycopyrrolate, and formoterol fumarate was evident at all doses on Day 90 relative to Day 1.

After inhalation of BFF, formoterol was not detectable in the plasma at the LD on Day 1 or Day 90. Increases of AUC for budesonide were approximately dose proportional for males and females on Days 1 and 90. Increases of exposure (AUC) for formoterol fumarate from the MD to HD were less than dose proportional on Day 1 and approximately dose proportional on Day 90. Drug accumulation for budesonide and formoterol fumarate was evident at all doses on Day 90 relative to Day 1.

Table 8. Toxicokinetic Data From BGF Treated Dogs on Day 1

		Budesonide		Glycopyrronium		Formoterol Fumarate	
		Male	Female	Male	Female	Male	Female
Low	C_{max} (ng/mL)	0.497±0.107	0.436±0.263	-	-	-	-
	T_{max} (hr)	0.292±0.241	0.292±0.241	-	-	-	-
	AUC_{last} (hr*ng/mL)	0.297±0.062	0.233±0.094	-	-	-	-
	$t_{1/2}$ (hr)	0.310±0.099	0.407±0.090	-	-	-	-
Mid	C_{max} (ng/mL)	1.64±0.69	2.27±1.64	0.0294	0.0401±0.0108	0.0234	0.0204
	T_{max} (hr)	0.083±0.00	0.083±0.00	0.083	0.083±0.00	0.083	0.542
	AUC_{last} (hr*ng/mL)	1.19±0.19	1.40±0.79	0.0190	0.0247±0.0069	0.0135	0.0273
	$t_{1/2}$ (hr)	0.688±0.208	0.753±0.265	1.19	0.762±0.272	0.766	1.09
High	C_{max} (ng/mL)	7.08±4.39	8.67±3.26	0.0668±0.0152	0.0904±0.0479	0.0787±0.0461	0.107±0.079
	T_{max} (hr)	0.083±0.00	0.083±0.00	0.083±0.00	0.083±0.00	0.312±0.459	0.083±0.00
	AUC_{last} (hr*ng/mL)	5.26±2.03	6.12±2.86	0.119±0.073	0.0873±0.0773	0.164±0.084	0.169±0.104
	$t_{1/2}$ (hr)	1.36±0.22	1.24±0.14	3.22±1.76	2.06±2.62	1.69±0.39	1.70±0.25

Abbreviations: C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; AUC_{last} = area under the curve to the last quantifiable time point; $t_{1/2}$ = half-life; BGF = budesonide, glycopyrrolate, and formoterol fumarate
Source: Excerpted from the Applicant's submission

Table 9. Toxicokinetic Data From BGF Treated Dogs on Day 90

		Budesonide		Glycopyrronium		Formoterol Fumarate	
		Male	Female	Male	Female	Male	Female
Low	C_{max} (ng/mL)	0.822±0.706	0.446±0.153	-	-	-	-
	T_{max} (hr)	0.187±0.209	0.083±0.00	-	-	-	-
	AUC_{last} (hr*ng/mL)	0.426±0.288	0.285±0.072	-	-	-	-
	$t_{1/2}$ (hr)	0.245±0.054	0.662±0.124	-	-	-	-
Mid	C_{max} (ng/mL)	1.90±1.31	4.99±1.94	0.0336±0.0172	0.0514±0.0193	0.0298±0.0146	0.0440±0.0187
	T_{max} (hr)	0.187±0.209	0.083±0.00	0.083±0.00	0.083±0.00	0.083±0.00	0.187±0.209
	AUC_{last} (hr*ng/mL)	1.96±1.19	3.12±1.18	0.0388±0.0434	0.0291±0.0084	0.0347±0.0210	0.0506±0.0375
	$t_{1/2}$ (hr)	1.25±0.41	1.19±0.52	2.10±2.23	0.599±0.130	3.64±1.77	1.40±0.92
High	C_{max} (ng/mL)	22.9±11.5	18.6±10.6	0.324±0.218	0.380±0.283	0.346±0.227	0.219±0.133
	T_{max} (hr)	0.083±0.00	0.083±0.00	0.083±0.00	0.083±0.00	0.083±0.00	0.187±0.209
	AUC_{last} (hr*ng/mL)	13.8±3.1	13.1±4.0	0.634±0.364	0.688±0.504	0.370±0.106	0.324±0.069
	$t_{1/2}$ (hr)	5.95±5.52	8.34±5.11	15.6±22.4	3.69±2.25	2.51±0.28	2.44±0.45

Abbreviations: C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; AUC_{last} = area under the curve to the last quantifiable time point; $t_{1/2}$ = half-life; BGF = budesonide, glycopyrrolate, and formoterol fumarate
Excerpted from the Applicant's submission

5.8.2. Genetic Toxicology

In genetic toxicology studies, glycopyrrolate was not mutagenic in the in vitro reverse mutation assay in bacterial cells (Study No. AD91RW.502ICH.BTL) or clastogenic in the in vitro mammalian cell micronucleus assay in TK6 Cells (Study No. AD91RW.361ICH.BTL) and in vivo micronucleus assay in rats (Study No. AD91RW.125012ICH.BTL)

Budesonide was not mutagenic or clastogenic in six different test systems: Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster, and DNA repair analysis in rat hepatocyte culture. (Excerpted from NDA 21929, Symbicort, label)

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. (Excerpted from NDA 208294, Bevespi Aerosphere, label)

5.8.3. Carcinogenicity

Glycopyrrolate

Refer to Nonclinical Review in DARRTS (NDA 212122 dated August 19, 2019 authored by PharmTox reviewer Ijeoma Uzoma, PhD) for a complete review of the 2-year carcinogenicity studies conducted with glycopyrrolate in rats and mice. A summary of the studies and the ECAC conclusions are provided below.

In a 2-year carcinogenicity study, Sprague Dawley rats received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 151.7/165.93 (LD, M/F), 302.9/330.66 (MD, M/F), and 620.45/684.14 (HD, M/F) µg/kg/day. The study included an interim sacrifice of 10 rats/sex/group after 52 weeks of treatment. Doses are represented as the estimated achieved pulmonary doses with the quaternary ammonium bromide salt form of the drug substance (glycopyrrolate). Prior concurrence for doses used in this study was not obtained from the ECAC.

Treatment with glycopyrrolate had no effects on survival of male or female rats. Dose-related decreases of absolute body weights were observed in male and female rats beginning at approximately week 12 and continued over the course of the study. At Week 81, absolute body weights were reduced for drug-treated male groups by 11.8% (LD), 19.9% (MD), and 20% (HD) and for female drug-treated groups by 16% (LD), 11.4% (MD), and 23.4% (HD), relative to air-control groups. Decreases of absolute body weights appeared to be potentially excessive (>10%). The Applicant did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights.

The Applicant elected to terminate the entire study early (starting at Week 82) for all male and female groups due to low survival (22 of 60 [37%] females remaining) in the female air-control group at week 82. According to ECAC criteria for study termination, if the number of animals of a sex within the control group declines to 20, then all groups of that sex including drug-treated should be terminated. Based on these criteria, it was inappropriate to terminate female groups at that time. Further, in the male air-control and vehicle-control groups, 37 of 60 (62%) and 27 of 60 (45%) animals, respectively, were alive at week 82. Male groups were inappropriately terminated per ECAC criteria for study termination. The study duration was potentially inadequate to assess drug-induced tumor development.

Final results of this study were presented to the ECAC on April 16, 2019. The Committee concluded that the carcinogenicity study was inadequate in male and female rats due to early termination of the study.

A 2-year oral carcinogenicity study with glycopyrrolate in rats was conducted to support approval of NDA 022571 for Cuvposa (glycopyrrolate) oral solution. The description of the carcinogenicity study in rats from the Cuvposa label was adapted to the intended dosing of BGF pMDI with total daily administration of glycopyrrolate at 36 µg:

In a 24-month carcinogenicity study in rats, glycopyrrolate produced no significant changes in tumor incidences when administered to males or females by oral gavage at dosages up to 40,000 mcg/kg/day (approximately 11,000 times the maximum recommended daily inhalation dose of glycopyrrolate on a µg/m^2 basis).

In a 2-year carcinogenicity study, B6C3F1 mice received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control; CaCl2 and Distearoyl-sn-Glycero-3-phosphocholine [DSPC]), 0.347/0.335 (LD, M/F), 0.705/0.7 (MD, M/F), and 1.46/1.42 (HD, M/F) mg/kg/day.

Prior concurrence for doses used in this study was not obtained from the ECAC. Treatment with glycopyrrolate had no effects on survival in male or female mice up to 104 weeks. Dose-related decreases of absolute body weights were observed in males and females beginning around Week 3 and Week 11, respectively, and continued over the course of the study. Decreases of absolute body weights at the end of the study appeared to be potentially excessive (>10%) for MD Females (-15.9%), HD males (-15%), and HD females (-27.7%). The Applicant did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights.

There were no statistically significant test article-related tumor findings in male mice in the LD and MD groups and female mice in the LD group.

Final results of this study were presented to the ECAC on April 16, 2019. The Committee concluded that body weight decreases in HD males and mid and HD females could confound interpretation. The Committee concurred that no drug-related neoplasms were observed at the LD in females and the mid and LD in males.

Budesonide

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

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (at 0.8 times the maximum recommended human daily intranasal dose (MRHDID) in adults on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (at 0.4 and 0.8 times the MRHDID in adults on a mcg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (at 0.8 times the MRHDID in adults on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (at 0.8 times the MRHDID in adults on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 1.5 times the MRHDID in adults on a mcg/m2 basis). (Excerpted from NDA 21929, Symbicort, label). As needed, dose multiples were adjusted due to rounding.

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 at oral doses of 100 mcg/kg and above (approximately 25 times the MRHDID in adults on a mcg/m2 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 130 mcg/kg (approximately 70 times the MRHDID in adults on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 11 times the MRHDID in adults on a mcg/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.
(Excerpted from NDA 21929, Symbicort, label)

5.8.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study Title: Subcutaneous Reproductive Toxicity Study (Segment I) of Glycopyrrolate in Rats	
Study no.:	14-764
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 15, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot: 9-ABY-76-1; 98% purity

Key Study Findings

- Rats received subcutaneous (SC) doses of 0 (vehicle, sterile saline), 0.1, 1.0, or 10 mg/kg/day glycopyrrolate (salt) to assess potential drug-related effects on reproductive performance and fertility. Males were dosed 4 weeks prior to mating, up to 2 weeks during the mating period, and continuing until terminal necropsy (Day 52 at minimum). Females were dosed for 2 weeks prior to mating, up to 2 weeks during the mating

period, and gestation days (GD) 0 to 6. Male rats were mated with female rats within the same control or drug-treated group. Dams underwent cesarean sections on GD 13 after receiving a minimum of 28 daily doses.

- There were no treatment related mortalities.
- Body weight gains were decreased for all female drug-treated groups from Days 0 to 14 of the pre-mating period by -23% at the LD, -53% at the MD, and -67% at the HD, relative to the control group. Males were observed with dose dependent decreases in BWG that persisted throughout the study (Day 50: LD -15.6%, MD -14%, HD -38%, relative to the control).
- TK analysis demonstrated systemic exposure to the test article was achieved in treated animals; however; low levels of the test article were also detected in the controls. C_{max} and AUC increases were generally dose proportional on Day 1 in males and females and greater than dose proportional in females on Day 14. Increases of C_{max} were generally dose proportional on Day 28 in males while increases of AUC were greater than dose proportional.
- Mating indexes were at 100% for all control and drug-treated groups and fertility indexes were unaffected by treatment.
- The mating and fertility indexes were unaffected with SC doses of glycopyrrolate up to 10 mg/kg/day. NOAELs were not established for paternal or maternal toxicity based upon observed decreases of BWG in drug-treated male and female groups.

Table 10. Subcutaneous Reproductive Toxicity Study (Segment I) of Glycopyrrolate in Rats, Study No. 14-764 Methods

Study No. 14-764	
Methods	**Details**
Doses:	0 (vehicle control), 0.1, 1, or 10 mg/kg/day
Frequency of dosing:	daily
Dose volume:	1 ml/kg
Route of administration:	Subcutaneous
Formulation/Vehicle:	Sterile saline
Species/Strain:	Rat/ Sprague-Dawley
Number/Sex/Group:	25/sex/group
Satellite groups:	TK: 3/sex/group

Abbreviations: TK = toxicokinetics

Study Design

Glycopyrrolate was administered by subcutaneous injection in a vehicle of saline at dose levels of 0 (vehicle control), 0.1, 1, or 10 mg/kg/day to male and female Sprague-Dawley rats (from [redacted] (b) (4), males received at 6-7 weeks of age and females were 5-6 weeks of age) and were approximately 9 weeks old at treatment initiation. Males were dosed for 4 weeks prior to mating, up to 2 weeks during the mating period, and continuing until their scheduled necropsy. Females were dosed for at least 2 weeks prior to mating, up to 2 weeks during the mating period, and from GD 0 to GD 6 (i.e., implantation). Drug-treated male rats were mated with drug-treated female rats within the same dose group. Dams underwent cesarean sections on

GD 13 after receiving a minimum of 28 daily doses. Males received at least 52 daily doses and were sacrificed after mating.

Basis for Dose Selection

Dose levels of Glycopyrrolate were selected by the Applicant based on findings from a dose range-finding developmental toxicity study in rats ((b) (4) Study No.: 14-762, this study was not submitted under the NDA.) The HD was anticipated to cause toxicity and the LD was anticipated to be a no-effect level.

Observations and Results

See Key Study Findings (above) for descriptions of study results. Study results not reported in Key Study Findings and/or more detailed descriptions of results will be discussed below.

Body Weight

Rats were weighed weekly until cohabitation (mating) but were not weighed during the mating period. Males were weighed once prior to their scheduled sacrifice. Dams (i.e., impregnated females) were weighed on GD 0, 3, 6, 9, 12 and prior to scheduled necropsy (i.e., day 13), and BWG were calculated.

In females during the premating period (Day 0 to Day 14), BWG were reduced for the low-, mid-, and high-dose groups by 23%, 53%, and 67%, respectively, relative to the control group. However, during the gestation period (GD 0 to GD 6), BWG were unaffected.

In males, body weights for the low-, mid-, and high-dose groups were reduced by 15.6%, 14%, and 38%, respectively, relative to the control group.

Table 11. BW Changes in Female Rats in FEED Study From Pre-Mating to GD 6

BW grams Female Rats Treated with Glycopyrrolate				
Doses	**0.0**	**0.1**	**1.0**	**10.0**
Pre-mating Day 0	216	218	220	221
Pre-mating Day 7	235	233	225	220
Pre-mating Day 14	246	241	234	231
Δ, BW gain (g) Days 0 to 14	30	23	14	10
% Change of Day 0 BW	14	11	6	5
% of Control	0	-23	-53	-67
GD 0	245	240	230	220
GD 3	259	253	245	235
GD 6	270	265	257	248
Δ, BW gain (g) GD 0 to GD 6	25	25	27	28
% Change of Day 0 BW	10	10	12	13
% of Control	0	0	8	12

Abbreviations: BW = body weight; FEED = fertility and early embryonic development; GD = gestation day

Table 12. BW Changes in Male Rats in FEED Study From Treatment Day 0 to 50

BW grams in Male Rats Treated with Glycopyrrolate				
Doses	**0**	**0.1**	**1**	**10**
Day 0	288	296	289	288
Day 7	345	337	337	316
Day 14	390	377	377	350
Day 21	427	409	403	368
Day 28	465	446	440	396
Day 50	536	511	502	441
Δ, BW gain (g) Day 0 to Day 50	248	215	213	153
% Change of Day 0 BW	86	73	74	53
% change of control	0	-15	-14	-38

Abbreviations: BW = body weight; FEED = fertility and early embryonic development; GD = gestation day

Toxicokinetics

TK samples were collected from males on days 1 and 28 of the pre-mating period, and TK samples were collected from females on days 1 and 14 of the pre-mating period. Glycopyrrolate was measured in plasma samples using LC-MS/MS.

On Days 1 and 14, low levels of glycopyrrolate were detected in the female control TK samples, and in the male control TK samples on Day 28, at concentrations approximately 10-fold less than the LD group. This contamination of the controls was not observed in the dosing solution analysis. The Applicant provided justification that the levels present in the controls were not evidence of accidental dosing of control animals with glycopyrrolate.

On Day 1, C_{max} and AUC increased in a generally dose proportional manner in males and females from the LD to MD to HD. T_{max} occurred at 0.5 hr post dose.

On Day 14, C_{max} and AUC increased in a greater than dose proportional manner in females.

On Day 28, C_{max} and AUC increased in a greater than dose proportional manner in males from the LD to MD. C_{max} increased in a dose proportional manner and AUC increased in a greater than dose proportional manner from the MD to HD. T_{max} occurred at 0.5 hr post dose in the control, LD, and MD and at 1 hr in the HD.

Table 13. Toxicokinetic Analysis of Male and Female Rats on Day 1, Day 14, and Day 28 in FEED Study

		Day 1		Day 14/28		
Dose	**Sex**	**C_{max} (ng/mL)**	**AUC_{0-4} (ng*hr/mL)**	**C_{max} (ng/mL)**	**AUC_{0-4} (ng*hr/mL)**	**AUC_{0-24} (ng*hr/mL)**
Low	M	13.2	9.23	10.8	7.54	11.95
Low	F	20.7	18.8	6.5	5.4	13.4
Mid	M	158	140	203	197	223
Mid	F	184	146	175	142	190

		Day 1		Day 14/28		
Dose	Sex	C_{max} (ng/mL)	AUC_{0-4} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{0-4} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)
High	M	962	2269	1813	3920	6443
High	F	1843	2198	1397	1333	3371

Abbreviations: AUC_{0-4} = area under the curve from zero to four hours; AUC_{0-24} = area under the curve from zero to 24 hours; C_{max} = maximum plasma concentration; M = male; F = female; FEED = fertility and early embryonic development

Embryo-Fetal Development

Study Title: Definitive Subcutaneous Developmental Toxicity Study (Seg II) of Glycopyrrolate in Rabbits	
Study no.:	14-763
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 27, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # 77146B002, Purity 99.8%

Key Study Findings

- Glycopyrrolate at doses of 0 (vehicle: sterile saline), 0.1, 1.0, and 10 mg/kg/day were administered subcutaneously in gravid rabbits (23/group) to evaluate embryofetal development. Animals were treated from GD 6 to GD 17 and sacrificed on GD 29.
- From GD 6 to GD 18, decreased BWG was evident for MD rabbits and body weight loss was evident for HD rabbits, relative to the control group. Based on the decreased BWG for the MD group and body weight loss for the HD group, it appeared that maternal toxicity dose was achieved, although these doses were excessive. BWG for the LD group was comparable to the concurrent control group. Using body weights and BWG corrected for gravid uterus weights confirmed maternal toxicity was present at the MD and HD.
- Based on C_{max} and AUC values, there were dose-proportional increases of exposures to glycopyrrolate over the dosing period from GD 6 to GD 18.
- There were no dose dependent changes in cesarean section parameters, or test article related malformations or variations up to the HD of 10 mg/kg, which was associated with a C_{max} of 6940 ng/mL in gravid females on GD 18.
- The NOAEL for maternal toxicity was 1 mg/kg based on reduced BWG at the MD and body weight loss at the HD.
- The NOAEL for developmental toxicity was the MD, 1 mg/kg, based on reduced body weights for male fetuses in the 10 mg/kg treated group; however, this could be attributed to excessive maternal toxicity at the HD.

Table 14. Definitive Subcutaneous Developmental Toxicity Study (Seg II) of Glycopyrrolate in Rabbits, Study No. 14-763 Methods

Study No. 14-763	
Methods	**Details**
Doses:	0, 0.1, 1, 10 mg/kg
Frequency of dosing:	Daily (GD 6-17)
Dose volume:	1 mL/kg
Route of administration:	subcutaneous injection
Formulation/Vehicle:	Sterile saline
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	23/females/group
Satellite groups:	TK group 3 females/group

Abbreviations: GD = gestation day

Study Design

Dose levels of glycopyrrolate 0, 0.1, 1, or 10 mg/kg/day were chosen for this study based on the results from a dose range-finding developmental toxicity study in rabbits ((b) (4) SN 14-761) for which the NOAEL for maternal and developmental toxicity was 5 mg/kg/day. In the present study, doses were administered once daily at a constant dose volume of 1 mL/kg during the period of major organogenesis (GD 6 to GD 18) and covered implantation until closure of the hard palate. Maternal body weight, body weight gain, and food consumption were measured throughout the gestation period. Dams were euthanized on the GD 29 and subjected to a cesarean section and gross necropsy. The uteri were weighed, opened and inspected for implantation sites; fetuses were harvested, weighed, given a gross external examination.

Observations and Results

See Key Study Findings (above) for descriptions of study results. Study results not reported in Key Study Findings and/or more detailed descriptions of results will be discussed below.

Clinical Signs

A hand-held clinical observation was performed on all animals at the time of weighing (days 6, 7, 8, 9, 12, 15, 18, 21, 24, 27 and 29).

Scant feces were noted at increasing incidence with the dose from GD 6 to GD 18. Scant feces were associated with reduced food consumption.

Signs of abortion were noted including red discharge or placenta in the excrement pan, beginning around GD 17 and up to day 24, in three control rabbits, two mid-dose rabbits, and five HD rabbits. These findings were judged to be unrelated to drug treatment.

Table 15. Summary of Clinical Signs During Gestation in Female Rabbits (Treatment With Glycopyrrolate From GD 6 to GD 18)

Observations Number Examined	Vehicle Control n=23	Low Dose n=23	Mid Dose n=23	High Dose n=23
Red Material Excrement Pan	1		2	3
Red Material	1		1	2
Placenta	1		1	4
Loose Stool	1		3	4
Scab		1		6
Scant Feces	3	6	21	23

Abbreviations: GD = gestation day

Body Weight

Each doe was weighed by the supplier on GD 0 (sperm-positive day), at receipt and on days 6, 7, 8, 9, 12, 15, 18, 21, 24, 27 and 29.

From GD 6 to GD 18, decreased BWG was evident for MD females and body weight loss was evident for HD rabbits, relative to the control group. Based on the decreased BWG for the MD group and body weight loss for the HD group, maternal toxicity was achieved, although these doses were excessive. BWG for the LD group was comparable to the concurrent control group. Corrections of body weights and body weight gains for gravid uterus weights confirmed that maternal toxicity was present at the MD and HD.

Table 16. Body Weight Changes in Pregnant Female Rabbits During Gestation (Treatment With Glycopyrrolate From GD 6 to GD 18)

	Glycopyrrolate mg/kg/day			
Parameter	0	0.1	1	10
GD 6 (grams)	3022	3026	2995	3007
GD 18 (grams)	3209	3213	3063	2909
GD 29 (grams)	3374	3437	3296	3169
GD 6 to GD 18, Δ (grams)	187	187	68	-98
% Change of GD 6 BW	6.2	6.2	2.3	-3.3
% of Control	0.0	0	-63.6	-
GD 18 to GD 29, Δ (grams)	165	224.0	233.0	260.0
% Change of GD 18 BW	5.1	7.0	7.6	8.9
% of Control	0.0	35.8	41.2	57.6

Abbreviations: BW = body weight; GD = gestation day

Feed Consumption

Food consumption measurements corresponded with body weight collection and were measured for each rabbit over GD 4 to GD 6 (pre-treatment), 6-7, 7-8, 8-9, 9-12, 12-15, 15-18, 18-21, 21-24, 24-27 and 27-29.

Reduced food consumption was observed in all treatment groups from GD 7 to GD 12 and persisted to GD 18 in the 1 and 10 mg/kg groups. Decreased food consumption paralleled

decreased body weight gains or body weight losses. Discontinuation of treatment reversed decreased food consumption.

Toxicokinetics

Blood specimens were collected from the central ear artery into tubes containing K_2EDTA as anticoagulant. Samples were collected prior to treatment initiation (pre-dose, this sample may be collected prior to GD 6) and at 0.5, 1, 2 and 4 hours post-dose on GD 6 and 18. Approximately 0.5 ml of whole blood/animal was collected at any one time. Glycopyrrolate was measured in plasma samples using LC-MS/MS.

Average C_{max} values on GD 6 were 36.9, 413, and 4887 ng/mL, for the low-, mid-, and high-dose groups, respectively. Average AUC_{0-4} values on GD 6 were 46.0, 444, and 4112 ng*hr/mL, for the low-, mid-, and high-dose groups, respectively.

C_{max} values on GD 18 were 45.2, 484, and 6940 ng/mL, for the low-, mid-, and high-dose groups, respectively. Average AUC_{0-4} values on GD 18 were 47.4, 452, and 5225 ng*hr/mL, for the low-, mid-, and high-dose groups, respectively.

Summary of Fetal Litter Viability Parameters

Fetal body weights were significantly decreased for HD males; however, HD female fetal weights were unaffected. Reduced litter weight can be attributed to excessive maternal toxicity at the HD (maternal body weight loss). Numbers of male fetuses were reduced in drug-treated groups relative to the concurrent control; however, the number of males as well as the male to female ratio (1.3/1) were high for the control group. Male to female ratios in drug-treated groups were 0.9/1, which was within the expected range.

Table 17. Summary of Rabbit Fetal Data

Rabbit Fetal Data				
Mean fetal body weight, g (male)	39.92	40.17	40.53	35.84*
Mean fetal body weight, g (female)	37.51	39.49	40.08	35.69
Mean fetal body weight (M and F combined), g	39.19	39.78	40.37	36.06
Total number of male fetuses per group (sum of all litters)	91	79*	72*	60*
Total number of female fetuses per group (sum of all litters)	72	86	83	69
Male : Female Ratio	1.3 : 1	0.9 : 1	0.9 : 1	0.9 : 1

*p≤0.05

Fetal Observations

Incidences of incomplete ossification of the skull were increased in the mid- and high-dose groups relative to the concurrent control; however, these findings might be attributed to maternal toxicity.

Study Title: Definitive Subcutaneous Developmental Toxicity Study (Seg II) of Glycopyrrolate in Rats	
Study no.:	14-762
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 11, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # 9-ABY-76-1; Purity 98%

Key Study Findings

- Glycopyrrolate at doses of 0 (vehicle: sterile saline), 0.1, 1.0, and 10 mg/kg/day were administered subcutaneously in gravid rats (23/group) to evaluate embryofetal development. Animals were treated from GD 6 to GD 17 and sacrificed on GD 21.
- Dose dependent decreases in BWG were observed during the dosing period from GD 6 to GD 18 at the MD (-14%) and HD (-32.6%), relative to the control. Based on decreased BWG, it appeared that maternal toxicity was achieved, although the HD appeared to be excessive.
- Based on C_{max}, dose-related increases of exposures to glycopyrrolate were achieved from GD 6 to GD 17. Increases in AUC were greater than dose proportional on GD 6 and GD 17.
- There were no dose dependent changes in cesarean section parameters, or test article related malformations or variations up to the HD of 10 mg/kg, which was associated with a C_{max} of 2050 ng/mL in gravid females on Day 17.
- Fetal body weights at the HD were decreased by approximately 10% relative to the control group. These findings were attributed to maternal toxicity.
- The NOAEL for maternal toxicity was the LD of 0.1 mg/kg based on reduced BWG at the MD and HD
- The NOAEL for developmental toxicity was the MD, 1 mg/kg, based on reduced fetal body weights in the 10 mg/kg treated group. Reduced fetal body weight at the HD was attributed to maternal toxicity.

Table 18. Definitive Subcutaneous Developmental Toxicity Study (Seg II) of Glycopyrrolate in Rats, Study No. 14-762 Methods

Study No. 14-762	
Methods	**Details**
Doses:	0, 0.1, 1, or 10 mg/kg
Frequency of dosing:	Daily (GD 6-17)
Dose volume:	1 mL/kg
Route of administration:	subcutaneous injection
Formulation/Vehicle:	sterile saline
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	23 females/group
Satellite groups:	TK group 3 females/group

Abbreviations: TK = toxicokinetic; GD = gestation day

Study Design

Dose levels of glycopyrrolate 0, 0.1, 1, and 10 mg/kg/day were chosen for this study based on the results from a dose range-finding developmental toxicity study in rats ((b) (4) SN 14-760). Dose levels used in the dose range finding study were 0.2, 1, 5, and 10 mg/kg/day of glycopyrrolate on GD 6 to GD 17, where the NOAEL for maternal toxicity was 0.2 mg/kg/day and the NOAEL for developmental toxicity was 10 mg/kg. In the present study, doses were administered once daily at a constant dose volume of 1 mL/kg during the period of major organogenesis (GD 6 to GD 17) and covered implantation until closure of the hard palate. Maternal body weight, body weight gain and food consumption were measured throughout the gestation period. Dams were euthanized on the GD 21 and subjected to a cesarean section and gross necropsy. The uteri were weighed, opened, and inspected for implantation sites. Fetuses were harvested, weighed, and given a gross external examination. One-half of the fetuses in each litter were subjected to visceral examinations, while control and HD fetuses were subjected to skeletal and/or cephalic examinations.

Body Weight

Each dam was weighed at receipt for randomization and on GD 6, 9, 12, 15, 18 and 21.

The was a dose dependent decrease in BWG observed from GD 6 to GD 18 at the MD (-14%) and HD (-32.6%), relative to the control. The decreases in BWG appeared to recover following the end of the dose period (GD 18 to GD 21).

Table 19. Body Weight Changes in Pregnant Females Rats During Gestation (Treatment From GD 6 to GD 17)

	Glycopyrrolate mg/kg/day			
Parameter	**0**	**0.1**	**1**	**10**
GD 6 (grams)	233	233	235	235
GD 18 (grams)	319	315	309	293
GD 21 (grams)	367	366	361	339
GD 6 to GD 18, Δ (grams)	86	82	74	58
% Change of GD 6 BW	36.9	35.2	31.5	24.7
% of Control	0.0	-4.7	-14	-32.6

	Glycopyrrolate mg/kg/day			
Parameter	**0**	**0.1**	**1**	**10**
GD 18 to GD 21, Δ (grams)	48	51	52	46
% Change of GD 18 BW	15	16.2	16.8	15.7
% of Control	0.0	8.0	12	4.7

Abbreviations: BW = body weight; GD = gestation day

Feed Consumption

Food consumption measurements corresponded with body weight collection and were measured for each dam over GD 6 to GD 9, GD 9 to GD 12, GD 12 to GD 15, GD 15 to GD 18 and GD 18 to GD 21.

Dose dependent reductions of food consumption were noted at all doses from GD 7 to GD 18. Reduced food consumption persisted in the MD and HD group throughout the treatment period. Following the dosing period, reduced food consumption was noted at GD 21 in the HD group only.

Toxicokinetics

Blood samples were collected prior to treatment initiation (pre-dose, this sample may be collected prior to GD 6) and at 0.5, 1, 2 and 4 hours postdose on GD 6 and 17. Glycopyrrolate was measured in plasma samples using LC-MS/MS.

Following toxicokinetic analysis, T_{max} was 0.5 hr at the LD and MD groups, and up to 2 hrs at the HD post dose. The mean C_{max} values on Day 6 were 13.6, 163, and 999 ng/mL at the LD, MD, and HD, respectively. It was noted that C_{max} were less than dose proportional from the MD to the HD. The mean AUC_{0-4} values on GD 6 were 8.81, 168, and 2538 ng*hr/mL, for the low-, mid-, and high-dose groups, respectively. The increases in AUC were greater than dose proportional.

C_{max} values on Day 17 were 16.2, 182, and 1840 ng/mL at the LD, MD, and HD respectively, and noted to be similar to the LD and MD values on Day 6; however, the C_{max} was approximately two-fold higher at the HD. The mean AUC_{0-4} values on GD 17 were 10.6, 192, and 3279 ng*hr/mL, for the low-, mid-, and high-dose groups, respectively. The mean AUC_{0-24} values on GD 17 were 23, 214, and 3575 ng*hr/mL, for the low-, mid-, and high-dose groups, respectively. The increases in AUC were greater than dose proportional.

Fetal Litter Viability

It is noted that combined (male and female) fetal body weights for the HD group were slightly reduced compared to controls (-9.6%). Reduced fetal body weights at the HD may be related to maternal toxicity (reduced BWG) in HD treated pregnant females.

Table 20. Summary of Rat Fetal Litter Viability Parameters (Treatment With Glycopyrrolate From GD 6 to GD 17)

Rat Fetal Data				
Fetal body Weight, g (male)	6.15	6.10	6.02	5.63* (-8.4%)
Fetal body Weight, g (female)	5.92	5.77	5.72	5.31* (-10.3%)
Combined (M/F) fetal body weight, g	6.04	5.95	5.86	5.46* (-9.6%)
Mean number of male fetuses per litter (mean)	5.9	6.7	5.6	6.2
Mean number of female fetuses per litter (mean)	5.6	5.8	6.0	6.0
Male:Female Ratio	1:1	1:1.2	1:0.9	1:1

Abbreviations: GD = gestation day; M = male; F = female
* $p \leq 0.05$

Prenatal and Postnatal Development

Study Title: Segment III Reproductive/Developmental Toxicity Study of Glycopyrrolate in Rats	
Study no.:	14-765
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 21, 2016 – (Treatment initiation date)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # 77146B002, Purity 98%

Key Study Findings

- In a PPND study, mated F0 female rats (24/group) received subcutaneous injections of the glycopyrrolate at doses of 0 (vehicle- sterile saline), 0.1, 1.0, or 10 mg/kg/day from GD 6 to Postnatal Day (PND/LD) 21-23.
- F0 females were observed with dose dependent decreases in BWG (MD -15%, HD -29%), compared to the control from GD 6 to GD 20, which correlated with decreased feed consumption. BWG were unaffected from LD0 to LD21. Maternal toxicity was achieved at the MD and HD based upon decreased BWG from GD 6 to GD 20; however, the level of toxicity was excessive at the HD.
- F0 dams showed no test article related effects on reproductive parameters. There were no test article related effects on the gestation length, the number of implantation sites, the number of live births, or on viability of F1 offspring.
- Absolute body weights of HD F1 generation pups (combined sexes) from PND 0-21 were decreased relative to the concurrent control, although statistical significance was not

achieved. BWG of F1 pups were unaffected from PND 0 to 21 and PND 28 to 70(M)/63(F).

- For F1 generation pups, physical and neurological development were unaffected with doses up to 10 mg/kg in F0 females. Mating and fertility indices were unaffected in F1 adults with doses up to 10 mg/kg in F0 females. The numbers of implantation sites, post-implantation loss, and average litter size (total born for combined sexes) were similar across F1 groups.
- The F2 generation was terminated at PDN 21; BW gains from birth (PND 0) to PND 21 in males or females were unaffected.
- The NOAEL for F0 maternal toxicity was the LD (0.1 mcg/kg/day) based on decreases of BWG at the mid- and high-doses. The NOAEL for the F1 pup development was the HD (10 mg/kg/day).

Table 21. Segment III Reproductive/Developmental Toxicity Study of Glycopyrrolate in Rats, Study No. 14-765 Methods

Study No. 14-765	
Methods	**Details**
Doses:	0 (vehicle control), 0.1, 1, and 10 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	1 ml/kg
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	Sterile saline
Species/Strain:	Sprague-Dawley
Number/Sex/Group:	F0 24 dams/group (3 TK animals per group)
Satellite groups:	None

Abbreviations: TK = toxicokinetic

Study Design

F0 dams were dosed by subcutaneous injection from GD 6 through parturition and lactation until weaning (postnatal day 21). F1 litters were culled on post-natal day 4. During the lactation phase of the study, the pups were not intentionally exposed to the test material (i.e., the test material was not directly administered to the F1 generation). During the lactation phase of the study, growth and development of the F0 offspring (F1 generation) was evaluated. F1 rats were group-housed at weaning (i.e., postnatal day 22) for at least 24-72 hours for acclimation purposes; after which at least one male and one female from each F1 litter within a treatment group were randomly selected for pairing at a future mating trial.

Gross sensory function and reflex responses, as well as automated acoustical startle, motor activity and water (learning and memory paradigm) were evaluated in the F1 pups selected to produce the F2 generation.

At sexual maturity (approximately 10-12 weeks of age), the F1 rats were mated for a period of at least 2 weeks; siblings were not inter-mated. Mating procedures (one-to-one) for the F1 generation were the same as those used for the F0 generation. F1 males were euthanized and

necropsied when they were no longer needed for mating. F1 pups not selected for mating and all F0 dams were sacrificed at F1 weaning. A gross necropsy with limited tissue collection was performed on all F0 dams and F1 pups selected to produce the F2 generation. All F1 dams were allowed a natural parturition and their F2 litters were culled. F1 dams and their F2 litters were euthanized at weaning (PND 21).

Observations and Results

See Key Study Findings (above) for descriptions of study results. Study results not reported in Key Study Findings and/or more detailed descriptions of results will be discussed below.

Body Weight

Each F0 dam was weighed at randomization, and on GD 6, 7, 8, 9, 12, 15, 18 and 20. In F0 dams there were dose dependent decreases in BWG in the MD (-15%) and HD (-29%) groups from gestation (GD 6 to GD 20) (Table 22).

Table 22. BW and BWG in F0 Rats Treated With GP During Gestation

BW Grams Female Rats Treated With Glycopyrrolate				
Doses	**0**	**0.1**	**1**	**10**
GD 6	229	235	232	228
GD 7	234	238	229	220
GD 8	240	243	233	213
GD 12	265	270	259	244
GD 15	283	288	275	262
GD 18	321	326	309	294
GD 20	353	358	337	316
Δ, BW gain (g) GD 6 to GD 20	124	123	105	88
% Change of GD 6 BW	54	52	45	39
% change of control	0	-1	-15	-29

Abbreviations: BW = body weight; BWG = body weight gain; GD = gestation day; GP = glycopyrrolate

During lactation, all drug-treated groups had increased BWG relative to the control group. Overall, there were larger increases in BWG in treated dams during the lactation period at the LD (14%), MD (64%), and HD (95%), relative to the control group (Table 23).

Table 23. BW in F0 Rats Treated With GP During Lactation

BW grams Female Rats Treated With Glycopyrrolate				
Doses	**0**	**0.1**	**1**	**10**
LD 0	272	283	262	247
LD 4	288	299	278	260
LD 7	297	307	285	274
LD 14	314	326	301	289
LD 21	294	308	298	290
Δ, BW gain (g) Day LD 0 to LD 21	22	25	36	43
% Change of LD 0 BW	8	9	14	17
% change of control	0	14	64	95

Abbreviations: BW = body weight; LD = low dose; GP = glycopyrrolate

F0 Dams and their litters were weighed on the day of observed parturition (postnatal day 0), and again on postnatal days 4, 7 and weekly thereafter until their scheduled termination.

Pup weights were lower in the HD group relative to the controls at PND 21 (-7%). The decreases in pup weight may be related to the significant reductions in maternal body weight in the HD group.

Body weight gains of F1 pups from PND 0 to 21 and PND 28 to 70 (males)/63 (females) were unaffected.

Table 24. BW of F1 Generation Pups Pre-Weaning

Body Weights: F1 Generation Pups (Pre-Weaning PNDs 0-21)				
Days	**0**	**0.1**	**1**	**10**
PND 0	6.89	6.94	6.6	6.48
PND 4	11.06	11.58	11.06	10.18
PND 7	17.2	18	16.7	15.6
PND 14	33.6	35.1	32.2	29.4
PND 21	54	58.1	54.8	50.2
Δ, BW gain (g) Day 0 to Day 21	47.11	51.16	48.2	43.72
% Change of Day 0 BW	683.74	737.18	730.30	674.69
% change of control	0	8.60	2.31	-7.20

Abbreviations: PND = postnatal days; BW = body weight

Table 25. BW of F1 Generation Male Pups Post-Weaning

Body Weights: F1 Generation Male Pups (Post-Weaning PNDs 28-70)				
Days	**0**	**0.1**	**1**	**10**
PND 28	91	93	88	84
PND 35	155	156	147	145
PND 42	220	222	210	210
PND 49	290	291	275	277
PND 56	354	356	337	342
PND 63	411	415	391	398
PND 70	446	448	423	429
Δ, BW gain (g) PND 28 to PND 70	355	355	335	345
% Change of Day 0 BW	390.11	381.72	380.68	410.71
% change of control	0	-2.15	-2.42	5.28

Abbreviations: PND = postnatal days; BW = body weight

Table 26. BW of F1 Generation Female Pups Post-Weaning

Body Weights: F1 Generation Female Pups (Post-Weaning PNDs 28-63)				
Days	**0**	**0.1**	**1**	**10**
PND 28	88	93	87	83
PND 35	155	156	147	145
PND 42	220	222	210	210
PND 49	290	291	275	277
PND 56	354	356	337	342
PND 63	411	415	391	398
Δ, BW gain (g) PND 28 to PND 63	323	322	304	315
% Change of Day 0 BW	367.05	346.24	349.43	379.52
% change of control	0	-0.31	-5.88	-2.48

Abbreviations: PND = postnatal days; BW = body weight

Budesonide

In a fertility and reproduction study, male rats were subcutaneously dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were dosed up until weaning of their offspring. Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg (approximately 1.2 times the MRHDID on a mcg/m^2 basis). Budesonide caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal BWG, at 0.3 times the MRHDID (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and above). No such effects were noted at a dose 0.08 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 5 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from GD 6 to GD 18, budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at doses 0.75 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 25 mcg/kg/day). In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from GD 6 to GD 15, budesonide produced similar adverse fetal effects at doses approximately 8 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 500 mcg/kg/day). In another embryo-fetal development study in pregnant rats, no teratogenic or embryocidal effects were seen at doses up to 4 times the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 250 mcg/kg/day).

In a peri-and post-natal development study, rats dosed from GD 15 to postpartum day 21, budesonide had no effects on delivery, but did have an effect on growth and development of offspring. Offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation at doses 0.3 times the MRHDID and higher (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred 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 GD

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 1500 times and greater than the MRHDID (on a mcg/m^2 basis at maternal oral doses of 3000 mcg/kg/day and higher). Brachygnathia was observed in rat fetuses at a dose 7600 times the MRHDID (on a mcg/m2 basis at a maternal oral dose of 15,000 mcg/kg/day). Pregnancy was prolonged at a dose 7600 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Fetal and pup deaths occurred at doses approximately 1500 times the MRHDID and higher (on a mcg/m^2 basis at oral doses of 3000 mcg/kg/day and higher) during gestation.

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from GD 6 to GD 15, no teratogenic, embryocidal or developmental effects were seen at doses up to 350 times the MRHDID (on a mcg/m^2 basis with maternal inhalation doses up to 690 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from GD 6 to GD 18, subcapsular cysts on the liver were observed in the fetuses at a dose 61,000 times the MRHDID (on a mcg/m^2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed at doses up to 3500 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 3500 mcg/kg/day).

In a pre-and post-natal development study, pregnant female rats received formoterol at oral doses of 0, 210, 840, and 3400 mcg/kg/day from GD 6 through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 110 times the MRHDID and higher (on a mcg/m^2 basis at maternal oral doses of 210 mcg/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.

Formoterol fumarate is present in rat milk.

In the fertility and reproduction study in rats, plasma levels of formoterol were measured in pups on post-natal day 15. 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).

5.8.5. Safety Margins for Clinical Doses of Budesonide, Glycopyrrolate, and Formoterol Fumarate

Dose and exposure multiples achieved in nonclinical studies were compared to clinical doses of budesonide, glycopyrrolate, and formoterol fumarate in the tables below.

Table 27. Comparison of Daily Clinical Doses of Budesonide, Glycopyrrolate, and Formoterol Fumarate in Symbicort, Bevespi, and Breztri BGF for COPD

Drug Substance	Symbicort	Bevespi	Breztri (BGF)
Budesonide	640 µg	--	640 µg
Glycopyrrolate	--	36 µg	36 µg
Formoterol Fumarate	19.2 µg	19.2 µg	19.2 µg

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; COPD = chronic obstructive pulmonary disease

Table 28. Systemic Safety/Exposure Margins for Breztri (BGF) on AUC Basis Using the 90-Day Inhalation Toxicology Study With BGF in Dogs

90-Day Dog Inhalation Study With BGF	Estimated Inhaled Dose at the HD µg/kg/day		Dog AUC_{last} Day 90 (ng*hr/mL)		*Clinical AUC_{24hr} Day 8 (ng*hr/mL)	Animal to Human Exposure Margin
	Male	Females	Male	Female		Avg (M/F)
Budesonide	58.39	61.37	13.8	13.1	6	2.2
Glycopyrrolate	3.39	3.56	0.634	0.688	0.148	4.5
Formoterol Fumarate	1.94	2.03	0.370	0.324	0.094	3.7

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; AUC = area under the curve; AUC_{last} = area under the curve to the last quantifiable time point; HD = high dose; AUC_{24hr} = area under the curve at 24 hours; AVG = average; M = male; F = female

*From clinical Study PT010018 after 7 days of twice daily dosing of BGF to patients with moderate to severe COPD. Mean AUC_{0-12} value for B, G, and F were multiplied by 2 to estimate AUC_{24hr} values.

Table 29. Animal to Human Local Exposure Margins for BGF Based on Lung Weight for the Proposed Daily Clinical Doses

90-Day Dog inhalation study with BGF	Estimated inhaled dose at the HD µg/kg/day[1]		Pulmonary Deposited Dose (µg/kg)[2]		Dose by Lung weight (µg/g)[3]		Local Lung Safety Margin[4]	
	Male	Females	Male	Females	Males	Females	Males	Females
Budesonide	58.39	61.37	14.60	15.34	2.18	1.92	3.4	3
Glycopyrrolate	3.39	3.56	0.85	0.89	0.13	0.11	3.6	3
Formoterol Fumarate	1.94	2.03	0.49	0.51	0.07	0.06	3.6	3.1

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; HD = high dose

[1]Estimated inhaled dose was calculated with the following formula: $RMV = 0.499BW^{0.809}$

[2]Pulmonary deposited dose is 25% of the estimated inhaled dose for dogs

[3]Dose by lung weight was calculated by multiplying the pulmonary deposited dose by the body weight then dividing by the lung weight.

-Lung weights were calculated by adding the weights for the 6 sections weighed for the HD group. Males- 77 g, Females 68 g.

-Average BGF HD body weights at Day 91 were used. Males- 11.5 kg, Females 8.5 kg

[4]Local lung safety margins were calculated by dividing the nonclinical lung weight dose by the clinical lung weight dose (Budesonide =0.64 µg/g; Glycopyrrolate =0.036 µg/g, Formoterol fumarate =0.0192 µg/g)

Table 30. Exposure and Safety Margins for Glycopyrrolate, Formoterol Fumarate and Budesonide

Toxicity Studies With Glycopyrrolate			AUC_{0-24} (ng*hr/mL)		Animal to Human Exposure Margin
Study	NOAEL (mg/kg/day)	TK Analysis	Male	Female	Human AUC_{24}hr 0.148 (ng*hr/mL)
Reproductive and developmental toxicity (subcutaneous)					
FEED rat (No. 14-746)	HD =10 (NOAEL fertility)	M = Day 28 F = Day 14	6443	3371	43533/22777
EFD rat (No. 14-762)	MD =1 (NOAEL developmental)	GD 17	n/a	214	1446
	HD =10 (LOAEL)		n/a	3575	24155
EFD rabbit (No. 14-763)	MD =1 (NOAEL developmental)	GD 18	n/a	452*	3054
	HD =10 (LOAEL)			5693	38466
PPND rat (No. 14-765)	HD =10 (NOAEL) (F1 and F2 males and females)	GD 17	n/a	3575**	24155

Carcinogenicity Studies with Glycopyrrolate (inhalation)		ROA	Nonclinical Dose ($\mu g/m^2$)	Animal to Human Safety Margin (Clinical Daily dose =22.2 $\mu g/m^2$)
Mouse	MD =705 µg/kg (males)	inhalation	2115	95
	LD =335 µg/kg (females)	inhalation	1005	45
Rat***	HD =40,000 µg/kg	Oral	240,000	10,810
***Rat carcinogenicity information comes from Cuvposa Oral Glycopyrrolate Solution Label (NDA 22571)				

Reproductive and Developmental Toxicity Studies with Formoterol Fumarate			Nonclinical Dose $\mu g/m^2$		Animal to Human Safety Margin (Clinical Daily dose =11.84 $\mu g/m^2$)	
Study	NOAEL/LOAEL µg/kg/day	ROA	Male	Female	Male	Female
Reproductive and Developmental Toxicity						
FEED rat (No. T3015)	Male =3000 Female =15000 (NOAEL fertility)	oral	18,000	90,000	1520	7,601
EFD rat (No. T2628)	690 (NOAEL)	inhalation	n/a	4140	n/a	350
	3000 (LOAEL)	oral	n/a	18,000	n/a	1520
EFD rabbit (No. 93025)	3500 (NOAEL)	oral	n/a	42,000	n/a	3,547
	60,000 (LOAEL)		n/a	720,000	n/a	60810

Reproductive and Developmental Toxicity Studies with Formoterol Fumarate			Nonclinical Dose µg/m²		Animal to Human Safety Margin (Clinical Daily dose =11.84 µg/m²)	
PPND rat (No. T2905)	210 (LOAEL)	oral	n/a	1,260	n/a	106
Carcinogenicity Studies with Formoterol Fumarate						
Mouse	100 (LOAEL)	oral	300		25.3	
Rat	22 (NOAEL)	inhalation	132		11	
	130 (LOAEL)		780		66	

Reproductive and Developmental Toxicity Studies with Budesonide			Nonclinical Dose (µg/m²)		Animal to Human Safety Margin (Clinical Daily dose =396 µg/m²)	
Study	**NOAEL/LOAEL (µg/kg/day)**	**ROA**	**Male**	**Female**	**Male**	**Female**
FEED rat	80 (NOAEL fertility)	S.C.	480		1.2	
	20 (LOAEL prenatal viability)		120		0.3	
EFD rat	250 (NOAEL)	S.C.	1500		3.8	
	500 (LOAEL)		3000		7.6	
EFD rabbit	25 (LOAEL)	S.C.	n/a	300	n/a	0.75
PPND rat	25 (LOAEL)	S.C.	n/a	150	n/a	0.38
Carcinogenicity Studies with Budesonide						
Rat	Male =25 Female =50 (NOAEL)	oral	150	300	0.4	0.8
	Male =50 (LOAEL)		300	n/a	0.8	n/a
Mouse	M/F =200 (NOAEL)	oral	600		1.51	

Abbreviations: LD = low dose; MD = mid dose; HD = high dose; EFD = embryofetal development; PPND = pre and postnatal development; AUC_{24hr} = area under the curve at 24 hours; $AUC_{0\text{-}24h}$ = area under the curve from 0 to 24 hours; FEED = fertility and early embryonic development; LOAEL = lowest observed adverse effect level; NOAEL = no observable adverse effect level; GD = gestation day; M = male; F = female; ROA = route of administration; TK = toxicokinetics
*AUC0-4 was used because AUC0-24 could not be calculated for this TK group
**AUC at 10 mg/kg from EFD rat study (No. 14-762) was used for PPND study exposure at 10 mg/kg

6. Clinical Pharmacology

6.1. Executive Summary

AstraZeneca submitted NDA 212122 for the fixed-dose triple-combination product on November 30, 2018 via 505(b)(2) path for the (b) (4) (b) (4), maintenance treatment of (b) (4) (b) (4) patients with COPD (b) (4) The drug product is a metered-dose inhaler, each actuation from which provides a metered dose of 160 µg

budesonide (BD), 9 µg of glycopyrrolate (glycopyrronium bromide, GP), and 4.8 µg of formoterol fumarate (FF). The proposed product is to be administered as two inhalations twice daily.

One of the listed products cited in this submission is Bevespi Aerosphere (NDA 208294), which was approved via 505(b)(2) path in 2016 that borrowed results of some glycopyrrolate clinical pharmacology studies from Robinul Injection [NDA 017558, approved in 2005 via 505(b)(1) path]. With the same approach, AstraZeneca borrowed the results of mass balance study from NDA 017558 in the proposed label of NDA 212122: "*After IV administration of a 0.2 mg radiolabeled glycopyrrolate, 85% of dose recovered was recovered in urine 48 hours post dose and some of radioactivity was also recovered in bile*". Therefore, the 505(b)(2) path is appropriate for NDA 212122 from clinical pharmacology perspective.

In this submission, AstraZeneca submitted reports from 8 clinical pharmacology studies and a population pharmacokinetic (popPK) analysis report.

The clinical pharmacology review focuses on the following:

1. Whether there is drug-interaction between three components [budesonide (BD), glycopyrronium (GP), and formoterol) at pharmacokinetic (PK) level in Breztri Aerosphere
2. Whether the Phase 2 dose-ranging studies support the dose selection of BD in Phase 3 studies
3. Whether the Phase 2 PD study supports the combination of BD with GP and FF in patients with COPD
4. The effect of BD on hypothalamic-pituitary-adrenal gland (HPA) axis

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology II and Pharmacometrics have reviewed the information contained in NDA 212122. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
	For evaluation of PK drug interaction between BD, GP, and formoterol, the Reviewer agrees that: the systemic exposure of BD is comparable with or without co-administration of glycopyrronium and/or formoterol in healthy subjects (Study PT010002) and patients with COPD [Study PT0090001 and PT010006 (Trial 06)];
General dosing instructions	the systemic exposure of glycopyrronium is comparable with or without co-administration of BD in healthy subjects (Study PT010001) and patients with COPD Trial 06); the systemic exposure of formoterol is comparable with or without co-administration of BD in healthy subjects (Study PT010001) and patients with COPD (Trial 06).

	The Reviewer agrees with the dose selection of GP (18 µg) and formoterol fumarate (FF, 9.6 µg) for Phase 3 studies is appropriate as they are approved doses under NDA 208294. The Reviewer agrees that the optimal dose of BD was adequately explored in Phase 2 studies and selection of the higher BD doses (320 µg and 160 µg) for Phase 3 studies is appropriate. PT008001 demonstrated that two high doses BD MDIs (320 µg and 160 µg) were numerically higher (~30 mL) than two lower doses BD MDIs (80 µg and 40 µg) in improving trough FEV_1 over 4-week treatment in patients with mild-to-moderate asthma. PT009001 demonstrated that BFF MDI 320/9.6 µg was numerically higher (~30 mL) than BFF MDI 160/9.6 µg and BFF MDI 80/9.6 µg in improving FEV1 AUC_{0-12} over 4-week treatment in patients with moderate-to-severe COPD. The Reviewer agrees that PD results from Study PT009001 supports combination use of BD with FF in patients with COPD. All doses of BFF MDIs (320/9.6, 160/9.6, and 80/9.6 µg) were statistically superior ($p<0.05$) to BD MDI 320 µg as measured by the primary endpoint, the mean change from baseline in FEV_1 AUC_{0-12} on Day 29 in mITT population. FEV1 AUC_{0-12} was about 200 mL higher for all doses of BFF MDIs compared to BD MDI 320 µg. This 200 mL improvement is considered clinically meaningful. BFF MDI 320/9.6 µg was statistically superior to FF MDI 9.6 µg for the change from baseline in FEV_1 AUC_{0-12} on Day 29. Numerically, BFF MDI 320/9.6 µg had 56 mL greater improvement in FEV1 AUC_{0-12} compared to FF MDI 9.6 µg. For HPA axis evaluation, the Reviewer agrees that: the systemic exposure of BD is comparable following single dose inhalation of BGF MDI 320/18/9.6 µg and Symbicort MDI 320/9 µg in healthy subjects (Study PT010001) there was a slight numerical reduction in 0-24hr weighted mean serum cortisol ratio (Week 24/baseline) following BGF MDI 320/18/9.6 µg BID treatment compared to Symbicort MDI 320/9 µg BID and GFF MDI 18/9.6 µg BID treatment in patients with COPD. The clinical meaning of this small reduction is unclear. For discussion of efficacy and safety results from Phase 3 Trial 06, and efficacy comparison between dual-combination and triple-combination products, refer to Section 8 statistical and clinical evaluation.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The Reviewer agrees that Breztri Aerosphere® should be used with caution when co-administered with the following: Strong cytochrome P450 3A4 inhibitors (e.g. ritonavir); may cause systemic corticosteroid effect Additional adrenergic drugs Non-potassium sparing diuretics, xanthine derivatives or steroids; may potentiate hypokalemia or ECG change Monoamine oxidase inhibitors and tricyclic antidepressants; may potentiate effect of formoterol fumarate on cardiovascular system

	Beta-blockers; may block bronchodilatory effects of beta-agonists and produce severe bronchospasm The Reviewer agrees that the use of Breztri Aerosphere® should be avoided with other anticholinergics. The Reviewer agrees that signs of increased drug exposure should be monitored in patients with severe hepatic impairment: The systemic exposure of budesonide and formoterol may increase in patients with severe hepatic impairment. Monitor patients for signs of increased drug exposure.
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed drug formulation was used in all the pivotal clinical studies. There was a minor change in the MDI device (tightening of spray orifice diameter) during Phase 3 Trial 06. For details, refer to the CMC and CDRH review.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Budesonide:

- **Mechanism of action:** BD is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

- **Effect of BD on HPA axis:**
  - The systemic exposure of BD is comparable following single dose inhalation of BGF MDI 320/18/9.6 µg and Symbicort MDI 320/9 µg in healthy subjects (Study PT01001).
  - Effect of BGF MDI 320/18/9.6 µg on the HPA axis was assessed by measurement of 24-hour plasma cortisol at Baseline and at Week 24 in patients with COPD. The mean geometric mean ratio (Week 24/Baseline) was 0.86 (CV =39%) and 0.94 (CV =36.6%) for BGF MDI 320/18/9.6 µg and GFF MDI 18/9.6 µg, respectively. The clinical meaning of this small numerical reduction is unclear.

- **Absorption:** Following inhaled administration of BGF MDI 320/18/9.6 µg in patients with COPD, C_{max} of BD occurred within 20 to 40 minutes. Steady state of C_{max} is achieved following the first day of dosing. The area under the curve from 0 to 12 hours (AUC_{0-12}) at steady state is approximately 1.3 times higher than after the first dose.

- **Distribution:** The estimated BD apparent volume of distribution at steady-state in patients with COPD is approximately 1200 L via popPK analysis. Over the concentration range of 1-100 nmol/L, plasma protein binding of budesonide is approximately 86%.

- **Elimination:** The effective half-life of BD derived via popPK analysis was approximately 5 hours.
  - Metabolism: *In vitro* studies with human liver homogenates have shown that BD is rapidly and extensively metabolized. Two major metabolites formed via CYP3A4 catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6ß-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.
  - Excretion: BD is excreted in urine and feces in the form of metabolites. Only negligible amounts of unchanged BD have been detected in the urine.

Glycopyrronium:

- **Mechanism of action:** GP is a long-acting anti-muscarinic/cholinergic agent with similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation.

- **Absorption:** Following inhaled administration of BGF MDI 320/18/9.6 µg in patients with COPD, C_{max} of glycopyrronium occurred at 6 minutes post-dose. Steady state is achieved after approximately 3 days of repeated dosing and the AUC_{0-12} at steady state is approximately 1.8 times higher than after the first dose.

- **Distribution:** The estimated glycopyrronium apparent volume of distribution at steady-state in patients with COPD is approximately 5500 L via popPK analysis. Over the concentration range of 2-500 nmol/L, plasma protein binding of glycopyrronium ranged from 43% to 54%.

- **Elimination:** The effective terminal elimination half-life of glycopyrronium derived via popPK analysis was approximately 15 hours.
  - Metabolism: Based on literature, and an *in vitro* human hepatocyte studies, metabolism plays a minor role in the overall elimination of glycopyrronium. CYP2D6 was found to be the predominant enzyme involved in the metabolism of GP.

- Excretion: After IV administration of a 0.2 mg radiolabeled glycopyrronium, 85% of dose recovered was recovered in urine 48 hours post-dose and some of radioactivity was also recovered in bile.

Formoterol:

- **Mechanism of action:** Formoterol is a long-acting selective beta2-adrenergic agonist (beta2-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 beta2-receptors than at beta1- receptors.

- **Absorption:** Following inhaled administration of BGF MDI 320/18/9.6 µg in patients with COPD, C_{max} of formoterol occurred within 20 to 60 minutes. Steady state is achieved after approximately 2 days of repeated dosing and the AUC_{0-12} at steady state is approximately 1.4 times higher than after the first dose.

- **Distribution:** The estimated formoterol apparent volume of distribution at steady-state in patients with COPD is approximately 2400 L via popPK analysis. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%.

- **Elimination:** The effective terminal elimination half-life derived via popPK analysis was approximately 10 hours.
  - Metabolism: The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6, CYP2C19, CYP2C9 and CYP2A6 have been identified as being primarily responsible for O-demethylation.
  - Excretion: The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In the study, 62% of the drug related radioactivity of formoterol was excreted in the urine while 24% was eliminated in the feces.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Evaluation of PK interaction between BD, glycopyrronium, and formoterol

The PK drug-drug interaction potential between glycopyrronium and formoterol in an inhalation aerosol was reviewed previously under NDA 208294 by Dr. Sheetal Agrawal archived

March 14, 2016. The clinical pharmacology reviewer concluded that there was no drug-drug PK interaction between glycopyrronium and formoterol.

In this NDA, the reviewer will focus on the evaluation of drug-drug PK interaction potential between BD and glycopyrronium/formoterol.

Effect of BD on Glycopyrronium Systemic Exposure

The effect of BD on glycopyrronium systemic exposure was evaluated in Study PT010001 in healthy subjects following single dose inhalation and in Trial 06 in patients with COPD following BID chronic treatment. Glycopyrronium systemic exposure was compared between BGF MDI 320/18/9.6 µg and the approved GFF MDI 18/9.6 µg (NDA 208294, Bevespi Aerosphere). Glycopyrronium systemic exposure is generally comparable between BGF MDI 320/18/9.6 µg and Bevespi Aerosphere both in healthy subjects following single dose inhalation and in patients with COPD following BID chronic treatment (Table 31). Therefore, BD is unlikely to affect glycopyrronium systemic exposure when the two drugs are co-administered.

Table 31. Comparison of Glycopyrronium PK Parameters [Geometric Mean (CV%, N)] between BGF MDI and GFF MDI

			Treatment	
Study	**Dose/Population**	**PK Parameter**	**BGF MDI 320/18/9.6 µg**	**GFF MDI 18/9.6 µg**
PT010001	Single dose in healthy subjects	AUC_{0-12} (h•pg/mL)	11.9 (189%, 81)	10.2 (211%, 78)
		AUC_{0-t} (h•pg/mL)	9.1 (215%, 81)	7.8 (221%, 78)
		C_{max} (pg/mL)	8.7 (126%, 81)	7.0 (147%, 78)
		T_{max} (hour)*	0.1	0.1
PT010006	BID for 24 weeks in patients with moderate-to-severe COPD	AUC_{0-12} (h•pg/mL)	74.0 (69%, 53)	79.3 (84%, 54)
		C_{max} (pg/mL)	17.8 (92%, 74)	19.8 (97%, 61)
		T_{max} (hour)*	0.08	

Abbreviations: AUC_{0-12} = area under the curve from 0 to 12 hours; $AUC_{0-\tau}$ = area under the curve to the last quantifiable time point; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; BGF = budesonide, glycopyrrolate, and formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; MDI = metered dose inhaler; COPD = chronic obstructive pulmonary disease; BID = twice daily; PK = pharmacokinetics; CV = coefficient of variation
* median
Source: adapted from pt010001-clinical-study-report.pdf, page 103, Table 31; and pt010006-clinical-study-report.pdf, page 226, Table 68

Effect of BD on Formoterol Systemic Exposure

The effect of BD on formoterol systemic exposure was evaluated in Study PT010001 in healthy subjects following single dose inhalation and in Trial 06 in patients with COPD following BID chronic treatment. Formoterol systemic exposure was compared between BGF MDI 320/18/9.6 µg and the approved GFF MDI 18/9.6 µg (NDA 208294, Bevespi Aerosphere). The formoterol systemic exposure was generally comparable between BGF MDI 320/18/9.6 µg and Bevespi Aerosphere both in healthy subjects following single dose inhalation and in patients with COPD following BID chronic treatment (Table 32). Therefore, BD is unlikely to affect formoterol systemic exposure when the two drugs are co-administered.

Table 32. Comparison of Formoterol PK Parameters [Geometric Mean (CV%, N)] between BGF MDI and GFF MDI

			Treatment	
Study	Dose/Population	PK Parameter	BGF MDI 320/18/9.6 µg	GFF MDI 18/9.6 µg
PT010001	Single dose in healthy subjects	AUC_{0-12} (h•pg/mL)	55.7 (42%, 81)	49.5 (60%, 78)
		AUC_{0-t} (h•pg/mL)	55.1 (48%, 81)	48.8 (66%, 78)
		C_{max} (pg/mL)	10.8 (52%, 81)	9.2 (69%, 78)
		T_{max} (hour)*	0.333	0.583
PT010006	BID for 24 weeks in patients with moderate-to-severe COPD	AUC_{0-12} (h•pg/mL)	55.1 (57%, 53)	56.2 (53%, 49)
		C_{max} (pg/mL)	8.4 (70%, 74)	10.5 (80%, 61)
		T_{max} (hour)*	0.96	0.92

Abbreviations: AUC_{0-12} = area under the curve from 0 to 12 hours; AUC_{0-T} = area under the curve to the last quantifiable time point; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; BGF = budesonide, glycopyrrolate, and formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; MDI = metered dose inhaler; COPD = chronic obstructive pulmonary disease; BID = twice daily; PK = pharmacokinetics; CV = coefficient of variation
* median
Source: adapted from pt010001-clinical-study-report.pdf, page 108, Table 34; and pt010006-clinical-study-report.pdf, page 223, Table 66

Effect of Formoterol on BD Systemic Exposure

The effect of formoterol on BD systemic exposure was evaluated in Study PT009001 in patients with COPD following BID chronic treatment. BD systemic exposure was compared between BFF MDI 320/9.6 µg and BD MDI 320 µg. BD systemic exposure was generally comparable between BFF MDI 320/9.6 µg and BD MDI 320 µg in patients with COPD following BID chronic treatment (Table 33). Therefore, formoterol is unlikely to affect BD systemic exposure when the two drugs are co-administered.

Table 33. Comparison of BD PK Parameters [Geometric Mean (CV%, N)] Between BFF MDI and BD MDI

			Treatment	
Study	Dose/Population	PK Parameter	BFF MDI 320/9.6 µg	BD MDI 320 µg
PT009001	BID for 29 days in patients with moderate-to-severe COPD	AUC_{0-12} (h•pg/mL)	2705 (45%, 62)	2685 (48%, 44)
		C_{max} (pg/mL)	722 (50%, 62)	658 (51%, 45)
		T_{max} (hour)*	0.67	0.67

Abbreviations: AUC_{0-12} = area under the curve from 0 to 12 hours; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; MDI = metered dose inhaler; COPD = chronic obstructive pulmonary disease; BID = twice daily; BD = budesonide; BFF = budesonide and formoterol fumarate; PK = pharmacokinetics; CV = coefficient of variation
* median
Source: adapted from pt009001-clinical-study-report.pdf, page 129, Table 31

Effect of Glycopyrronium on BD Systemic Exposure

Since formoterol does not affect BD systemic exposure when the two drugs are co-administered, the effect of glycopyrronium on BD systemic exposure was evaluated in the presence of formoterol. The effect of glycopyrronium on BD systemic exposure was evaluated in Study PT010002 in healthy subjects following single dose inhalation and in Trial 06 in patients with COPD following BID chronic treatment. BD systemic exposure was compared between BGF MDI 320/18/9.6 µg and BFF MDI 320/9.6 µg. The BD systemic exposure was generally

comparable between GFF MDI 320/18/9.6 µg and BFF MDI 320/9.6 µg in patients with COPD following BID chronic treatment (Table 34). Therefore, glycopyrronium is unlikely to affect BD systemic exposure when two components are co-administered.

Table 34. Comparison of BD PK Parameters [Geometric Mean (CV%, N)] Between BGF MDI and BFF MDI

			Treatment	
Study	**Dose/Population**	**PK Parameter**	**BGF MDI 320/18/9.6 µg**	**BFF MDI 320/9.6 µg**
PT010002	Single dose in healthy subjects	AUC_{0-12} (h•pg/mL)	1598 (50%, 64)	1657 (50%, 65)
		AUC_{0-inf} (h•pg/mL)	1734 (48%, 64)	1778 (50%, 64)
		C_{max} (pg/mL)	422 (81%, 64)	431 (68%, 65)
		T_{max} (hour)*	0.33	0.67
PT010006	BID for 24 weeks in patients with moderate-to-severe COPD	AUC_{0-12} (h•pg/mL)	2551 (70%, 65)	2583 (56%, 35)
		C_{max} (pg/mL)	631 (80%, 75)	654 (59%, 39)
		T_{max} (hour)*	0.37	0.97

Abbreviations: AUC_{0-12} = area under the curve from 0 to 12 hours; AUC_{0-inf} = area under the curve from zero to infinity; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; BGF = budesonide, glycopyrrolate, and formoterol fumarate; BFF = budesonide and formoterol fumarate; MDI = metered dose inhaler; COPD = chronic obstructive pulmonary disease; BID = twice daily; PK = pharmacokinetics; CV = coefficient of variation
* median
Source: adapted from pt010002-clinical-study-report.pdf, page 64, Table 18; and pt010006-clinical-study-report.pdf, page 219, Table 64

Evaluation of BD Phase 2 Dose-Ranging Studies

Two BD dose-ranging Phase 2 studies were conducted prior to Phase 3 studies.

Study PT008001

Study PT008001 was a randomized, double-blind, chronic dosing (4 weeks), 4-period, 5-treatment (BD MDI 40 µg, BD MDI 80 µg, BD MDI 160 µg, BD MDI 320 µg, and placebo MDI BID regimen), incomplete block, cross-over, multi-center study in adult subjects with mild-to-moderate persistent asthma. In total 147 subjects were randomized and 97 subjects (66%) completed the study. The primary endpoint of the study was the change from baseline in morning pre-dose trough FEV1 between BD MDI treatments and placebo MDI at the end of the Treatment Period (i.e., Week 4). The PD/efficacy result of the primary endpoint is displayed in Table 35.

Table 35. Change from Baseline in Morning Pre-Dose Trough FEV1 at the End of the Treatment Period from Study PT008001 (mITT Population)

	BD MDI 320 µg (N=112)	BD MDI 160 µg (N=118)	BD MDI 80 µg (N=57)	BD MDI 40 µg (N=58)	Placebo MDI (N=118)
Change from baseline in morning pre-dose trough FEV_1 (L)					
n	109	109	56	56	111
LS mean (SE)	-0.002 (0.0175)	-0.001 (0.0174)	-0.034 (0.0242)	-0.031 (0.0242)	-0.116 (0.0173)
95% CI	-0.036, 0.033	-0.035, 0.033	-0.081, 0.014	-0.079, 0.016	-0.150, -0.082
Difference versus Placebo MDI (L)					
LS mean (SE)	0.114 (0.0229)	0.115 (0.0229)	0.083 (0.0285)	0.085 (0.0284)	NA
95% CI	0.069, 0.160	0.070, 0.161	0.027, 0.139	0.029, 0.141	
P-value	<0.0001	<0.0001	0.0039	0.0029	

Abbreviations: BD =budesonide; MDI = metered dose inhaler; CI = confidence interval; NA = not applicable; mITT = modified intent to treat; FEV_1 = forced expiratory volume in 1 second; LS = least square; SE = standard error; P-value = probability value
LS means are for the linear mixed model, which included the following covariates: treatment, baseline, and period
The Reviewer's analysis obtained similar results. The Reviewer did not identify treatment period and trough FEV1 baseline as significant covariates for the linear mixed model.
Source: pt008001-clinical-study-report.pdf, page 84, Table 7-1

All BD MDI treatment arms were statistically superior ($p<0.05$) to placebo MDI for the primary endpoint (the mean change from baseline in morning pre-dose trough FEV_1) at the end of the Treatment Period in mITT population. Compared to placebo, the trough FEV_1 at the end of the Treatment Period was about 115 mL higher following BD MDI 320 µg and 160 µg, and about 84 mL higher following BD MDI 80 µg and 40 µg. In addition, the two higher dose treatment arms of BD MDIs (320 µg and 160 µg) were about 30 mL higher than two lower dose treatment arms of BD MDIs 80 µg and 40 µg on trough FEV_1.

Study PT009001

Additional BD dose-ranging was explored in patients with COPD in the background therapy of FF. Study PT009001 was a randomized, double-blind, chronic dosing (28 days), four-period, five-treatment, incomplete block, multicenter, crossover study to assess the efficacy and safety following BFF MDI 320/9.6, 160/9.6, and 80/9.6 µg, BD MDI 320 µg, and FF MDI 9.6 µg BID treatment in patients with moderate-to-severe COPD. In total 180 subjects were randomized and 133 (74%) completed the study. The primary endpoint was FEV1 AUC_{0-12} on Day 29. The PD/efficacy result of the primary endpoint is displayed in Table 36.

Table 36. Comparisons of FEV1 AUC_{0-12} Change from Baseline on Day 29 between BFF MDIs, BD MDI, and FF MDI from Study PT009001 (mITT Population)

Treatment[a]	FEV_1 AUC_{0-12}	LS Mean Differences Between Treatments (L)			
		BD MDI 320µg	FF MDI 9.6µg	BFF MDI 160/ 9.6µg	BFF MDI 80/ 9.6µg
BFF MDI 320/ 9.6 µg					
LS Mean (SE), L	0.231 (0.0174)	0.221 (0.0195)	0.056 (0.0172)	0.034 (0.0195)	0.027 (0.0197)
95% CI	0.197, 0.266	0.182, 0.259	0.022, 0.090	-0.004, 0.073	-0.012, 0.065
P value	NA	<0.0001	0.0013	0.0779	0.1742
BFF MDI 160/ 9.6 µg					
LS Mean (SE), L	0.197 (0.0198)	0.186 (0.0221)	0.021 (0.0198)	NA	-0.008 (0.0222)[b]
95% CI	0.158, 0.236	0.143, 0.230	-0.018, 0.060	NA	-0.051, 0.036[b]
P value	NA	<0.0001	0.2827	NA	0.7290[b]
BFF MDI 80/ 9.6 µg					
LS Mean (SE), L	0.205 (0.0200)	0.194 (0.0222)	0.029 (0.0198)	Shown above[b]	NA
95% CI	0.165, 0.244	0.150, 0.237	-0.010, 0.068	Shown above[b]	NA
P value	NA	<0.0001	0.1436	Shown above[b]	NA

Abbreviations: AUC_{0-12} = area under the curve from 0 to 12 hours; BD = budesonide; BFF = budesonide and formoterol fumarate; FF = formoterol fumarate; MDI = metered dose inhaler; CI = confidence interval; NA = not applicable; FEV_1 = forced expiratory volume in 1 second; LS = least square; SE = standard error; P-value = probability value
[a.] LS mean changes for BD MDI 320 µg and FF MDI 9.6 µg are not presented here
[b.] The LS mean difference, CI of the mean difference, and the p-value for the comparison of BFF MDI 160/9.6 µg vs. BFF 80/9.6 µg are as shown above in the BFF MDI 160/9.6 µg vs. BFF 80/9.6 µg comparison.
LS means are for the linear mixed model, which included the following covariates: treatment, baseline, percent reversibility to Ventolin HFA, and period.
The Reviewer's analysis obtained similar results. The Reviewer identified Treatment Periods and percent reversibility to Ventolin HFA as a significant covariate for the linear mixed model.
Source: pt009001-clinical-study-report.pdf, page 107, Table 24The Reviewer's analysis obtained similar results.

All BFF MDI treatment arms were statistically superior ($p<0.05$) to BD MDI 320 µg as measured by the primary endpoint, the mean change from baseline in FEV1 AUC_{0-12} on Day 29 in mITT population. Change from baseline in FEV1 AUC_{0-12} of BFF MDI 320/9.6 µg at the end of the Treatment Period (Day 29) was numerically higher (~ 30 mL) than two lower dose treatment arms of BFF MDIs (160/9.6 µg and 80/9.6 µg).

Studies PT008001 and PT009001 demonstrated a numerically higher (~30 mL) improvement in lung function with the HD of BD MDI (320 µg) compared to the lower doses on both trough FEV1 change from baseline in asthma patients and FEV1 AUC_{0-12} change from baseline in COPD patients. Therefore, the Applicant's decision to carry the two HDs (320 and 160 µg) of BD for Phase 3 drug development appears reasonable.

Evaluation of Combination of BD With GP and/or FF in Patients with COPD (Study PT009001)

Clinical studies evaluating the combination of BD with GP and/or FF MDIs under NDA 212122 are listed in Table 37. Among the 5 clinical studies, only one Phase 2 clinical study PT009001 was submitted under Clinical Pharmacology section. For review of results from other studies, refer to Section 8 Statistical and Clinical and Evaluation.

Table 37. Clinical Studies Evaluating Combination of BD With GP and/or FF

Comparison	MDIs	Clinical Studies
Dual components vs. single component	BFF, BD, and FF	PT009001 and PT009002
	BFF and FF	PT009003
Triple components vs. dual components	BGF, GFF, and BFF	PT010005 and PT010006

Abbreviations: MDI = metered dose inhaler; BD = budesonide; BFF = budesonide and formoterol fumarate; FF = formoterol fumarate; GFF = glycopyrrolate and formoterol fumarate; BGF = budesonide, glycopyrrolate, and formoterol
Source: reviewer's summary

To comply with the combination rule (21 CFR 300.50), ideally the two dual-component products of BFF MDI and BGP MDI should be evaluated against mono-component products (i.e., BD, FF, and GP MDIs) during the drug development of the proposed triple-component product, BGF MDI. However, due to the lack of clinical need for developing a stand-alone ICS/LAMA combination product (i.e., BGP MDI) for treatment of COPD, the Applicant's approach to compare BFF MDI (ICS/LABA) vs. BD (ICS) and FF (LABA) MDIs at dual-component stage is reasonable, even though the BFF MDI was co-developed with the BGF MDI concurrently.

Study PT009001 was a randomized, double-blind, chronic dosing (28 days), four-period, five-treatment, incomplete block, multi-center, crossover study to assess the efficacy and safety of BFF MDI 320/9.6, 160/9.6, and 80/9.6 µg, BD MDI 320 µg, and FF MDI 9.6 µg BID in patients with moderate-to-severe COPD. In total, 180 subjects were randomized with 133 (74%) completing the study. The primary endpoint was FEV_1 area under the curve from 0 to 12 hours (AUC_{0-12}) on Day 29 post-treatment. The PD/efficacy result of the primary endpoint is displayed in Table 36.

All BFF MDI treatment arms were statistically superior ($p<0.05$) to BD MDI 320 µg as measured by the primary endpoint, the mean change from baseline in FEV_1 AUC_{0-12} on Day 29 in mITT population. FEV_1 AUC_{0-12} at the end of the Treatment Period was about 200 mL higher following treatment with all BFF MDIs (with different BD dosing levels) compared to BD MDI 320 µg. This 200 mL improvement is considered clinically meaningful. In addition, in an un-prespecified analysis, BFF MDI 320/9.6 µg was also statistically superior to FF MDI 9.6 µg on the change from baseline in FEV_1 AUC_{0-12} on Day 29 post-treatment. The improvement of mean change from baseline in FEV_1 AUC_{0-12} was 56 mL.

Therefore, PD results from Study 009001 support the combination use of BD with FF as a dual-component product (BFF MDI) in patients with moderate-to-severe COPD. For comparison of triple component product BGF MDI vs. dual-component products BFF MDI and GFF MDI, refer to Section 8 statistical and clinical evaluation.

6.2.2.2. Therapeutic Individualization

Drug Interactions

BD is a substrate of CYP3A4 enzyme. In line with the approved NDA 021929 Symbicort®, Breztri Aerosphere should be used **with caution** when co-administered with strong cytochrome P450 3A4 inhibitors (e.g. ritonavir).

Formoterol is a beta-adrenergic receptor agonist. In line with the approved NDA 208294 Bevespi Aerosphere® (GFF MDI), Brezti Aerosphere should be used **with caution** when co-administered with:

- other adrenergic drugs
- non-potassium sparing diuretics, xanthine derivatives or steroids which may potentiate hypokalemia or ECG changes.
- monoamine oxidase inhibitors and tricyclic antidepressants which may potentiate effect of formoterol fumarate on cardiovascular system.
- beta-blockers which may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.

GP is a cholinergic receptor antagonist. In line with the approved NDA 208294 Bevespi Aerosphere® (GFF MDI), the concomitant use of Breztri Aerosphere should be **avoided** with other anticholinergics which may interact additively.

Specific Population

Hepatic impairment: BD and formoterol are primarily eliminated via hepatic metabolism. Although dedicated hepatic impairment studies for Breztri Aerosphere® were not conducted in the clinical development program, an increased exposure can be expected in patients with severe liver hepatic impairment. In line with the approved NDA 021929 Symbicort®, patients with severe hepatic impairment should be **monitored for signs** of increased drug exposure.

Renal impairment: Glycopyrronium is primarily eliminated via renal excretion. Although dedicated renal impairment study for Breztri Aerosphere was not conducted in the clinical development program, popPK simulation results indicate that the systemic exposure (AUC_{0-12}) of glycopyrronium in COPD patients with moderate renal impairment (eGFR of 45 mL/min) increases by approximately 68% compared to COPD patients with normal renal function (eGFR of >90 mL/min). In line with the approved NDA 208294 Bevespi Aerosphere®, the use of Breztri Aerosphere in patients with severe renal impairment should be considered **if the potential benefit of the treatment outweighs the risk**.

6.2.3. Evaluation of the Effect of BGF MDI on the HPA axis

In lieu of a dedicated HPA axis trial, the Applicant supported the effect of BD in BGF 320/18/9.6 µg MDI on the HPA axis function through comparative systemic exposure (PK) comparison in

healthy subjects (Study PT010001) and pharmacodynamic assessment in patients with COPD (Trial 06).

The systemic exposure of BD was compared between BGF MDI µg and approved NDA 021929 Symbicort MDI (BD and FF inhalation aerosol) following single-dose administration in healthy subjects in Study PT010001.

Study PT010001 was a Phase 1, single-dose, randomized, double-blind within device, 4-period, 12-sequence, 6-treatment, crossover study in healthy subjects. Eighty-four subjects were randomized and 76 completed the study. The geometric mean of BD PK parameters following single-dose inhalation of BGF MDI 320/18/9.6 µg, 160/18/9.6 µg, Symbicort MDI 320/9 µg, and Symbicort MDI 160/9 µg are listed in Table 38.

Table 38. Comparison of BD PK Parameters [Geometric Mean (CV%, N)] Between BGF MDIs and Symbicort MDIs From Study PT010001

	BD 320 µg		BD 160 µg	
PK Parameter	BGF MDI 320/18/9.6 µg	Symbicort MDI 320/9 µg	BGF MDI 160/18/9.6 µg	Symbicort MDI 160/9 µg
AUC_{0-12} (h•pg/mL)	1661 (44%, 81)	1410 (52%, 79)	883 (46%, 27)	845 (40%, 28)
AUC_{0-t} (h•pg/mL)	1661 (44%, 81)	1410 (52%, 79)	883 (46%, 26)	845 (40%, 28)
C_{max} (pg/mL)	484 (67%, 81)	462 (92%, 79)	248 (58%, 27)	268 (59%, 28)
T_{max} (hour)*	0.367	0.333	0.333	0.333

Abbreviations: AUC_{0-12} = area under the curve from 0 to 12 hours; AUC_{0-T} = area under the curve to the last quantifiable time point; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; MDI = metered dose inhaler; BD = budesonide; BGF = budesonide, glycopyrrolate, and formoterol; PK = pharmacokinetics; CV = coefficient of variation
Source: adapted from pt01001-clinical-study-report.pdf, page 95, Table 25

The systemic exposure of BD was generally comparable between BGF MDI µg and Symbicort MDI. A bioequivalence analysis demonstrates that the 90% CI of geometric mean ratio of systemic exposure of BD (AUC_{0-12}, AUC_{0-t}, and C_{max}) between BGF MDI 320/18/9.6 µg and Symbicort MDI 320/9 µg were within 0.8 to 1.25.

Table 39. Statistical Comparison of BD PK Parameters Between BGF MDI 320/18/9.6 µg and Symbicort MDI 320/9 µg (Safety Population)

Comparison/ PK Parameter	Geometric LSM		Geometric LSM Ratio (%)	Ratio of 90% CI [a]
	BGF MDI	Symbicort MDI		
BGF MDI 320/14.4/9.6 µg vs. Symbicort 320/9 µg,				
N	79	77	-	-
AUC_{0-12} (h*pg/mL)	1612.21	1406.39	114.63	106.13, 123.82
AUC_{0-t} (h*pg/mL)	1611.68	1406.65	114.58	106.05, 123.79
C_{max} (pg/mL)	472.04	461.47	102.29	91.45, 114.42

Abbreviations: AUC_{0-12} = area under the curve from 0 to 12 hours; AUC_{0-T} = area under the curve to the last quantifiable time point; C_{max} = maximum plasma concentration; MDI = metered dose inhaler; BD = budesonide; BGF = budesonide, glycopyrrolate, and formoterol; CI = confidence interval; PK = pharmacokinetics; LSM = least square mean
Source: pt01001-clinical-study-report.pdf, page 97, Table 26

The effect of BD on change in 0-24 hr serum cortisol was evaluated in COPD patients in Trial 06.

Trial 06 was a Phase 3, randomized, double-blind, parallel-group, 24-week, active-controlled study to assess the efficacy and safety following BID treatment of BGF MDI, GFF MDI, BFF MDI, compared with Symbicort TBH as an active control in subjects with moderate-to-severe COPD. Approximately 1800 patients were randomized in a 2:2:1:1 scheme. HPA function was assessed in a subset of subjects in the PK sub-study. Serum cortisol was measured in approximately 108 randomized subjects over 24 hours, between Visits 3 and 4 prior to dosing at Randomization and at Visit 10a (Week 24). Serum cortisol samples were collected within 30 minutes prior to dosing, and 1, 2, 4, 8, 10, 12, 14, 16, 20, 22, and 24 hours post-dose. The geometric mean of 0-24 hr weighted mean serum cortisol at baseline and Week 24 following BID treatment of 4 products are listed in Table 40.

The geometric mean ratio (Week 24/baseline) of 0-24hr weighted mean serum cortisol were the same between GFF MDI [0.94 (CV =37%)] and Symbicort TBH [0.94 (CV =29%)], showing a small numerical reduction of mean serum cortisol from the baseline. There was an additional small numerical reduction of geometric mean ratio of serum cortisol following BGF MDI [0.86 (CV =39%)].

Table 40. Geometric Mean and Ratio of 0-24 Hr Weighted Mean Serum Cortisol at Baseline and Week 24 [HPA Sub-Study Population in Trial 06

Visit Statistic	BGF MDI 320/14.4/9.6 µg (N=56)	GFF MDI 14.4/9.6 µg (N=53)	BFF MDI 320/9.6 µg (N=28)	Symbicort TBH 400/12 µg (N=31)	Model-estimated between-treatment ratio	90% CI [a]
n	44	33	19	17		
Baseline (nmol/L)						
Mean (SD) [b]	189.19 (59.22)	187.95 (54.98)	211.83 (52.37)	182.08 (49.11)		
Median	193.77	181.17	210.54	167.42		
Min, Max	58.50, 309.58	124.79, 404.67	108.62, 300.73	128.69, 293.50		
Geometric Mean (CV%)	178.54 (37.9)	181.61 (26.1)	205.11 (27.5)	176.27 (26.4)		
Week 24 Actual Value (nmol/L)						
Mean (SD)	162.87 (52.91)	179.75 (55.06)	157.55 (52.79)	173.98 (65.97)		
Median	164.68	176.50	147.60	163.75		
Min, Max	55.00, 313.42	55.00, 342.63	63.10, 257.58	104.71, 398.90		
Geometric Mean (CV%)	153.68 (37.4)	171.54 (33.1)	149.18 (35.7)	165.64 (31.0)		
Ratio to Baseline						
Mean (SD)	0.93 (0.46)	1.00 (0.35)	0.76 (0.20)	0.98 (0.30)	(BGF MDI vs GFF MDI): 0.90	(0.80, 1.02)
Median	0.83	0.96	0.72	0.95	(BGF MDI vs BFF MDI): 1.11	(0.96, 1.27)
Min, Max	0.41, 3.31	0.42, 2.23	0.27, 1.19	0.60, 1.75	(BFF MDI vs Symbicort TBH): 0.82	(0.69, 0.98)
Geometric Mean (CV%)	0.86 (38.8)	0.94 (36.6)	0.73 (31.0)	0.94 (29.4)		

Abbreviations: MDI = metered dose inhaler; BFF = budesonide and formoterol fumarate; GFF = glycopyrrolate and formoterol fumarate; BGF = budesonide, glycopyrrolate, and formoterol; CI = confidence interval; SD = standard deviation; CV = coefficient of variation; HPA = hypothalamic-pituitary-adrenal
[a] 90% CI of the ratio was based on the ANCOVA model for log-transformed data, which included log-transformed baseline value, gender, age, and treatment groups as covariates
[b] the weighted mean at baseline was computed using all of the available baseline time points over a 24-hour period between Visits 3 and 4.
The Reviewer's analysis obtained similar results. The Reviewer identified baseline cortisol concentration as a significant covariate.
Source: pt010006-clinical-study-report.pdf, page 269, Table 89

In summary, the systemic exposure of BD was generally comparable between BGF MDI µg and Symbicort MDI. There was a slight numerical reduction of 0-24hr weighted mean serum cortisol ratio (Week 24/baseline) following BGF MDI 320/18/9.6 µg BID treatment compared to GFF MDI 18/9.6 µg BID treatment in COPD patients. The clinical meaning of this small reduction is unclear.

6.2.4. Outstanding Issues

There was no clinical pharmacology-related outstanding issue for this submission.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 41. Summary of Clinical Pharmacology and Pharmacokinetics of BD

Pharmacology Review Issues	Recommendations and Comments
Mechanism of Action	BD is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.
Active Moieties	BD is the active moiety
QT Prolongation	A TQT study was not performed with Breztri Aerosphere as budesonide is not known to affect the QT interval.
General Information	
Bioanalysis	BD plasma concentration was measured using validated liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS).
Healthy Volunteers vs. Patients with COPD	BD systemic exposure was generally higher in patients with COPD compared to healthy subjects following single dose inhalation of BGF 320/18/9.6 µg. The geometric mean AUC_{0-12} was 1660, 1598, 1748, and 2165 pg•h/mL in healthy subjects from Study PT010001 (86% subjects were Black), Study PT010002 (86% subjects were Black), Study PT010010 (Chinese), and Study PT010003 (Japanese), respectively. The geometric mean AUC_{0-12} was 2407 pg•h/mL in patients with COPD from Study PT010018 (97% were White). The geometric mean C_{max} values showed the same pattern.
Drug exposure at steady-state following the therapeutic dosing regimen	Study PT010018 demonstrated that the steady-state for C_{max} of BD was reached following single-dose administration. The steady state of C_{trough} was reached no later than Day 7 post-dose following BID dosing.
Minimal effective dose or exposure	A Phase 2 dose-ranging Study PT008001 of BD MDI in patients with asthma demonstrated that the two lower doses of BD (40 and 80 µg) were only marginally superior to placebo for the primary PD endpoint (i.e., change from baseline in trough FEV1 on Day 29), whereas the two higher doses of BD (160 and 320 µg) showed a statistically significant and clinically meaningful increase in trough FEV1 compared to placebo.
Maximal tolerated dose or exposure	320 µg is the highest dose of BD investigated under this NDA
Dose Linearity	Study PT010001 and Study PT009001 demonstrated linear PK of budesonide from 80 µg to 320 µg in healthy subjects and patients with COPD, respectively.
Accumulation	Multiple-dose Study PT010018 demonstrated that there was no accumulation of C_{max} for BD following 7-day BID treatment of BGF 320/18/9.6 µg in patients with COPD. The accumulation ratio of AUC_{0-12} was approximately 1.3 on Day 8.

Pharmacology Review Issues	Recommendations and Comments
PK Variability	The inter-subject variability (CV%) of BD C_{max} from different studies ranged from 26% to 81% by non-compartment analysis. The inter-subject variability (CV%) of BD AUC_{0-12} ranged from 26% to 50% by non-compartment analysis. The variability is similar between healthy subjects and patients with COPD except low variability in Japanese population (26%).
Absorption	
Bioavailability	The absolute bioavailability of BD following oral inhalation of BGF MDI was not evaluated in this NDA. Study PT010011 demonstrated that following single dose inhalation of BGF MDI 320/36/9.6 µg, BD mean AUC increased by 36% with a spacer compared to without a spacer in healthy subjects. In addition, BD mean AUC decreased by 39% when administered concurrently with ingestion of charcoal compared to without ingestion of charcoal. This indicates that 40% of the systemic exposure of BD may be due to absorption from the GI tract.
t_{max}	Median t_{max} of BD ranged from 20 minutes to 40 minutes from Studies PT010018 and PT010006 following single dose or multiple dose inhalation of BGF MDI 320/18/9.6 µg in patients with COPD.
Distribution	
Volume of Distribution	The estimated BD apparent volume of distribution at steady-state in COPD patients is approximately 1200 L via popPK analysis.
Plasma protein binding	Over the concentration range of 1-100 nmol/L, plasma protein binding of budesonide is approximately 86%.
Blood to-plasma ratio	The blood-to-plasma ratio of BD was not evaluated in this NDA
Substrate transporter systems [in vitro]	Information not available.
Elimination	
Mean Terminal Elimination half-life	The effective half-life of BD derived via popPK analysis was approximately 5 hours.
Metabolism	
Primary metabolic pathway(s) [*in vitro*]	*In vitro* studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via CYP3A4 catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6ß-hydroxybudesonide. The corticosteroid activity of the two BD metabolites was less than 1% of that of BD.
Inhibitor/Inducer	Information not available.
Excretion	
Primary excretion pathway	BD is excreted in urine and feces in the form of metabolites. Only negligible amounts of unchanged BD have been detected in the urine.

Abbreviations: BD = budesonide; COPD = chronic obstructive pulmonary disease; AUC_{0-12} = area under the curve from 0 to 12 hours; MDI = metered dose inhaler; LC = liquid chromatography; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; BGF = budesonide/glycopyrrolate/formoterol fumarate; BID = twice daily; NDA = new drug application; PK = pharmacokinetics; popPK = population pharmacokinetic; CV = coefficient of variation

Table 42. Summary of Clinical Pharmacology and Pharmacokinetics of Glycopyrronium

Pharmacology Review Issues	Recommendations and Comments
Mechanism of Action	GP is a long-acting anti-muscarinic/cholinergic 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 the M3 receptor at the smooth muscle leading to bronchodilation.
Active Moieties	Glycopyrronium, the cation of GP, is the active moiety responsible for the anticholinergic activity.
QT Prolongation	From the approved label of NDA 208294 Bevespi Aerosphere, "The potential for QTc interval prolongation was assessed in a double-blind, single-dose, placebo-and positive-controlled crossover trial in 69 healthy subjects. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected QTcI for 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms."
General Information	
Bioanalysis	Glycopyrronium plasma concentration was measured using validated liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS).
Healthy Volunteers vs. Patients with COPD	Glycopyrronium systemic exposure was generally higher in patients with COPD compared to healthy subjects following single dose inhalation of BGF 320/36/9.6 µg. The geometric mean AUC_{0-12} was 11.9, 19.7, 29.4, and 29.5 pg•h/mL in healthy subjects from Study PT010001 (86% subjects were Black), Study PT010002 (86% subjects were Black), Study PT010010 (Chinese), and Study PT010003 (Japanese), respectively. The geometric mean AUC_{0-12} was 42.5 pg•h/mL in patients with COPD from Study PT010018 (97% were White). The geometric mean C_{max} is also higher in patients with COPD compared to healthy subjects.
Drug exposure at steady-state following the therapeutic dosing regimen	Study PT010018 demonstrated that the steady state of C_{max} for glycopyrronium was reached following single dose administration. The steady state of C_{trough} was reached no later than Day 7.
Minimal effective dose or exposure	The dose selection of GP under this NDA is based on dose-ranging results from NDA 208294 Bevespi Aerosphere. For details, refer to Clinical Pharmacology Review by Dr. Sheetal Agarwal archived March 14, 2016.
Maximal tolerated dose or exposure	36 µg is the highest dose of GP investigated under this NDA.
Dose Linearity	For evaluation of dose linearity of glycopyrronium, refer to Clinical Pharmacology Review for NDA 208294 by Dr. Sheetal Agarwal archived March 14, 2016.
Accumulation	Multiple-dose Study PT010018 demonstrated that there was little accumulation (~7%) of C_{max} for glycopyrronium following 7-day BID treatment of BGF 320/18/9.6 µg in patients with COPD. The accumulation ratio of AUC_{0-12} was approximately 1.8 on Day 8.
PK Variability	The inter-subject variability (CV%) of glycopyrronium C_{max} from different studies ranged from 45% to 126% by non-compartment analysis. The inter-subject variability (CV%) of glycopyrronium AUC_{0-12} ranged from 28% to 189% by non-compartment analysis. The variability of patients with COPD is within the range of healthy subjects (26%).

Pharmacology Review Issues	Recommendations and Comments
Absorption	
Bioavailability	The absolute bioavailability of glycopyrronium following oral inhalation of BGF MDI was not evaluated in this NDA. Study PT010011 demonstrated that following single dose inhalation of BGF MDI 320/36/9.6 µg, glycopyrronium mean AUC increased by 55% with a spacer compared to without a spacer in healthy subjects. In addition, glycopyrronium mean AUC decreased by 58% when administered concurrently with ingestion of charcoal compared to without ingestion of charcoal. This indicates that 60% of the systemic exposure of glycopyrronium may be due to absorption from the GI tract.
t_{max}	Median t_{max} of glycopyrronium was 6 minutes following multiple dose inhalation of BGF MDI 320/18/9.6 µg in patients with COPD from both Studies PT010018 and PT010006.
Distribution	
Volume of Distribution	The estimated glycopyrronium apparent volume of distribution at steady-state in subjects with COPD is approximately 5500 L via popPK analysis.
Plasma protein binding	Over the concentration range of 2-500 nmol/L, plasma protein binding of GP ranged from 43% to 54%.
Blood-to-plasma ratio	The blood-to-plasma ratio of glycopyrronium was not evaluated in this NDA.
Substrate transporter systems [in vitro]	Information not available.
Elimination	
Mean Terminal Elimination half-life	The effective half-life of glycopyrronium derived via popPK analysis was approximately 15 hours.
Metabolism	
Primary metabolic pathway(s) [*in vitro*]	Based on the literature, and an *in vitro* human hepatocyte study, metabolism plays a minor role in the overall elimination of glycopyrronium. CYP2D6 was found to be the predominant enzyme involved in the metabolism of glycopyrronium.
Inhibitor/Inducer	Information not available.
Excretion	
Primary excretion pathway	After IV administration of a 0.2 mg radiolabeled GP, 85% of the dose was recovered in urine 48 hours post-dose and some of radioactivity was also recovered in bile.

Abbreviations: BD = budesonide; COPD = chronic obstructive pulmonary disease; MDI = metered dose inhaler; GP = glycopyrrolate; BGF = budesonide, glycopyrrolate, and formoterol; NDA = new drug application; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; AUC_{0-12} = area under the curve from 0 to 12 hours; PK = pharmacokinetics; τ_{max} = time to maximum plasma concentration; popPK = population pharmacokinetic; CV = coefficient of variation

Table 43. Summary of Clinical Pharmacology and Pharmacokinetics of Formoterol

Pharmacology Review Issues	Recommendations and Comments
Mechanism of Action	FF is a long-acting selective beta2-adrenergic agonist (beta2-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 beta2-receptors than at beta1- receptors.
Active Moieties	Formoterol, the cation of FF, is the active moiety responsible for the anticholinergic activity.

Pharmacology Review Issues	Recommendations and Comments
QT Prolongation	From the approved label of NDA 208294 Bevespi Aerosphere, "The potential for QTc interval prolongation was assessed in a double-blind, single-dose, placebo-and positive-controlled crossover trial in 69 healthy subjects. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected QTcI for 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms."
General Information	
Bioanalysis	Formoterol plasma concentration was measured using validated liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS).
Healthy Volunteers vs. Patients with COPD	Formoterol systemic exposure is generally lower in patients with COPD compared to healthy subjects following single dose inhalation of BGF 320/36/9.6 µg. The geometric mean AUC_{0-12} was 55.7, 39.2, 47.8, and 56 pg•h/mL in healthy subjects from Study PT010001 (86% subjects were Black), Study PT010002 (86% subjects were Black), Study PT010010 (Chinese), and Study PT010003 (Japanese), respectively. The geometric mean AUC_{0-12} was 32.6 pg•h/mL in patients with COPD from Study PT010018 (97% were White). The geometric mean C_{max} was also lower in patients with COPD compared to healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen	Study PT010018 demonstrated that the steady state of C_{trough} was reached no later than Day 7.
Minimal effective dose or exposure	The dose selection of FF under this NDA is based on dose-ranging studies from NDA 208294 Bevespi Aerosphere. For details, refer to Clinical Pharmacology Review by Dr. Sheetal Agarwal archived March 14, 2016.
Maximal tolerated dose or exposure	9.6 µg is the only formoterol dose investigated under this NDA.
Dose Linearity	For evaluation of dose linearity of formoterol, refer to Clinical Pharmacology Review by Dr. Sheetal Agarwal archived March 14, 2016.
Accumulation	Multiple-dose Study PT010018 demonstrated that there was little accumulation (~16%) of C_{max} for formoterol following 7-day BID treatment of BGF 320/18/9.6 µg in patients with COPD. The accumulation ratio of AUC_{0-12} was approximately 1.4 on Day 8.
PK Variability	The inter-subject variability (CV%) of formoterol C_{max} from different studies ranged from 32% to 58% by non-compartment analysis. The inter-subject variability (CV%) of formoterol AUC_{0-12} ranged from 26% to 46% by non-compartment analysis. The variability of patients with COPD is within the range of healthy subjects (30% for AUC_{0-12} and 48% for C_{max}).

Pharmacology Review Issues	Recommendations and Comments
Absorption	
Bioavailability	The absolute bioavailability of formoterol following oral inhalation of BGF MDI was not evaluated in this NDA. Study PT010011 demonstrated that following single dose inhalation of BGF MDI 320/36/9.6 µg, formoterol mean AUC was comparable with or without a spacer in healthy subjects. In addition, formoterol mean AUC decreased by 77% when administered concurrently with ingestion of charcoal compared to without ingestion of charcoal. This indicates that 77% of the systemic exposure of formoterol may be due to absorption from the GI tract.
t_{max}	Median t_{max} of formoterol ranged from 20 to 60 minutes following inhalation of BGF MDI 320/18/9.6 µg in patients with COPD from both Studies PT010018 and PT010006.
Distribution	
Volume of Distribution	The estimated formoterol apparent volume of distribution at steady-state in subjects with COPD is approximately 2400 L via popPK analysis.
Plasma protein binding	Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%.
Blood-to-plasma ratio	The blood-to-plasma ratio of formoterol was not evaluated in this NDA.
Substrate transporter systems [in vitro]	Information not available.
Elimination	
Mean Terminal Elimination half-life	The effective half-life of formoterol derived via popPK analysis was approximately 10 hours.
Metabolism	
Primary metabolic pathway(s) [*in vitro*]	The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.
Inhibitor/Inducer	Information not available.
Excretion	
Primary excretion pathway	The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the drug related radioactivity of formoterol was excreted in the urine while 24% was eliminated in the feces.

Abbreviations: BD = budesonide; COPD = chronic obstructive pulmonary disease; AUC = area under the curve; MDI = metered dose inhaler; GP = glycopyrrolate; BGF = budesonide, glycopyrrolate, and formoterol; NDA = new drug application; C_{max} = maximum plasma concentration; τ_{max} = time to maximum plasma concentration; AUC_{0-12} = area under the curve from 0 to 12 hours; popPK = population pharmacokinetic; CV = coefficient of variation

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes, the clinical pharmacology information provides supportive evidence of effectiveness of BGF 320/18/9.6 µg from Phase 2 dose-ranging Study PT008001 in subjects with mild-to-moderate persistent asthma and Study PT009001 in subjects with moderate-to-severe COPD.

Study PT008001 was a randomized, double-blind, chronic dosing (4 weeks), 4-period, 5-treatment (BD MDI 40 µg, BD MDI 80 µg, BD MDI 160 µg, BD MDI 320 µg, and placebo MDI), incomplete block, cross-over, multi-center study in adult subjects with mild to moderate persistent asthma. The primary endpoint of the study was the change from baseline in morning pre-dose trough FEV1 between BD MDI treatments and placebo MDI at the end of the Treatment Period (Week 4).

The study results showed that all BD MDIs were statistically superior ($p<0.05$) to placebo MDI as measured by the primary endpoint (the mean change from baseline in morning pre-dose trough FEV1) at the end of the Treatment Period in mITT population (Table 35).

Study PT009001 was a randomized, double-blind, chronic dosing (28 days), 4-period, 5-treatment, incomplete block, multicenter, crossover study to assess the efficacy and safety of BFF MDI 320/9.6, 160/9.6, and 80/9.6 µg, BD MDI 320 µg, and FF MDI 9.6 µg in patients with moderate-to-severe COPD. In total, 180 subjects were randomized and 133 (74%) completed the study. The primary endpoint was FEV1 AUC_{0-12} on Day 29.

The study results showed that all BFF MDIs were statistically superior ($p<0.05$) to BD MDI 320 µg as measured by the primary endpoint, the mean change from baseline in FEV1 AUC_{0-12} on Day 29 in mITT population (Table 36).

For discussion of efficacy from Phase 3 Trial 06, refer to Section 8 statistical and clinical evaluation.

6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication Is Being Sought?

Yes, the proposed dose and dosing regimen is appropriate. The dose-ranging studies for GP and FF were conducted under the clinical development program for Bevespi Aerosphere (NDA 208294; refer to the clinical pharmacology review by Dr. Sheetal Agrawal archived March 14, 2019) for details. The dose of GP and FF in the proposed product is the same as Bevespi Aerosphere. Additionally, there are only minor modifications made to the inhalation device in the proposed product compared to Bevespi Aerosphere. The dose-ranging exploration of BD in the two Phase 2 studies is considered adequate. Additionally, the BID dosing regimen of BD is the approved dosing regimen for NDA 208294 Symbicort®.

Study PT008001 in subjects with mild-to-moderate persistent asthma demonstrated that all doses of BD MDI were statistically superior to Placebo MDI as measured by the primary endpoint, trough FEV1 response at Week 4. The two higher doses of BD MDIs (320 µg and 160 µg) resulted in a clinically meaningful increase in change from baseline in the LS mean change from baseline in trough FEV1 compared to placebo. Additionally, the two higher doses were about 30 mL higher than the two lower doses of BD MDIs (80 µg and 40 µg) on the primary endpoint, change from baseline in morning pre-dose trough FEV1 Table 35.

Study PT009001 in subjects with moderate-to-severe COPD demonstrated that all doses of BFF MDI resulted in a greater improvement in FEV1 AUC_{0-12} response on Day 29 in comparison to BD MDI 320 µg. Improvement over budesonide therapy was 221 mL for BFF MDI 320/9.6 µg, 186 mL for the BFF MDI 160/9.6 µg, and 194 mL for BFF MDI 80/9.6 µg. In addition, BFF MDI 320/9.6 µg resulted in a statistically significant improvement versus FF 9.6 µg (56 mL). (Table 36).

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

Yes, there is management strategy required for subpopulations based on intrinsic factors. The proposed strategies are reasonable.

Patients With Hepatic Impairment

BD and formoterol are primarily eliminated via hepatic metabolism. Although dedicated hepatic impairment studies for Breztri Aerosphere evaluating the effect of hepatic impairment on the PK of BD and formoterol were not conducted, an increased exposure can be expected in patients with severe liver hepatic impairment. In line with the approved NDA 021929 Symbicort®, patients with severe hepatic impairment should be **monitored for signs** of increased drug exposure.

Patients With Renal Impairment

Glycopyrronium is primarily eliminated via renal excretion. Although dedicated renal impairment study for Breztri Aerosphere evaluating the effect of renal impairment on the PK of glycopyrronium was not conducted, popPK simulation results indicate that the systemic exposure (AUC_{0-12}) of glycopyrronium in subjects with COPD with moderate renal impairment (eGFR of 45 mL/min) increased by approximately 68% compared to subjects with COPD with normal renal function (eGFR of >90 mL/min). In line with the approved NDA 208294 Bevespi Aerosphere®, the use of Breztri Aerosphere in patients with severe renal impairment should be considered **if the potential benefit of the treatment outweighs the risk**.

6.3.2.4. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What Is the Appropriate Management Strategy?

Yes, there are clinically relevant drug-drug interactions proposed with appropriate management strategy. Food effect study was not conducted for the proposed product as food is not expected to impact the delivery performance of this inhaled drug product.

BD is a substrate of CYP3A4 enzyme. In line with the approved NDA 021929 Symbicort®, Breztri Aerosphere is recommended to be used **with caution** when co-administered with strong cytochrome P450 3A4 inhibitors (e.g. ritonavir), which may cause systemic corticosteroid effects.

FF is a beta-adrenergic receptor agonist. In line with the approved NDA 208294 Bevespi Aerosphere® (GFF MDI), Breztri Aerosphere is recommended to be used **with caution** when co-administered with:

- other adrenergic drugs
- non-potassium sparing diuretics, xanthine derivatives or steroids which may potentiate hypokalemia or ECG changes.
- monoamine oxidase inhibitors and tricyclic antidepressants which may potentiate effect of formoterol fumarate on cardiovascular system.
- beta-blockers which may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.

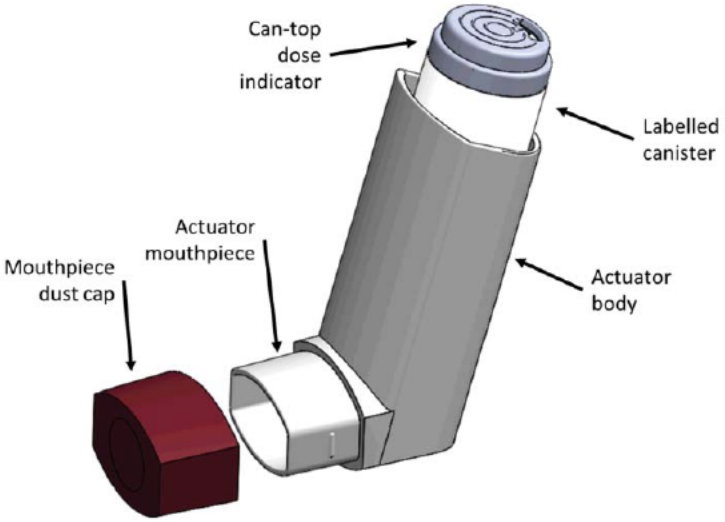
GP is a cholinergic receptor antagonist. In line with the approved NDA 208294 Bevespi Aerosphere® (GFF MDI), the concomitant use of Breztri Aerosphere should be **avoided** with other anticholinergics which may interact additively.

6.3.2.5. Is the To-Be-Marketed Formulation the Same as the Clinical Trial Formulation, and if Not, Are There Bioequivalence Data To Support the To-Be-Marketed Formulation?

Yes, the to-be-marketed BGF MDI formulation is the same as the clinical trial formulation.

BD, GP, and FF inhalation aerosol is an FDC product. The formulation, a white suspension, is contained within a (b) (4) aluminum can fitted with a metering valve, a white plastic actuator, a grey plastic dust cap, and a can-top dose indicator. The product is foil overwrapped with desiccant. A diagram of the BGF MDI product is shown in Figure 2.

Figure 2.Diagram of the BGF MDI Product (for Representative Purposes Only)



Abbreviations: BGF = budesonide, glycopyrrolate, and formoterol; MDI = metered dose inhaler
Source: drug-product.pdf, Page 1, Figure 1

BGF MDI 160 is formulated as a suspension formulation with micronized BD, micronized GP, and micronized FF co-suspended with a porous particle excipient, comprised of 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride, in an HFA propellant. The BGF MDI 160 product is formulated to deliver a minimum of (b) (4) actuations per canister. Four priming actuations are performed prior to first use. The composition of BGF MDI is summarized in Table 44.

Table 44. Composition of BGF MDI 160/7.2/4.8 µg Per Actuation

Component	Manufacturing concentration (% w/w)	Quantity per canister[a]/number of inhalations			Metered dose (ex-valve)[b]	Delivered dose (ex-actuator)	Function	Reference to standard
		120	(b) (4)	28				
Budesonide, micronised	(b) (4)			(b) (4)	(b) (4)	160 µg	Active ingredient	USP / AstraZeneca
Glycopyrronium bromide, micronised						7.2 µg[d]	Active ingredient	USP / AstraZeneca
Formoterol fumarate, micronised						4.8 µg	Active ingredient	USP / AstraZeneca
Porous particles								(b) (4)
HFA-134a								

Abbreviations: MDI = metered dose inhaler; BGF = budesonide, glycopyrrolate and formoterol; HFA = hydrofluoroalkane; USP = United States Pharmacopeia

(b) (4)

Source: drug-product.pdf, page 3, Table 1

The BGF MDI formulation remained consistent throughout the clinical development and is the same as the proposed commercial product. Minor formulation adjustments (b) (4)

occurred throughout the development program as manufacturing and device overages were better understood.

The comparison of to-be-marketed Aerosphere inhalation device and the Aerosphere device under approved NDA 208294 is listed in Table 45. Both devices were used in the Phase 3 Trial 06.

Table 45. Container Closure Comparison of the To-Be-Marketed BGF MDI and the Approved NDA 208294 Product

Component	NDA 208294 product	BGF MDI
Can	(b) (4)	
Valve		
Actuator body		
Actuator dust cap		
Dose indicator		
Canister label		
Secondary pack		

Abbreviations: (b) (4) (b) (4) MDI = metered dose inhaler; BGF = budesonide, glycopyrrolate, and formoterol; NDA = new drug application
[a] Spray orifice tolerance range is contained within the range for the NDA 208294 product
Source: Response to clinical pharmacology IR dated January 14 2019.pdf, page 2-3, Table 1.

The main changes of the to-be-marketed device and device under approved NDA 208294 are:

- Color change of actuator dust cap (orange to grey)
- Tightening of the SOD (b) (4)

For evaluation the acceptability of these changes, refer to the CMC and CDRH review.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Phase 3 clinical trials reviewed to evaluate the safety and efficacy of BGF are shown in Table 46. Note that this table does not contain all clinical studies submitted with the NDA.

Table 46. Listing of Clinical Trials Relevant to This NDA

Trial Identity	NCT no.	Trial Design	Treatment (mcg)	Primary Endpoints(s)	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Trials to Support Efficacy and Safety								
PT010006 (Trial 06)	02497001	R, DB, PG, AC	BGF 320/18/9.6 BID GFF 18/9.6 BID BFF 320/9.6 BID TBH (OL) 400/12 BID	- Change from baseline FEV_1 AUC_{0-4} at week 24 (BGF vs. BFF) -Change from baseline trough FEV_1 at week 24 (BGF vs. GFF)	24 weeks	1902	Moderate to very severe COPD	215 (CA, JP, US, CN)
Trials to Support Safety								
PT010008 (Trial 08)	03313570	R, DB, PG, AC, extension study	BGF 320/18/9.6 BID GFF 18/9.6 BID BFF 320/9.6 BID	-Safety	28-week extension in a subset of PT010006 subjects	627	Moderate to very severe COPD	71 (all US)
Other Trials Pertinent to the Review of Efficacy or Safety								
PT009002 (Trial 02)	02766608	R, DB, PG, AC	BFF 320/9.6 BID BFF 160/9.6 BID FF 9.6 BID BD 320 BID TBH (OL) 400/12 BID	-Change from baseline FEV1 AUC_{0-4} at week 24 (BFF vs. FF) -Change from baseline trough FEV1 at week 24 (BFF vs. BD)	24 weeks	2389	Moderate to very severe COPD	253 (CA, CZ, DE, HU, PL, RU, US)
PT009003 (Trial 03)	02727660	R, DB, PG, AC	BFF 320/9.6 BID BFF 160/9.6 BID FF 9.6 BID	-Change from baseline trough FEV1 at week 24	12 weeks	1876	Moderate to very severe COPD	292 (AR, AT, BE, BR, CA, CL, DE, DK, IT, MX, NO, PE, RU, ZA, ES, SE, UK, US)

Abbreviations: AUC_{0-4} = area under the curve from 0 to 4 hours; AC = active comparator; AR = Argentina; AT = Austria; BD = budesonide; BE = Belgium; BFF = budesonide/formoterol fumarate; BGF = budesonide/glycopyrrolate/formoterol fumarate; BID = twice daily; BR = Brazil; CA = Canada; CL = Chile; CN = China; COPD = chronic obstructive pulmonary disease; CZ = Czech Republic; DB = double-blinded; DE = Germany; DK = Denmark; ES = Spain; FEV_1 = forced expiratory volume in 1 second; FF = formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; HU = Hungary; IT = Italy; JP = Japan; MX = Mexico; NO = Norway; OL = open-label; PC = placebo-controlled; PE = Peru; PG = parallel group; PL = Poland; R = randomized; RU = Russia; SE = Sweden; TBH = Symbicort Turbuhaler; UK = United Kingdom; US = United States; ZA = South Africa

7.2. Review Strategy

Support for the efficacy of BGF is based on a single phase 3 trial, Trial 06, with supporting evidence derived from the BFF development program (Trial 02 and Trial 03). BFF is not an approved product and a full development program for BFF was necessary to demonstrate the added benefit of the triple combination (BGF) over the double combinations (GFF and BFF). GFF (Bevespi Aerosphere) is an approved product and evidence for its efficacy and safety is derived from its approval (NDA 208294). Efficacy analysis was performed by FDA Biostatisticians to confirm the data shown in support of the Applicant's primary and secondary endpoints. The review of protocols and efficacy is in Section 8.1. Support for the safety of BGF is primarily based on the results of Trial 06 and its safety extension trial, Trial 08. Safety analysis was performed by the Clinical Reviewer and is in Section 8.2.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The review of efficacy focused on three phase 3 trials: Trial 06, 02 and 03.

BGF Trial 06 was designed to assess the contribution of ICS (budesonide) and LAMA (glycopyrrolate) to the BGF triple-combination products. BFF Trial 02 was designed to assess the contribution of ICS and LABA to the double combination product BFF, and BFF Trial 03 was designed to assess the contribution of ICS to the double combination product BFF.

The statistical reviewer evaluated the efficacy results of all the co-primary endpoints (or primary endpoint) and all the secondary endpoints which were specified in the Statistical Analysis Plan.

8.1.1. BGF Protocol Reviews: Trial 06 and Trial 08

8.1.1.1. Trial 06 (PT010006) – BGF 24-Week Lung Function Trial

Title: "A randomized, double-blind, parallel-group, 24-week, chronic-dosing, multi-center study to assess the efficacy and safety of PT010 (BGF), PT003 (GFF), and PT009 (BFF) compared with Symbicort Turbuhaler (TBH) as an active control in patients with moderate to very severe chronic obstructive pulmonary disease"

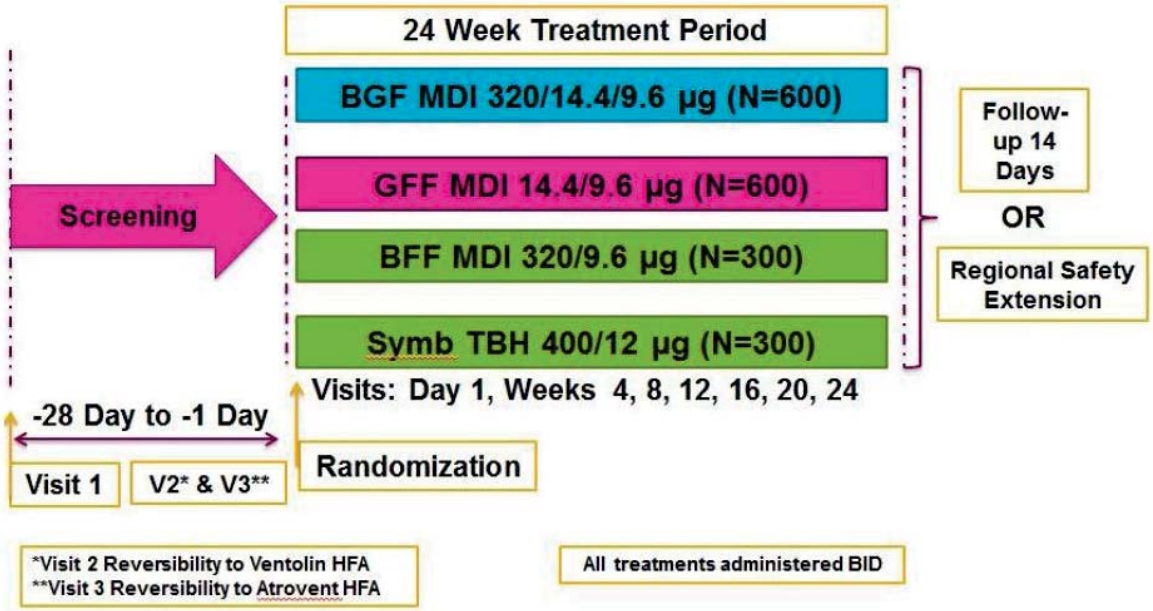
- Study dates: August 20, 2015 – January 5, 2018
- Study report date: June 6, 2018
- Study sites: United States, Canada, Japan, and China

Trial Design

This was a multicenter, randomized, double-blind, parallel-group, chronic-dosing (24 weeks) trial to assess the efficacy and safety of BGF MDI, GFF MDI, and BFF MDI, with Symbicort TBH as an active control, in patients with moderate to very severe COPD. At Visit 1, patients signed an informed consent form (ICF) prior to the conduct of any screening assessments and must have met spirometry criteria as re-screening was not allowed after Visit 1. Patients who met all entry criteria discontinued any prohibited COPD medications for the duration of the trial, with a minimum washout period observed between Visits 1 and 2. The screening period lasted a total of 4 weeks. Randomization occurred at Visit 4 and was followed by a 24-week double-blind treatment period ending at Visit 10a. Patients were randomized in a 2:2:1:1 ratio (BGF, GFF, BFF, or Symbicort, respectively). The trial schematic is shown in Figure 3 and the schedule of assessments is shown in Table 47.

This trial included the following 3 sub-studies: 12-hour serial spirometry, PK, and HPA axis function. Subject participation in the sub-studies was determined at screening, prior to any trial procedures.

Figure 3. Trial 06 Schematic



Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; MDI = metered dose inhaler; TBH = Turbuhaler
Source: PT010006 Protocol Version 3.0; Figure 1; pg 38

Table 47. Trial 06 Schedule of Assessments

	Screening Period				Treatment Period						Follow-Up TC
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10a	14 days Post-Dose
Study Day/Week[a]	Day -28 to -9	Day -21 to -2	Day -19 to -1	Day 1	Week 4 ±2 Days[a]	Week 8 ±2 Days[a]	Week 12 ±2 Days[a]	Week 16 ±2 Days[a]	Week 20 ±2 Days[a]	Week 24 ±2 Days[a]	
Procedures											
Obtain Informed Consent	X										
Review Incl/Excl Criteria	X	X	X	X							
Verify Continued Eligibility					X	X	X	X	X	X	
Reversibility[b]		X	X								
Demographics & Medical/Surgical History	X										
Smoking Status	X	X	X	X	X	X	X	X	X	X	
CAT[c]		X									
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X[d]	X
Spirometry[e]	X	X	X	X	X	X	X	X	X	X[e]	
Physical Examination[f]	X									X[f]	
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X[g]	
12-Lead ECG[h]	X	X	X	X	X		X			X[h]	
Pregnancy Test[i]	X						X			X[i]	
Clinical Laboratory Testing[j]	X			X	X		X			X[j]	
Chest Image or MRI[k]	X										
Adjust COPD Medications[b]	X									X[l]	
Adverse Events/COPD Exacerbations	X	X	X	X	X	X	X	X	X	X[m]	X
Inhalation Device and Dose Indicator Training	X	X	X	X							
Study Drug Dispensing/Collection	X[n]			X	X	X	X	X	X	X[o]	
Study Drug Administration				X	X	X	X	X	X	X	
BDI/TDI[m]				X	X	X	X	X	X	X[p]	
SGRQm				X	X	X	X	X	X	X[q]	
EQ-5D-5L Questionnaire[m]				X	X	X	X	X	X	X[r]	
12-hr PFTs (sub-study)										X	
PK Profile (sub-study)										X	
HPA Axis (sub-study)[s]			X							X	
eDiary Dispense/Collect[t]	X									X[t]	
Review of eDiary[u]		X	X	X	X	X	X	X	X	X	
HCRU					X	X	X	X	X	X[v]	
Telephone Contact[w]		X	X	X	X	X	X	X	X		X
Vital Status Check[x]										X	

BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; CAT=COPD Assessment Test; COPD=Chronic obstructive pulmonary disease; eDiary=electronic diary; ECG=electrocardiogram; EQ-5D-5L=European Quality-of-Life-5 Dimensions EXACT=Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes; HCRU=Healthcare Resource Utilization; HFA=Hydrofluoroalkane ; HPA Axis=hypothalamic-pituitary-adrenal axis; Incl/Excl=Inclusion/Exclusion; LABA=long acting β2 agonist; MDI=metered dose inhaler; MRI=Magnetic resonance imaging; PFTs=pulmonary function tests; PK=pharmacokinetic; Rand=randomization; SGRQ=St. George Respiratory Questionnaire; TC=Telephone call

Note: When data collection time points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, EQ-5D-5L, vital signs, ECG, clinical laboratory assessments, PK, and spirometry.

Source: PT010006 Protocol Version 3.0; Table 8; pgs 85-87

Overall, the design of the trial is reasonable to assess lung function and consistent with other programs for COPD inhaled products.

Objectives

- Primary objective: To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on lung function.
- Secondary objectives:
  - To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on dyspnea, quality of life, COPD symptoms, and COPD exacerbations.
  - To determine the time to onset of action of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH.

  - To assess the safety of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH.
  - To assess overall and COPD-specific Healthcare Resource Utilization of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH.
- 12-hour pulmonary function test (PFT) sub-study: To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on PFT parameters over 12 hours.
- PK sub-study: To characterize the steady state PK of budesonide, glycopyrronium, and formoterol based on PK assessments.
- HPA axis sub-study: To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on HPA axis function.

Trial Population

The trial consisted of 1902 randomized COPD patients.

Key Inclusion Criteria

- Signed informed consent to participate.
- Were at least 40 years of age and no older than 80 at Visit 1.
- A female was eligible to enter and participate in the study if she was of:
  - Non-childbearing potential.
  - Childbearing potential had a negative serum pregnancy test at Visit 1, and agreed to an acceptable form of contraception.
- COPD diagnosis as defined by the American Thoracic Society/European Respiratory Society or by locally applicable guidelines.
- Current or former smokers with a history of at least 10 pack-years of cigarette smoking.
- Patients with an established clinical history of COPD and severity defined as:
  - At Visit 1, FEV1/FVC ratio was <0.70 and FEV1 was <80% predicted normal value.
  - At Visit 2, post-bronchodilator FEV1/FVC ratio was <0.70 and post-bronchodilator FEV1 was ≥25% to <80% predicted normal value.
  - At Visit 4, the average of the 60 minutes and 30 minutes predose FEV1 assessments was <80% predicted normal value.
  - Symptomatic (CAT ≥10) at Screening (Visit 2).
- Use of 2 or more inhaled maintenance therapies for the management of their COPD for at least 6 weeks prior to Screening.
- Subject was willing and, in the opinion of the Investigator, able to adjust current COPD therapy, as required by the protocol.
- Screening clinical laboratory tests were acceptable to the Investigator.
- Screening ECG was acceptable to the Investigator.
- Chest x-ray or CT scan of the chest/lungs within 6 months prior to Visit 1 was acceptable to the Investigator.
- Patients must have been willing to remain at the study center as required per protocol to complete all visit assessments.

Key Exclusion Criteria

- Significant diseases or conditions other than COPD that in the opinion of the Investigator, may have put the patient at risk because of participation in the study or may have influenced either the results of the study or the subject's ability to participate in the study.
- Women who were pregnant or lactating, or were planning to become pregnant during the course of the study, or women of childbearing potential who were not using an acceptable method of contraception.
- Respiratory diseases including asthma, alpha-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, idiopathic pulmonary fibrosis, primary pulmonary hypertension, and uncontrolled sleep apnea.
- Patients who had undergone lung volume reduction surgery, lobectomy, or bronchoscopic lung volume reduction within 6 months
- Hospitalization for COPD within 3 months prior to Visit 1.
- Acute worsening of COPD that required treatment with oral steroids or antibiotics within 6 weeks prior to Visit 1.
- Lower respiratory tract infection that required antibiotics within 6 weeks prior to Visit 1.
- Upper respiratory tract infection not resolved at least 7 days prior to screening.
- Chest X-ray abnormalities requiring additional investigation/treatment or may put subject at risk because of study participation.
- Substantial risk of pneumonia in the opinion of the Investigator.
- Patients who could not perform acceptable and repeatable spirometry by ATS/ERS acceptability criteria.
- Long term oxygen therapy except for as needed oxygen.
- Use of non-invasive positive pressure ventilation device.
- Change in smoking status within 6 weeks of Visit 1.
- Pulmonary rehabilitation within 4 weeks prior to Visit 1.
- Initiated or altered use of intranasal corticosteroids and/or antihistamines within 7 days prior to Visit 1.
- Cardiac diseases including unstable ischemic heart disease, left ventricular failure, documented myocardial infarction within 6 months, percutaneous coronary intervention within 3 months, and coronary artery bypass graft within 3 months.
- Congestive heart failure with New York Heart Association Class III/IV symptoms.
- Clinically significant abnormal ECG including conduction abnormalities, arrhythmias, prolonged QT interval, ventricular bradycardia, significant ST-T wave abnormalities, or any other ECG abnormalities that are clinically significant in the opinion of the Investigator.
- Uncontrolled hypertension.
- Neurologic conditions including seizures requiring anticonvulsants within 12 months, changes in dose of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors within 4 weeks, or cerebrovascular accident within 6 months.

- Renal/urinary disorders including symptomatic prostatic hypertrophy or prostate resection within 6 months, bladder neck obstruction, urinary retention, and calculated creatinine clearance ≤30 mL/minute.
- Endocrine disorders including uncontrolled thyroid disease, hypokalemia, hyperadrenergic state, or diabetes.
- Abnormal liver function tests.
- Cancer that has not been in complete remission at least 5 years.
- Inadequately treated glaucoma.
- Drug allergy to BGF components or drugs of the same class.
- Substance abuse.
- Treatment with investigational drug or device within the last 30 days or within 5 half-lives prior to Visit 1.
- Previous enrollment in PT009 or PT010 studies.

Key Withdrawal Criteria

- Patient personal request.
- Calculated QTcF >500 msec and increased by 60 msec or more over baseline value
- Abnormal LFT ≥3 x ULN
- Use of prohibited medications.
- The Investigator will determine the suitability of the subject continuing on study drug if any of the following occur: Increase in heart rate >40 bpm or systolic blood pressure >40 mmHg after dosing, or decrease in creatinine clearance ≤30 mL/min.

The inclusion criteria and exclusion criteria are reasonable and consistent with other programs for COPD inhaled products. Based on these criteria, the study population will likely be representative of the target population.

Treatments

The trial consisted of 4 treatment groups. All treatments were taken twice daily. The treatment groups are as follows:

- BGF (budesonide/glycopyrrolate/formoterol) 320/18/9.6 µg
- GFF (glycopyrrolate/formoterol) 18/9.6 µg (approved dose in US)
- BFF (budesonide/formoterol) 320/9.6 µg
- Symbicort Turbuhaler (budesonide/formoterol) 400/12 µg (open-label; unapproved in US)
- BGF, GFF, and BFF were all administered via MDI. All patients were provided with albuterol sulfate inhalation aerosol 90 µg to be taken as directed on an as needed basis during the trial.

Restricted Medications

Prohibited medications with minimum washout period or prohibited time period are shown in Table 48. Note that patients who were dependent on steroids and maintained on an equivalent of up to 5 mg oral prednisone daily or up to 10 mg oral prednisone every other day for at least 3 months prior to Visit 1 were eligible for enrollment provided the dose remained consistent. Patients may have been treated with systemic corticosteroids during the treatment period if required.

Table 48. Prohibited Medications

Class of Medication	Minimum Washout Period Prior to Visit 2 or Minimum Cessation Period Prior to Visit 1
Long-acting muscarinic antagonists	Tiotropium: 14 days Aclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
Short-acting muscarinic antagonists	6 hours
Short-acting β2-adrenergic agonists	6 hours
Long-acting β2-adrenergic agonists	7 days (14 days for indacaterol and olodaterol)
Oral beta-agonists	2 days
Theophylline (total daily dose >400 mg/day)	7 days
Leukotriene antagonists	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen (eye drops allowed)	7 days
Any drug with significant QT-prolonging potential	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Non-selective beta-blocking agents (carvedilol allowed for treatment of heart failure when appropriate)	7 days
Cardiac antiarrhythmics class Ia, III	7 days (amiodarone 3 months)
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and free of seizures for 1 year
Tricyclic antidepressants (allowed if stable dose for at least 6 weeks and Investigator allows)	14 days
Monamine oxidase inhibitors	14 days
Anti-tumor necrosis factor alpha antibodies	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies (may be allowed on case-by-case basis after discussion with Medical Monitor)	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs (allowed if stable dose for at least 6 weeks and Investigator allows)	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors, and cimetidine	30 days
Systemic anticholinergics (unless used for overactive bladder and treatment is stable for 1 month)	30 days
Chinese complementary and alternative bronchodilatory medicines	10 days (Investigator may determine appropriate washout on case-by-case basis.

Source: PT010006 Protocol Version 3.0; Tables 1, 2, and 4; consolidated by Clinical Reviewer

The medication restrictions are typical for a COPD trial.

Trial Endpoints

Primary Endpoints

- FEV1 AUC_{0-4} hours at Week 24 (BGF vs.BFF)
- Change from baseline in morning pre-dose trough FEV_1 at Week 24(BGF vs.GFF)

Secondary Endpoints

- Change from baseline in morning pre-dose trough FEV1 over 24 weeks
- Percentage of subjects achieving a minimal clinically important difference (MCID) of ≥4 units in SGRQ total score at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Peak change from baseline in FEV1 within 4 hours post-dosing at Week 24
- Rate of moderate or severe COPD exacerbations over 24 weeks (BGF vs.BFF and GFF)
- Time to onset of action on Day 1

A COPD exacerbation was defined as a change in the subject's usual COPD symptoms that lasted 2 or more days, was beyond normal day-to-day variation, was acute in onset, and may have warranted a change in regular medication. The change in symptoms must have included at least 1 major COPD symptom (dyspnea, change in sputum volume, and change in sputum color) and at least 1 other major or minor symptom (cough, wheeze, sore throat, cold symptoms, and fever without other cause). An exacerbation was considered moderate if it resulted in use of systemic corticosteroids and/or antibiotics for at least 3 days. Exacerbations were considered severe if they resulted in an inpatient COPD-related hospitalization or death.

Safety Endpoints

- AEs
- ECGs
- Clinical laboratory testing
- Vital signs measurement

The trial endpoints and definition of COPD exacerbation are reasonable and consistent with the trial objectives and are similar to other COPD development programs. The co-primary endpoints are chosen to demonstrate the contribution of GP and BD to the triple combination. (BGF vs. GFF) (BGF vs. BFF). Overall the trial design is adequate to support the efficacy of BGF given that GFF is approved and provided that the BFF program demonstrates the efficacy of BFF.

12-Hour PFT Sub-Study Endpoints

- FEV1 AUC_{0-12} at Week 24

PK Sub-Study Endpoints

- AUC_{0-12}
- Time to reach maximum observed plasma concentration
- Maximum observed plasma concentration
- Terminal elimination rate constant
- Terminal elimination half-life
- Minimum observed plasma concentration
- Time-average concentration during a dosing interval
- %Fluctuation
- %Swing

HPA Axis Sub-Study Endpoints

- Ratio to Baseline of the 0- to 24-hour weighted mean serum cortisol concentration curve at Visit 10a (Week 24)

Statistical Analysis Plan

Analysis Population and Estimand

Four analysis populations were defined in this trial: intent-to-treat (ITT) population, modified intent-to-treat (mITT) population, per-protocol (PP) population and safety population.

The ITT Population was defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment.

The mITT Population was a subset of the ITT Population, defined as all subjects with post randomization data obtained prior to discontinuation from treatment.

The PP Population was a subset of the ITT Population, defined as all subjects with post randomization data obtained prior to any major protocol deviations. If the first treatment received is the wrong treatment, then the subject was excluded entirely from the PP population.

The safety population is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment.

Four estimands were defined in this trial: efficacy estimand, attributable estimand, treatment policy estimand and per protocol estimand.

The efficacy estimand is the effect of the randomized treatments in all subjects assuming continuation of randomized treatments for the duration of the trial regardless of actual compliance. This assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomized treatment had they remained on treatment.

The attributable estimand is the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized medication for reasons such as tolerability or lack of efficacy is considered a bad outcome.

The treatment policy estimand is the effect of randomized treatment over the trial period regardless of whether randomized treatment is continued.

The per protocol estimand is the effect of treatment on subjects who are compliant with the protocol without major protocol deviation, including the use of randomized medication.

All the primary efficacy analyses targeted the efficacy estimand. Only data obtained prior to subjects discontinuing from randomized treatment were utilized in the analyses.

There are four pairwise comparisons of treatments of interest, namely:

- BGF MDI vs. GFF MDI,
- BGF MDI vs. BFF MDI,
- BGF MDI vs. Symbicort TBH, and
- BFF MDI vs. Symbicort TBH.

In this review we only focus on the comparison of BGF versus GFF and comparison of BGF versus BFF to assess the contribution of ICS and LAMA to the triple-combination products BGF.

Statistical Analysis Model and Additional Analyses

Co-Primary Endpoints
Lung function contribution of ICS to BGF was assessed by the co-primary endpoint of change from baseline in morning pre-dose trough FEV_1 at Week 24; contribution of LAMA to BGF was assessed by the co-primary endpoint of change from baseline in FEV_1 AUC_{0-4} at Week 24.

The change from baseline in morning pre-dose trough FEV_1 and change from baseline in FEV_1 AUC_{0-4} at Week 24 were analyzed using a repeated measure linear mixed model. The model included treatment, visit, treatment by visit interaction, and ICS use at Screening as categorical covariates and baseline FEV_1, baseline eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates. Point estimates with two-sided 95% CIs and two-sided p-values were produced for each treatment difference of interest.

The Applicant also conducted analyses targeting alternative estimands, such as attributable

estimand and treatment policy estimand. Sensitivity analyses including tipping point analysis based on efficacy estimand were also conducted by the Applicant to assess impact of missing data on the primary analysis results.

Secondary Endpoints
The primary analyses of the secondary endpoints targeted the efficacy estimand.

There were six secondary endpoints. They are listed in the order of testing hierarchy:

1. Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
2. Percentage of subjects achieving an MCID of ≥4 units in SGRQ total score at Week 24
3. Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
4. Peak change from baseline in FEV_1 within 4 hours post-dosing at Week 24
5. Rate of moderate or severe COPD exacerbations over 24 weeks (BGF vs.BFF and GFF)
6. Time to onset of action on Day 1

The SGRQ responder was defined as subjects with an improvement of (i.e. a decrease in the total SGRQ score of) ≥4.0 points at Week 24. The analysis of SGRQ responder used logistic regression, including baseline SGRQ Score, baseline eosinophil count, baseline post bronchodilator percent predicted FEV_1, and percent reversibility to Ventolin HFA as continuous covariates, and treatment, country, and ICS use at Screening as categorical covariates. P-values and odds ratios with 95% CIs were produced for each treatment comparison.
Analysis of rate of moderate or severe COPD exacerbations used negative binomial regression adjusting for baseline post-bronchodilator percent predicted FEV1 and baseline eosinophil count as continuous covariates, and baseline COPD exacerbation history (Yes, No), country, and ICS use at Screening (yes/no) as categorical covariates.

Missing Data Handling and Sensitivity Analysis

The primary analysis of the co-primary endpoints and secondary endpoints targeted the efficacy estimand. Data collected after discontinuing the study treatment was excluded from the primary analysis and treated as missing.

The Applicant conducted tipping point analysis based on the efficacy estimand as a sensitivity analysis to assess impact of missing data.

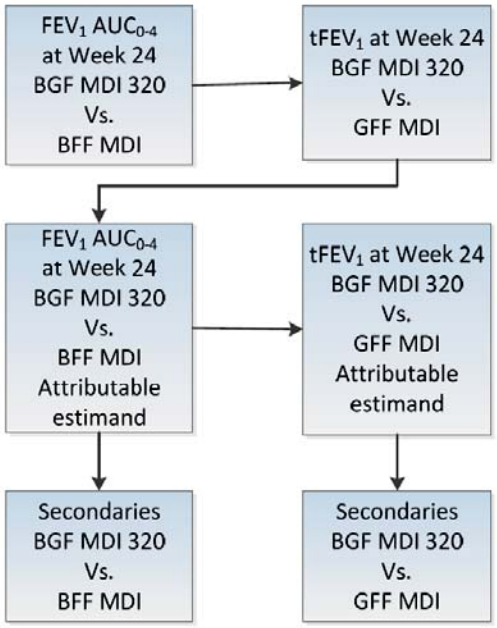
Multiplicity

The overall type I error probability was controlled using a hierarchical testing procedure between the co-primary and secondary endpoints. Figure 4 presents the testing order of the co-primary and key secondary endpoints.

Due to one of the co-primary endpoints failed to reach statistical significance, we only consider the nominal p-values of all the subsequent tests. Additionally, we mainly focus on the following two secondary endpoints:

- Percentage of subjects achieving an MCID of ≥4 units in SGRQ total score at Week 24
- Rate of moderate or severe COPD exacerbations over 24 weeks (BGF vs.BFF and GFF)

Figure 4. Type I Error Control of Trial 06



$tFEV_1$ = morning pre-dose trough FEV_1. Secondaries = secondary efficacy endpoints. Each subsequent hypothesis is tested only if statistical significance was attained in the precursor(s) hypotheses. Unless stated otherwise, all comparisons use the efficacy estimand.

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; MDI = metered dose inhaler; AUC_{0-4} = area under the curve from zero to four hours; FEV_1 = forced expiratory volume in 1 second
Source: Applicant's SAP Figure 5 (Page 3432 of Statistical Method and Analysis)

Subgroup Analysis and Bayesian Shrinkage Subgroup Analysis

For both co-primary endpoints, subgroup analyses were conducted on the following categories:

- Baseline characteristics
  - Baseline Eosinophil Counts
  - Percent Predicted Post-bronchodilator FEV_1
  - Severity of COPD
  - Gold Category
- Country
- Race
- Age

- Gender
- ICS Use at Screen

In this review, we focused on the following subgroup analyses using both traditional subgroup analysis and Bayesian shrinkage subgroup analysis:

- Age
- Gender
- Race
- Country

Protocol Amendments

The first version of the protocol dated May 18, 2015 was amended twice globally (all countries affected) on May 4, 2016 and August 25, 2017. Japan-specific amendments were also made. Global protocol amendments are summarized as follows:

August 25, 2017 Amendment

- Made rate of moderate or severe exacerbations a secondary endpoint instead of an exploratory endpoint
- US endpoints and Type I error control strategy added
- Provided more complete definition of the mITT population
- A separate margin of 75 mL is specified for post-dose FEV1 measures

May 4, 2016 Amendment

- Updated the adjudication committee name to Clinical Endpoint Committee (CEC) and clarify that there is one CEC with three CEC charters
- Clarify that the DMC provides assessment of all safety data and not just Serious Adverse Events (SAEs)
- Added health care resource utilization endpoints
- Hy's law added, which was initially omitted in error

The protocol amendments submitted do not affect the interpretation of results for Trial 06.

8.1.1.2. Trial 08 (PT010008) – BGF 28-Week Safety Extension of Trial 06

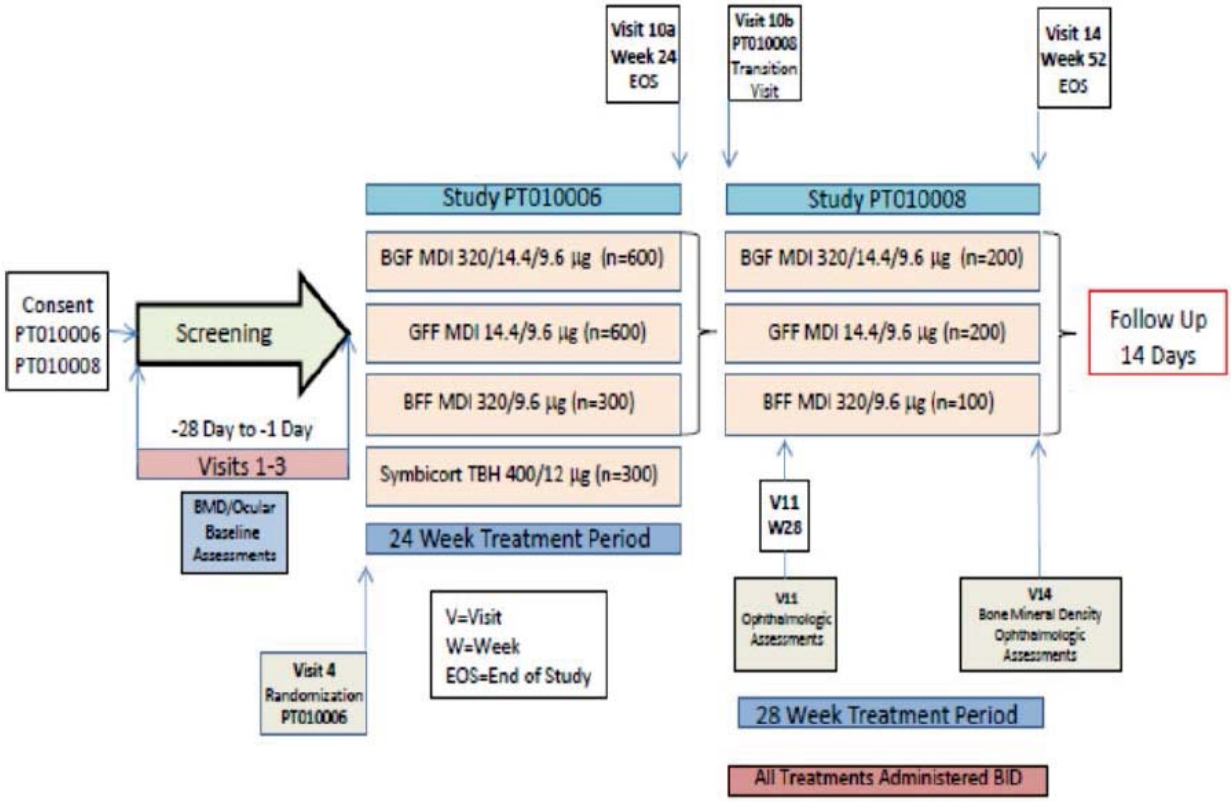
Title: "A randomized, double-blind, parallel-group, 52-week, chronic-dosing, multi-center study to assess the safety and tolerability of PT010 (BGF), PT009 (BFF), and PT003 (GFF) in subjects with moderate to very severe chronic obstructive pulmonary disease"

- Study dates: September 24, 2015 – September 6, 2017
- Study report date: April 27, 2018
- Study sites: United States

Trial Design

This was a randomized, double-blind, parallel-group, 52-week, chronic-dosing, multi-center safety extension trial of Trial 06 (28-weeks in addition to the 24-weeks completed in Trial 06 for a cumulative duration of 52-weeks) to assess the effects of BGF, BFF, and GFF on bone mineral density (BMD), ophthalmologic assessments, and safety and tolerability in subjects with moderate to very severe COPD. This extension trial was conducted in a subset of subjects who completed Trial 06 and a separate ICF was obtained prior to any trial procedures. Subjects randomized to open-label Symbicort TBH were not enrolled. The trial schematic is shown in Figure 5 and the schedule of assessments is shown in Table 49.

Figure 5. Trial 08 Schematic



Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; BMD = bone mineral density; GFF = glycopyrrolate/formoterol fumarate; TBH = Turbuhaler
Source: PT010008 CSR; Figure 1; pg 20

Table 49. Trial 08 Schedule of Assessments

Procedures	Treatment Period						Follow-Up
	Baseline Visits 1-4 (PT010006) -28 to -1	Transition Visit (from PT010006) Visit 10b Week 24	Visit 11 Week 28	Visit 12 Week 36	Visit 13 Week 44	Visit 14 Week 52	14 Days Post-Dose
Study Day/Week [a]			Week 28 ±7 Days [a]	Week 36 ±14 Days [a]	Week 44 ±14 Days [a]	Week 52 ±7 Days [a]	Week 54 +7 Days [a]
Obtain informed consent	X	X					
Review inclusion/exclusion criteria	X	X					
Verify continued eligibility			X	X	X	X	
Smoking status			X	X	X	X	
Physical examination [b]						X	
Prior/concomitant medications [c]			X	X	X	X	X
COPD exacerbations and AEs			X	X	X	X	X
Adjust COPD medications [d]						X	
Vital signs [e,f]			X	X	X	X	
Urine pregnancy test [g]				X			
Serum pregnancy test [g]						X	
12-lead ECG [g]				X		X	
Clinical laboratory testing [g]				X		X	
Bone mineral density assessments [g]	X					X	
Ophthalmologic assessments [g]	X		X			X	
Study drug dispensing/collection	X	X	X	X	X	X	
Review of electronic diary data [g]			X	X	X	X	
Study drug administration [g]	X	X					
Record dose indicator reading [g]	X		X	X	X	X	
Telephone contact [h]	X[h]		X[h]	X[h]	X[h]	X[h]	X[h]

Abbreviations: AE=adverse event; BMD=bone mineral density; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; eDiary=electronic subject diary.
Note: The Screening Period may have been extended up to a maximum of 21 days if additional time was needed to complete the assessments.
Note: For subjects who discontinued study drug and were withdrawn from the study at any time, ophthalmologic assessments were obtained as soon as possible. For subjects who discontinued study drug and were withdrawn from the study after Visit 10b (Week 24), BMD assessments were obtained as soon as possible; BMD assessments were only obtained for subjects who continued in Study PT010008 after Visit 10b (Week 24).
Note: Two post-baseline ophthalmologic assessments were performed at Visit 11 (Week 28) and Visit 14 (Week 52) only per exclusion criteria exception noted in Section 5.3.2.2. These post-baseline ophthalmologic assessments were scheduled to occur within 2 weeks prior to the scheduled clinic visit.

Source: PT010008 CSR; Figure 2; pgs 22-24

Overall, the design of the trial is reasonable to assess safety.

Objectives

- **Primary objectives:**
  - To evaluate the effect of BGF, GFF, and BFF on BMD over 52 weeks.
  - To evaluate the effect of BGF, GFF, and BFF on ocular assessments over 52 weeks
- **Secondary objective:** To assess the safety and tolerability of BGF, GFF, and BFF over 52 weeks.

Trial Population

The trial consisted of 627 COPD patients who were randomized in Trial 06 and also signed the ICF for Trial 08.

Inclusion Criteria

1. Signed inform consent to participate.
2. Must have agreed to participate in Trial 06 (see Trial 06 inclusion criteria)

Key Exclusion Criteria

1. Severe osteoporosis
2. T-score (measure of bone density) <-2.5 at baseline
3. Subjects unable to achieve an acceptable BMD scan
4. Inability to dilate pupil ≥6 mm
5. Intraocular pressure ≥21 mmHg
6. Implanted artificial intraocular lens

Key Withdrawal Criteria

1. Patient personal request.
2. Calculated QTcF >500 msec and increased by 60 msec or more over baseline value
3. Abnormal LFT ≥3 x ULN
4. Use of prohibited medications.
5. The Investigator will determine the suitability of the subject continuing on study drug if any of the following occur: Increase in heart rate >40 bpm or systolic blood pressure >40 mmHg after dosing, or decrease in creatinine clearance ≤30 mL/min.

Treatments

The trial consisted of 3 treatment groups. All treatments were taken twice daily. The treatment groups are as follows:

- BGF (budesonide/glycopyrrolate/formoterol) 320/18/9.6 µg
- GFF (glycopyrrolate/formoterol) 18/9.6 µg (approved dose in US)
- BFF (budesonide/formoterol) 320/9.6 µg

All patients were provided with albuterol sulfate inhalation aerosol 90 µg to be taken as directed on an as needed basis during the trial.

Restricted Medications

See Table 48 for Trial 06 prohibited medications. These are the same for Trial 08.
Overall, the inclusion and exclusion criteria are reasonable and consistent with the trial objectives.

8.1.2. BFF Protocol Reviews: Trial 02 and Trial 03

8.1.2.1. Trial 02 (PT009002) – BFF 24-week lung function trial

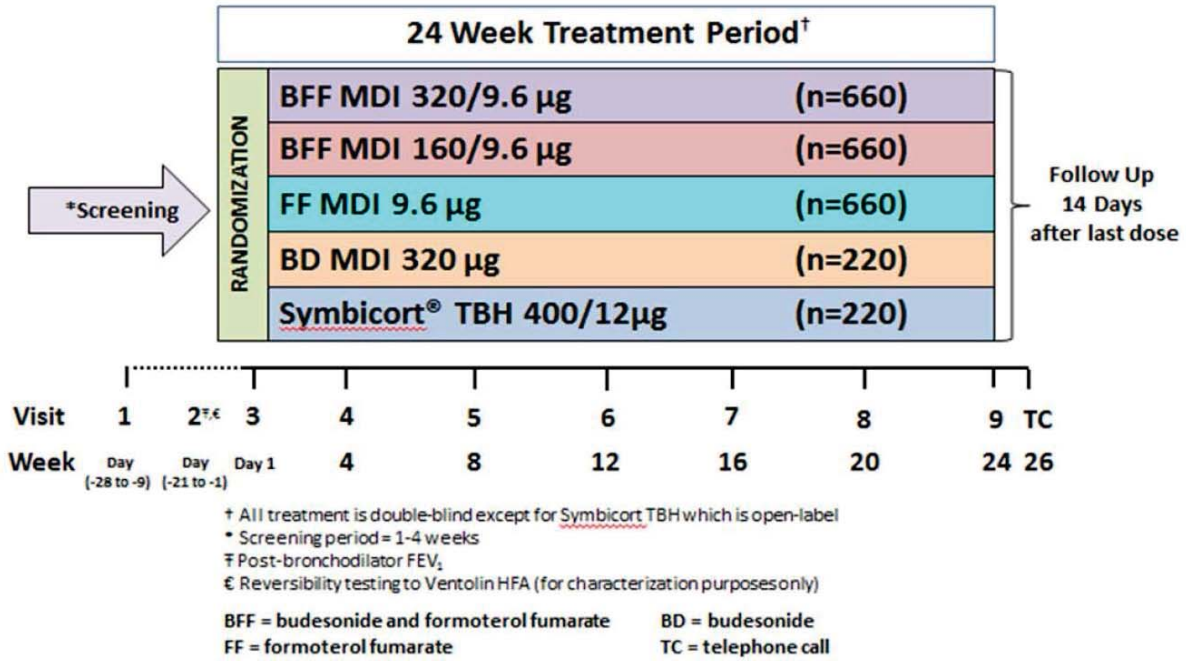
Title: "A randomized, double-blind, parallel group, multi-center study to assess the efficacy and safety of PT009 (BFF) compared to PT005 (FF), PT008 (BD), and open-label Symbicort Turbuhaler, as an active control, on lung function over a 24-week treatment period in patients with moderate to very severe COPD"

- Study dates: June 16, 2016 – November 30, 2017
- Study report date: May 17, 2018
- Study sites: United States, Canada, Germany, Czech Republic, Hungary, Poland, and Russia

Trial Design

This was a multicenter, randomized, double-blind, parallel-group, 24-week lung function trial with BFF MDI (budesonide/formoterol at 320/9.6 µg and 160/9.6 µg) compared to FF MDI (9.6 µg), BD MDI (320 µg), and open-label Symbicort TBH in patients with moderate to very severe COPD. Patients underwent a 1-4 week screening period. They were allowed to continue the ICS component of their inhaled maintenance therapy during this time. Patients were placed on Applicant-provided albuterol sulfate inhalation aerosol for rescue throughout the screening and treatment periods. Patients were randomized in a 3:3:3:1:1 ratio (BFF 320/9.6, BFF 160/9.6 µg, FF, BD, and Symbicort TBH, respectively). The trial schema is shown in Figure 6 and the schedule of events is shown in Table 50. The trial includes a PFT sub-study where 12-hour lung function data will be collected at week 12.

Figure 6. Trial 02 Schematic



Source: PT009003 Protocol Version 4.0; Figure 4-1; pg 25

Table 50. Trial 02 Schedule of Events

	Screening Period[a]		Treatment Period							Follow-up TC
	Visit 1	Visit 2	Visit 3 (R)	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12	Visit 7 Week 16	Visit 8 Week 20	Visit 9 Week 24	14 (+2) Days after Last Dose
Study Day[b]	Day -28 to -8	Day -21 to -1	Day 1	Day 28 ±2	Day 56 ±5	Day 84 ±5	Day 112 ±5	Day 140 ±5	Day 168 ±5	Day 182
Procedures										
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X	X	X	X	X	X	X	X	
Demographics & Medical/Surgical History	X									
Chest Image or MRI[c]	X									
CAT	X									
Physical Examination[d]	X								X[e]	
Prior/Concomitant Medications[f]	X	X	X	X	X	X	X	X	X[e]	X
Smoking Status	X	X	X	X	X	X	X	X	X	
Reversibility Testing[g]		X								
Vital Signs	X	X	X	X	X	X	X	X	X[e]	
Clinical Laboratory Testing	X		X			X			X[e]	
12-Lead ECG	X		X			X			X[e]	
Pregnancy Test[h]	X		X			X			X[e]	
Spirometry	X	X	X	X	X	X	X	X	X	
Adjust COPD Medications[i]	X								X[e]	
Adverse Events/COPD Exacerbations	X	X	X	X	X	X	X	X	X[e]	X
Inhalation Device and Dose Indicator Training	X	X	X							
Study Drug Dispensing/Collection	X[j]		X	X	X	X	X	X	X[e]	
eDiary: Dispense/Collect	X[k]								X[e]	
eDiary: Training/Review[l]		X	X	X	X	X	X	X	X[e]	
Study Drug Administration			X	X	X	X	X	X	X	
BDI/TDI[m]			X	X	X	X	X	X	X[e]	
SGRQ[m]			X	X	X	X	X	X	X[e]	
EQ-5D-5L Questionnaire[m]			X	X	X	X	X	X	X[e]	
HCRU				X	X	X	X	X	X[e]	X
Vital Status Check[n]									X	
PFT Sub-study						X				

Abbreviations: BDI=Baseline dyspnea index; CAT=Chronic Obstructive Pulmonary Disease Assessment Test; COPD=chronic obstructive pulmonary disease; CT=computed tomography; ECG=electrocardiogram; eDiary=electronic diary; EQ-5D-5L=European Quality-of-Life 5-Dimensions and 5-Levels; EXACT=Exacerbations of Chronic Pulmonary Disease Tool; HCRU=healthcare resource utilization; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; MRI=magnetic resonance imaging; PFT=pulmonary function test; R=randomization; SGRQ=St. George's Respiratory Questionnaire; TC=telephone call; TDI=transition dyspnea index.

Source: PT009002 Protocol Version 3.0; Table 8-1; pg 73-74

Overall, the design of the trial is reasonable to assess lung function and consistent with other programs for COPD inhaled products. No placebo arm was included in Trial 02 at the recommendation of FDA at the BFF EOP2 meeting. There were ethical concerns with treating moderate to severe COPD patients with placebo for 24-weeks. It was also the FDA's opinion that demonstration of added benefit of BFF over FF, which was found to be effective in the approval of GFF, as well as BD was sufficient to demonstrate efficacy of BFF.

Objectives

- Primary objective: To assess the effects of BFF MDI relative to FF MDI and BD MDI on lung function.
- Secondary objectives:
  - To assess the effects of BFF MDI relative to FF MDI, BD MDI, and Symbicort TBH on symptoms of COPD.
  - To assess the effects of BFFMDI relative to FF MDI, BD MDI, and Symbicort TBH on quality of life.
  - To determine the time to onset of action on Day 1.
- PFT sub-study: To characterize FEV1 over 12 hours at Week 12.

Trial Population

The trial consisted of 2389 randomized COPD patients.

Key Inclusion Criteria

The inclusion criteria were similar to those in Trial 06 except the following:

- At Visit 2, post-bronchodilator FEV1/FVC ratio was <0.70 and post-bronchodilator FEV1 was ≥30% to <80% predicted normal value.
- Use of 1 or more inhaled bronchodilators as maintenance therapy for the management of their COPD for at least 6 weeks (scheduled SABA and/or scheduled SAMA are included).

Key Exclusion Criteria

The exclusion criteria were similar to those in Trial 06 except the following:

- Receiving an ICS, LABA, and LAMA (as inhaled triple maintenance therapy) in the past 30 days.
- Hospitalized due to or has poorly controlled COPD within 6 weeks prior to Visit 1.
- Treatment with systemic corticosteroids and/or antibiotics for COPD or respiratory infection within 4 weeks prior to Visit 1.
- Received a live attenuated vaccine within seven days.
- Hospitalized for psychiatric disorder or attempted suicide within one year.

Key Withdrawal Criteria

- Patient personal request.
- The Investigator will determine the suitability of the subject continuing on study drug if any of the following occur:
  - QTc ≥500 msec or ≥60 msec from pre-dose baseline
  - Abnormal LFT ≥3 x ULN
  - Use of prohibited medications.
  - Increase in heart rate >40 bpm from pre-dose value
  - Heart rate >120 bpm
  - Systolic blood pressure >160 mmHg or >40 mmHg increase from pre-dose level
  - Decrease in creatinine clearance ≤30 mL/min.
- Female subject becoming pregnant

The inclusion criteria and exclusion criteria are reasonable and consistent with other programs for COPD inhaled products. Based on these criteria, the trial population will likely be representative of the target population.

Treatments

The trial consisted of 5 treatment groups. All treatments were taken twice daily. The treatment groups are as follows:

- BFF (budesonide/formoterol) 320/9.6 µg
- BFF (budesonide/formoterol) 160/9.6 µg
- FF (formoterol) 9.6 µg
- BD (budesonide) 320 µg
- Symbicort Turbuhaler (budesonide/formoterol fumarate) 400/12 µg (open-label; unapproved in US)

All except Symbicort Turbuhaler were administered via MDI. All patients were provided with albuterol sulfate inhalation aerosol 90 µg to be taken as directed on an as needed basis during the trial.

Restricted Medications

Prohibited medications with minimum washout period or prohibited time period are similar to those in Trial 06 and are shown in Table 48. One notable difference is for systemic anticholinergics, which required a 7-day washout. Note that patients who were dependent on steroids and maintained on an equivalent of up to 5 mg oral prednisone daily or up to 10 mg oral prednisone every other day for at least 3 months prior to Visit 1 were eligible for enrollment provided the dose remained consistent. Patients may have been treated with systemic corticosteroids during the treatment period if required.

Trial Endpoints

Primary Endpoints

- Change from baseline in morning pre-dose trough FEV1 at Week 24 (BFF vs.FF)
- Change from baseline in FEV1 AUC_{0-4} at Week 24 (BFF vs.BD)

Secondary Endpoints

- Percentage of patients achieving an MCID of 4 units or more in SGRQ total score at Week 24 (BFF vs.FF; BFF vs.BD)
- Change from baseline in morning pre-dose trough FEV1 at Week 24 (BFF vs.BD)
- Peak change from baseline in FEV1 at Week 24 (BFF vs.BD)
- Change from baseline in average daily rescue albuterol use over 24 weeks (BFF vs.BD)
- Time to onset of action on Day 1
- Time to first moderate or severe COPD exacerbation (BFF vs.FF)

Safety Endpoints

- AEs
- ECGs
- Clinical laboratory testing
- Vital signs measurement

PFT sub-study endpoints (over 12-hours post-dose at Week 12)

- FEV1 AUC_{0-12}

The trial endpoints are reasonable and consistent with the trial objectives and are similar to other COPD development programs.

Statistical Analysis Plan

Analysis Population and Estimand

Same as Trial 06, four analysis populations were defined in this trial: ITT population, mITT population, PP population and safety population; and four estimands were defined in this trial: efficacy estimand, attributable estimand, treatment policy estimand and per protocol estimand.

There were 5 pairwise comparisons of treatments of interest:

- BFF MDI 320/9.6 µg vs.FF 9.6 µg MDI
- BFF MDI 160/9.6 µg vs.FF 9.6 µg MDI
- BFF MDI 320/9.6 µg vs.BD 320 µg MDI
- BFF MDI 160/9.6 µg vs.BD 320 µg MDI
- BFF MDI 320/9.6 µg vs.Symbicort TBH

In this review we focused primarily on the comparison of BFF MDI 320/9.6 µg versus FF 9.6 µg MDI and comparison of BFF MDI 320/9.6 µg versus BD 320 µg MDI, given the proposed dose of the BGF.

Statistical Analysis Model and Additional Analyses

Co-Primary Endpoints
Lung function contribution of ICS to BFF was assessed by the co-primary endpoint of change from baseline in morning pre-dose trough FEV_1 at Week 24; contribution of LABA to BFF was assessed by the co-primary endpoint of change from baseline in FEV_1 AUC_{0-4} at Week 24.

The primary analysis was conducted for the efficacy estimand. The change from baseline in morning pre-dose trough FEV_1 at Week 24 and change from baseline in FEV_1 AUC_{0-4} at Week 24 were analyzed using a repeated measure linear mixed model. The model included treatment, visit, treatment by visit interaction, and ICS use at Screening as categorical covariates and baseline FEV_1, baseline eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates. Point estimates with two-sided 95% CIs and two-sided p-values were produced for each treatment difference of interest.

The Applicant also conducted analysis using attributable estimand. Sensitivity analysis of tipping point analysis based on efficacy estimand was conducted by the Applicant.

Secondary Endpoints
There were six secondary endpoints (see Figure 8 for Type I Error Control):

- Time to first moderate or severe COPD exacerbation (BFF vs.FF)
- Percentage of subjects achieving an MCID of ≥4 units in SGRQ total score at Week 24 (BFF vs.FF)
- Peak change from baseline in FEV1 post-dosing at Week 24 (BFF vs.BD)
- Change from Baseline in average daily Ventolin HFA use (puffs per day) over 24 weeks (BFF vs.BD)
- Time to onset of action as assessed by FEV_1 on Day 1 (BFF vs.BD)
- Change from baseline in morning pre-dose trough FEV1 at Week 24 (BFF vs.BD)
- SGRQ responder rate at Week 24 (BFF vs.BD)

All the primary analyses for the secondary endpoints targeted efficacy estimand.

Responder of SGRQ were defined as subjects with an improvement of ≥4.0 points at Week 24. SGRQ responder analysis used logistic regression with baseline SGRQ score, baseline eosinophil count, baseline post-bronchodilator percent predicted FEV1, and percent reversibility to Ventolin HFA as continuous covariates, and treatment and ICS use at Screening as categorical covariates. Contrasts were used to obtain estimates of the response odds ratios at Week 24.

Two-sided p-values and point estimates with two-sided 95% CIs were produced for each odds ratio.

The onset of action for BFF MDI was evaluated on Day 1 by comparing BFF MDI vs.BD MDI in the mean change from baseline in FEV_1 at the 5-minute post-dose timepoint. Analysis used a linear model for repeated measures. The model included baseline FEV_1, percent reversibility to Ventolin HFA, and baseline eosinophil count as continuous covariates and time point, treatment, the treatment by time point interaction, and ICS use at screening as categorical covariates.

The time to first moderate or severe COPD exacerbation was analyzed using a Cox regression model, adjusting for percent predicted post-bronchodilator FEV1, baseline eosinophil count, baseline COPD exacerbation history (Yes/No), country, and ICS use at Screening (Yes/No). Estimated adjusted hazard ratios relative to the comparator for each treatment comparison were reported along with the associated Wald two-sided 95% CIs and p-values.

Missing Data Handling and Sensitivity Analysis

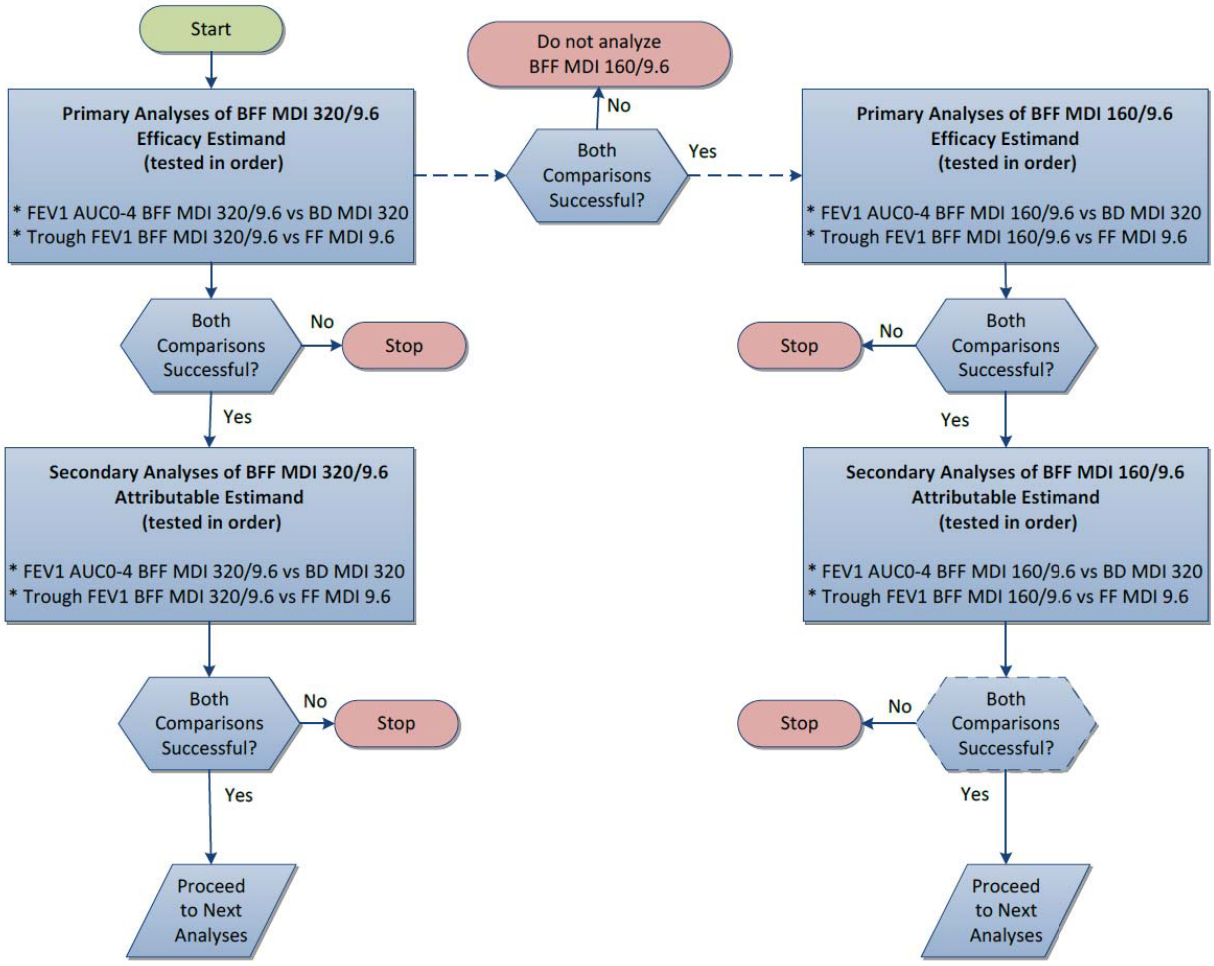
The primary analysis of the co-primary endpoints and secondary endpoints targeted efficacy estimand. Data collected after discontinuing the study treatment was excluded from the primary analysis and treated as missing.

The Applicant conducted tipping point analysis based on the efficacy estimand as a sensitivity analysis to assess impact of missing data. The statistical reviewer will address this issue in section 8.3 Statistical Issues.

Multiplicity

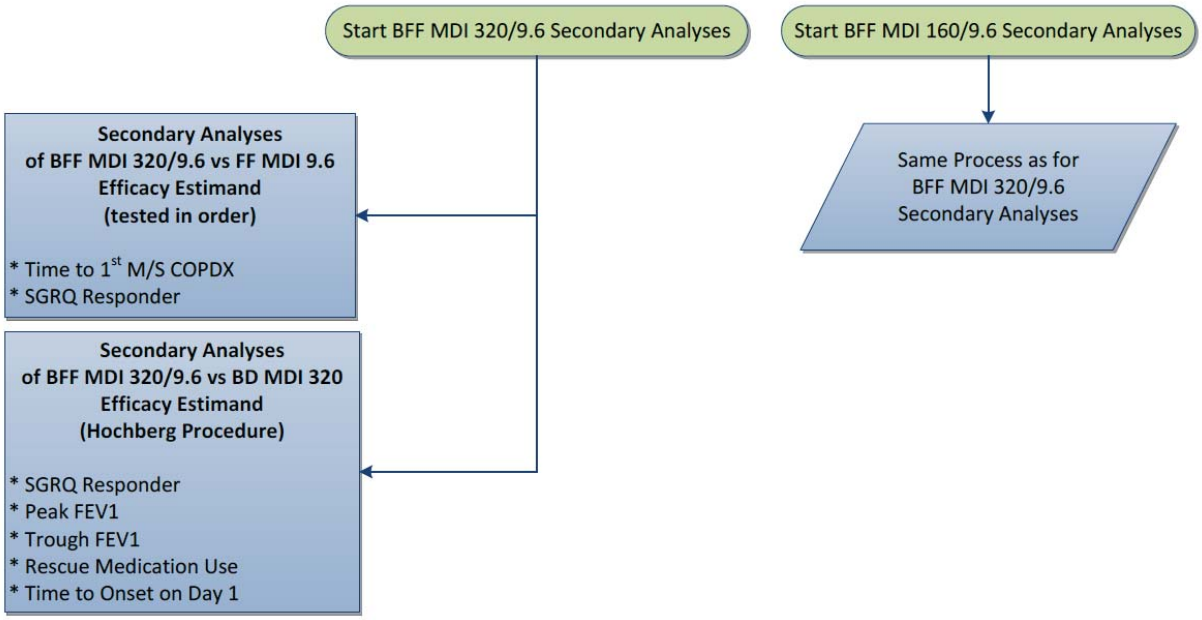
The overall type I error probability was controlled using a hierarchical testing procedure between the co-primary and secondary endpoints. Figure 7 presents the testing order of the co-primary endpoints, and Figure 8 presents the testing order of key secondary endpoints.

Figure 7. Group 1: Type I Error Control for the Analyses of the Primary Endpoints (Trial 02)



Abbreviations: BD = budesonide; BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; MDI = metered dose inhaler; AUC_{0-4} = area under the curve from zero to four hours; FEV_1 = forced expiratory volume in 1 second
Source: Applicant's SAP Figure 12 (Page 104 of Statistical Methods and Analysis)

Figure 8. Type I Error Control for the Analyses of the Secondary Endpoints (Trial 02)



Abbreviations: BD = budesonide; BFF = budesonide/formoterol fumarate; COPDX = COPD exacerbation; FF = formoterol fumarate; SGRQ = St. George's Respiratory Questionnaire; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler
Source: Applicant's SAP Figure 13 (Page 105 of Statistical Methods and Analysis)

Notice that in Figure 7 after testing the primary analyses of BFF 320/9.6 with statistically significant result on efficacy estimand, the alpha wasn't split between the test of secondary analyses of BFF 320/9.6 on attributable estimand and the test of primary analyses of BFF 160/9.6 on efficacy estimand. We will address this issue in section 8.3 Statistical Issues.

Subgroup Analysis and Bayesian Shrinkage Subgroup Analysis

To examine whether the treatment effects vary among the levels of a baseline factor, we conducted subgroup analyses on the co-primary endpoints, in the following categories using traditional subgroup analysis and the Bayesian shrinkage subgroup analysis:

- Age
- Gender
- Race
- Region

Protocol Amendments

The first version of the protocol dated March 8, 2016 was amended twice on July 1, 2016 and October 24, 2017. Protocol amendments are summarized as follows:

March 8, 2016 Amendment

- Increased hours of oxygen used as an exclusion from ≥12 hours to ≥15 hours
- Eliminated exclusion of nebulizer use for COPD maintenance medications
- Clarified that subjects discontinuing study treatment, but continuing trial participation will have all AEs/SAEs collected through their last visit

July 1, 2016 Amendment

- COPD exacerbations elevated to a secondary objective
- Time to first moderate or severe COPD exacerbation elevated to secondary efficacy endpoint
- FEV1 AUC_{0-12} identified as the primary endpoint in the PFT sub-study with all other spirometry parameters identified as other endpoints
- "Pneumonia Adjudication Committee" and "CCV and Mortality Adjudication Committees" clarified to "Clinical Endpoint Committee"
- Efficacy estimand will be the primary analysis for superiority
- Type I error control strategy updated to account for new secondary endpoints
- mITT population will be the primary efficacy analysis population

The protocol amendments submitted do not affect the interpretation of results for Trial 02.

8.1.2.2. Trial 03 (PT009003) – BFF 12-week lung function trial

Title: "A randomized, double-blind, parallel group, multi-center study to assess the efficacy and safety of PT009 (BFF) compared to PT005 (FF) in subjects with moderate to very severe COPD"

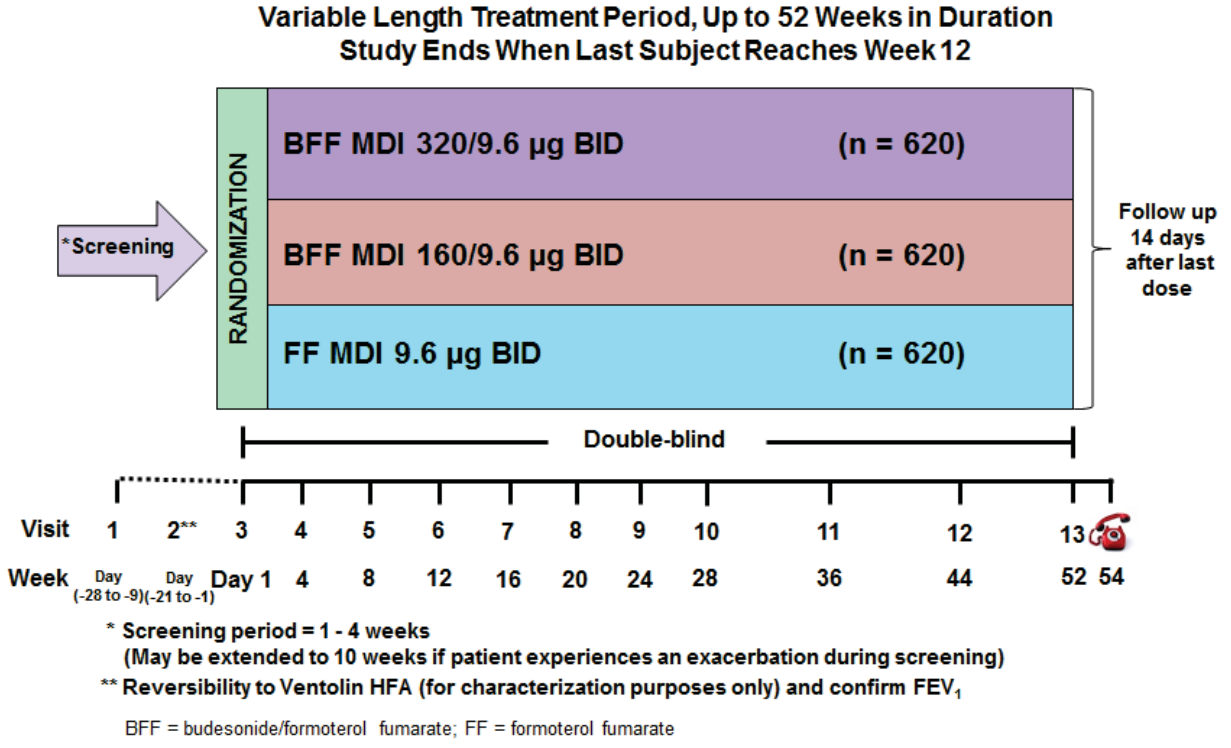
- Study dates: May 17, 2016 – April 4, 2018
- Study report date: July 25, 2018
- Study sites: A total of 259 study centers across 18 countries randomized subjects. Participating countries were located in North America, South America, Europe, and Asia.

Trial Design

This was a phase 3 randomized, double-blind, parallel group, multi-center, variable length trial to compare the efficacy and safety of BFF 320/9.6 µg, BFF 160/9.6 µg, and FF 9.6 µg. Subjects underwent a 1 to 4 week screening followed by a washout period of 1 week or longer depending on their medications prior to screening. Subjects on ICS or LABA/ICS were allowed to continue the ICS component through the screening period. Randomization was stratified by exacerbation history, post-bronchodilator FEV1, blood eosinophil count, and country. Enrollment was targeted to achieve a 2:1 ratio for the blood eosinophil strata with twice as many randomized subjects in the ≥150 cells per mm^3 category. The trial duration was variable, with subjects receiving at least 12 weeks and up to 52 weeks of randomized treatment. The trial was initially designed as a 52-week exacerbation trial. However, based on discussion at the teleconference meeting with the FDA on September 9, 2016, the Applicant amended the

protocol, changing it from an exacerbation trial to a bronchodilator trial. As a bronchodilator trial is typically required to be only 12-weeks in length, this amendment changed the end of the trial to when the last remaining randomized subject completed 12 weeks of treatment. As a result, the trial was of variable length because some subjects were already enrolled and completed more than 12 weeks at the time of the amendment. Endpoints were generally assessed over 12-weeks or at Week 12. Subjects were randomized 1:1:1 across the three treatment arms. The trial schematic is shown in Figure 9 and the schedule of events is shown in Table 51.

Figure 9. Trial 03 Schematic



Abbreviations: FEV_1 = forced expiratory volume in 1 second
Source: PT009003 Protocol Version 3.0; Figure 4-1; pg 32

Table 51. Trial 03 Schedule of Events

	Screening		Treatment Period											Follow-up TC
	Visit 1	Visit 2	Visit 3 (R)	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12	Visit 7 Week 16	Visit 8 Week 20	Visit 9 Week 24	Visit 10 Week 28	Visit 11 Week 36	Visit 12 Week 44	Visit 13 Week 52 or Final Study Visit	14 (+2) Days after last dose
Study Day[a]	Day -28 to -9	Day -21 to -1	Day 1	Day 28±2	Day 56±5	Day 84±5	Day 112±5	Day 140±5	Day 168±5	Day 196±5	Day 252±5	Day 308±5	Day 365±5	Day 379
In-Clinic	X	X	X	X		X			X		X		X	
Telephone Contact					X		X	X		X		X		X
Procedures														
Informed Consent	X													
Eligibility Criteria	X	X	X											
Verify Continued Eligibility		X	X	X		X			X		X		X	
Reversibility Testing[b]		X												
Demographics and Medical/Surgical History	X													
Smoking Status	X	X	X	X	X	X	X	X	X	X	X	X	X	
CAT[c]	X													
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[q]	X
Spirometry	X[el]	X	X	X		X			X		X		X	
Physical Examination[g]	X												X[q]	
Vital Signs	X	X	X	X		X			X		X		X[q]	
12-Lead ECG	X		X	X					X				X[q]	
Pregnancy Test[f]	X		X			X							X[q]	
Clinical Laboratory Testing	X		X	X					X				X[q]	
Chest Image or MRI[f]	X													
Adjust COPD Medications[h]	X												X[q]	
Adverse Events/COPD Exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X[q]	X
Inhalation Device and Dose Indicator Training	X	X	X											
Study Drug Dispensing/Collection	X[i]	X	X	X		X			X		X		X[q]	
Study Drug Administration			X	X		X			X		X		X	
BDI/TDI[f]			X	X		X			X		X		X[q]	
SGRQ[j]			X	X		X			X		X		X[q]	
EQ-5D-5L[j]			X	X		X			X		X		X[q]	
HCRU				X	X	X	X	X	X	X	X	X	X[q]	X
eDiary Dispensing/Collection[k]	X												X[q]	
eDiary Training / Re-Training[k]	X	X												
eDiary Review[l]		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Status Check[m]													X	

BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; CAT=COPD Assessment Test; eDiary=electronic diary; ECG=electrocardiogram; EQ-5D=European Quality-of-Life-5 Dimensions; Patient Reported Outcomes; HCRU=Healthcare Resource Utilization; MRI=Magnetic resonance imaging; R=randomization; SGRQ=St. George Respiratory Questionnaire; TC=Telephone call

Source: PT009003 Protocol Version 4.0; Figure 8-1; pg 63-64

Overall, the design of the trial is reasonable to assess lung function and consistent with other programs for COPD inhaled products. Note that the primary endpoint was changed from rate of moderate or severe exacerbation to trough FEV1 once the trial was already underway. This was amended prior to unblinding of data. While atypical to alter the length and endpoint once the trial is underway, the change is unlikely to change the interpretability of the trial.

Objectives

- Primary objective: To assess the effects of BFF MDI relative to FF MDI on lung function
- Secondary objectives:
  - To assess the effects of BFF MDI relative to FF MDI on COPD exacerbations
  - To assess the effects of BFF MDI relative to FF MDI on symptoms of COPD
  - To assess the effects of BFF MDI relative to FF MDI on quality of life

Trial Population

The trial consisted of 1876 randomized COPD patients. The inclusion and exclusion criteria were generally similar to Trial 02 and are not listed here. A key difference in inclusion criteria from Trial 02 to Trial 03 is that in Trial 03 subjects had to have a documented history of at least 1 moderate or severe COPD exacerbation in the previous 12 months. This reflects the original trial design as an exacerbation trial, which was subsequently amended (see Protocol Amendments below).

Key Withdrawal Criteria

The withdrawal criteria are similar to those in Trial 02.

The inclusion criteria and exclusion criteria are reasonable and consistent with other programs for COPD inhaled products. Based on these criteria, the trial population will likely be representative of the target population.

Treatments

The trial consisted of 3 treatment groups. All treatments were taken twice daily. The treatment groups are as follows:

- BFF MDI 320/9.6 µg
- BFF MDI 160/9.6 µg
- FF MDI 9.6 µg

All subjects were provided with albuterol sulfate inhalation aerosol 90 µg to be taken as directed on an as needed basis during the trial.

Restricted Medications

The prohibited medications were the same as those for Trial 02. Note that subjects who were dependent on steroids and maintained on an equivalent of up to 5 mg oral prednisone daily or up to 10 mg oral prednisone every other day for at least 3 months prior to Visit 1 were eligible for enrollment provided the dose remained consistent. Subjects may have been treated with systemic corticosteroids during the treatment period if required.

Trial Endpoints

Primary Endpoint

- Morning pre-dose trough FEV1 at Week 12

Secondary Endpoints

- Time to first moderate or severe COPD exacerbation
- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score at Week 12
- Change from baseline in average daily rescue albuterol use over 12 weeks

Safety Endpoints

- AEs
- ECGs
- Clinical laboratory testing
- Vital signs measurement

The trial endpoints and definition of COPD exacerbation are reasonable and consistent with the trial objectives and are similar to other COPD development programs. Note that the original endpoint was rate of moderate or severe exacerbations over 52 weeks. This was amended to morning pre-dose trough FEV1 at Week 12 based on regulatory feedback (see Regulatory Background above and Protocol Amendments below). While unconventional to make such an amendment to the protocol after the trial had begun, it is unlikely that this change had any impact on the interpretability of efficacy or safety as this amendment was made prior to unblinding.

Statistical Analysis Plan

Analysis Population and Estimand

Four analysis populations were defined: ITT population, mITT population, rescue Ventolin user population and safety population.

Three estimands were defined in this trial: the efficacy estimand, attributable estimand, and treatment policy estimand.

The primary analyses were conducted targeting the efficacy estimand on mITT population. There were 2 treatment comparisons of interest:

- BFF MDI 320/9.6 µg vs.FF MDI
- BFF MDI 160/9.6 µg vs.FF MDI

In this review, we focus primarily on the comparison of BFF MDI 320/9.6 versus FF MDI, given the proposed dose of the BGF.

Statistical Analysis Model and Additional Analyses

The primary endpoint of change from baseline in morning pre-dose trough FEV1 was analyzed using a repeated measures linear mixed model. The model included treatment, visit, treatment-by-visit interaction, and ICS use at Screening as categorical covariates and baseline FEV_1, baseline blood eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates. Two-sided p-values and point estimates with 2-sided 95% CIs were produced for treatment difference.

The Applicant conducted analysis on attributable estimand for change from baseline in morning pre-dose trough FEV_1.

Secondary endpoints analyses used same statistical model as Trial 06 and Trial 02.

Missing Data Handling

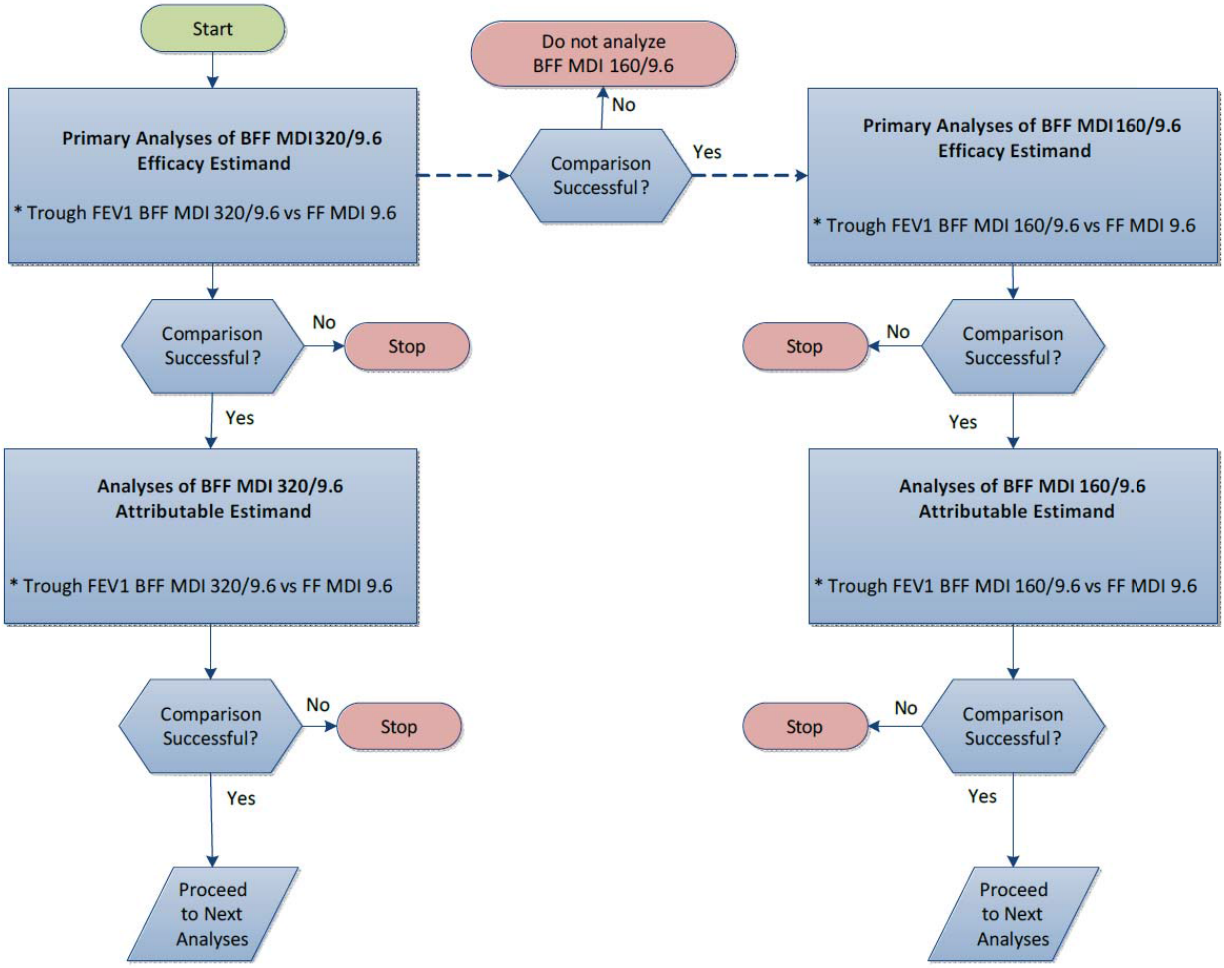
The primary analysis of primary endpoint and secondary endpoints targeted efficacy estimand. Data collected after discontinuing the trial treatment were excluded from the primary analysis and treated as missing.

The Applicant conducted tipping point analysis based on the efficacy estimand as a sensitivity analysis to assess impact of missing data. The statistical reviewer will address this issue in section 8.3 Statistical Issues.

Multiplicity

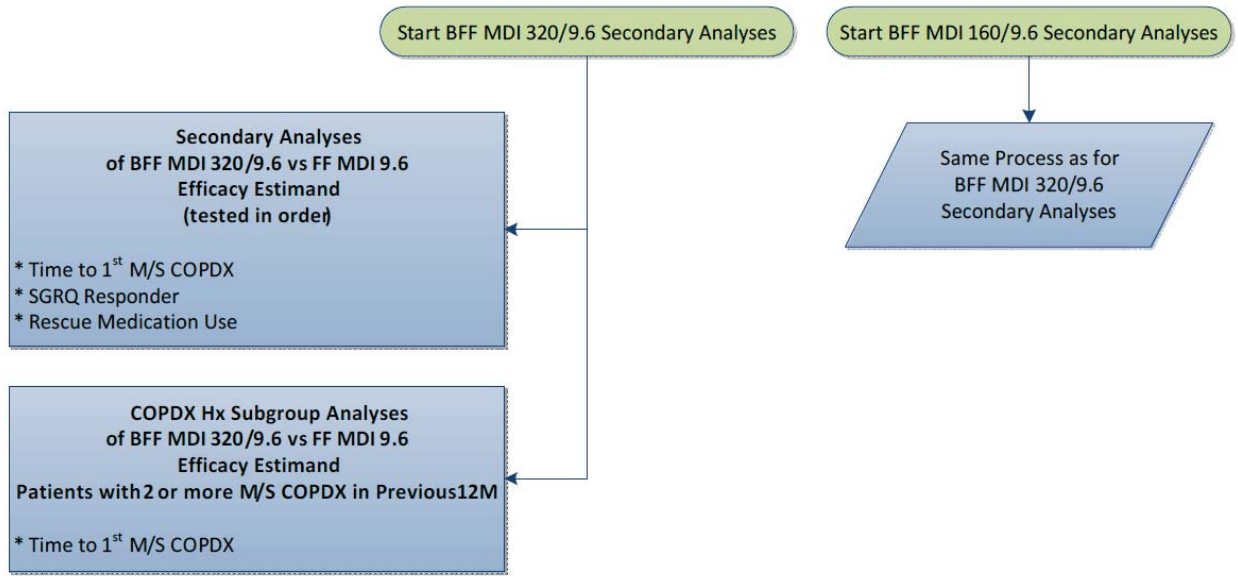
The Type I error rate was strongly controlled. Figure 10 presents the hypothesis testing order of the primary endpoint and Figure 11 presents the hypothesis testing order of the secondary endpoints.

Figure 10. Group 1: Type I Error Control for the Analyses of the Primary Endpoints (Trial 03)



Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler
Source: Applicant's SAP Figure 13 (Page 97 of Statistical Methods and Analysis)

Figure 11. Group 2: The Analysis of the Secondary Endpoints (Trial 03)



Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; COPDX = COPD exacerbation; MDI = metered dose inhaler
Source: Applicant's SAP Figure 14 (Page 98 of Statistical Methods and Analysis)

Notice that in Figure 10 after testing the primary analyses of BFF 320/9.6 statistically significant using efficacy estimand, the alpha wasn't split between the test of secondary analyses of BFF 320/9.6 on attributable estimand and the test of primary analyses of BFF 160/9.6 on efficacy estimand. We will address this issue in section 8.3 Statistical Issues.

Subgroup Analysis and Bayesian Shrinkage Subgroup Analysis

To examine whether the treatment effects vary among the levels of a baseline factor, we conducted subgroup analyses on the co-primary endpoints, in the following categories using traditional subgroup analysis and the Bayesian shrinkage subgroup analysis:

- Age
- Gender
- Race
- Region

Protocol Amendments

The first version of the protocol dated February 9, 2016 was amended 3 times on July 15, 2016, December 15, 2016, and January 8, 2018. Protocol amendments are summarized as follows:

July 15, 2016 Amendment

- Changed inclusion criteria to clarify that use of nebulized COPD medications were allowed prior to Visit 1 but could not be used during the study.
- Created separate subsections of Reasons for Treatment Discontinuation and Reasons for Study Withdrawal to reflect that subjects may discontinue from treatment without being withdrawn from the study.
- Clarified that subjects discontinuing study treatment, but continuing study participation will have all AEs/SAEs collected through their last visit.
- Clarified vital sign measurements.

December 15, 2016 Amendment

- Moved COPD exacerbations from a Primary Objective to a Secondary Objective
- Changed the study from 52-weeks to variable length with the study ending when the last randomized subject completes 12 weeks of treatment. This change was justified by the Applicant due to "refined regulatory requirements for the approval of dual and triple inhalation combination products." The new study design remained fully powered to demonstrate a lung function benefit and a numerical trend on COPD exacerbations.
- Changed the inclusion criteria for post-bronchodilator FEV1 from <70% to <80%

January 8, 2018 Amendment

- Included new text that clarified that the efficacy estimand will be the primary analysis, the attributable estimand will be a secondary analysis, and the treatment policy estimand will be a supportive analysis.
- Removed "time to first clinically important deterioration in COPD" from the secondary endpoints in the US approach
- Update to Type I Error control strategy to account for change in secondary endpoints.
- New sections to define the estimands used in the study and to describe the subgroup analyses to be performed.

The protocol amendments submitted do not affect the interpretation of results for Trial 03.

8.1.3. Study Results

Each section of the review of efficacy for BGF begins with the review of efficacy results from Trial 06, the dedicated BGF phase 3 efficacy trial. Because the dual component BFF is not an approved product and is included as a comparator in Trial 06, each section also reviews the efficacy results of the BFF phase 3 studies, Trial 02 and Trial 03. The efficacy for the dual component GFF was established under the approval of NDA 208294 (see review by Dr. Chin dated March 21, 2016) and will not be discussed here.

Compliance With Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in the clinical study report in Trials 06, 08, 02, and 03.

Financial Disclosure

See Section 15.1.

Patient Disposition

In Trial 06, the BGF 24-week lung function trial, 1902 patients were randomized and 1899 were treated. Of the randomized patients, 1689 completed the trial and 1634 completed treatment. Patient disposition for Trial 06 are presented in Table 52.

Table 52. BGF Trial 06 Subjects Disposition (All Subjects Randomized)

	BGF (N=640) n (%)	GFF (N=627) n (%)	BFF (N=316) n (%)	TBH (N=319) n (%)	Total (N=1902) n (%)
Not treated	1 (0.2)	0	1 (0.3)	1 (0.3)	3 (0.2)
Treated	639 (99.8)	627 (100.0)	315 (99.7)	318 (99.7)	1899 (99.8)
Completed 24 weeks of treatment with study drug	566 (88.6)	524 (83.6)	266 (84.4)	278 (87.4)	1634 (86)
Discontinued from study drug	73 (11.4)	103 (16.4)	49 (15.6)	40 (12.6)	265 (14.0)
Completed study	15 (2.3)	25 (4.0)	13 (4.1)	2 (0.6)	55 (2.9)
Withdrawn from study	48 (7.5)	74 (11.8)	35 (11.1)	36 (11.3)	193 (10.2)
Completed study	581 (90.9)	549 (87.6)	279 (88.6)	280 (88.1)	1689 (88.9)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler
Source: PT010006 CSR Edition 1; Table 16; pg 97; confirmed by Statistical Reviewer

Of the 1899 treated patients, 3 patients participated in multiple studies and were excluded from the mITT population (2 patients in the GFF group and 1 patient in the BFF group) for a total of 1896. In terms of treatment discontinuations in Trial 06, the GFF group had the highest rate of discontinuation (16.2%) and BGF had the lowest (11.4%). Reasons for discontinuation in Trial 06 for the mITT population were similar across groups and are shown in Table 53. The most common reason for discontinuation was subject discretion, which included withdrawal of consent as the most common reason.

Table 53. BGF Trial 06 Reasons for Discontinuation From Study Drug (mITT Population[a])

Reason for Discontinuation	BGF (N=639) n (%)	GFF (N=625) n (%)	BFF (N=314) n (%)	TBH (N=318) n (%)	Total (N=1896) n (%)
Discontinued from study drug	73 (11.4)	101 (16.2)	48 (15.3)	40 (12.6)	262 (13.8)
Subject discretion	14 (2.2)	37 (5.9)	19 (6.1)	15 (4.7)	85 (4.5)
Adverse events	28 (4.4)	30 (4.8)	11 (3.5)	11 (3.5)	80 (4.2)
Lack of efficacy	10 (1.6)	16 (2.6)	6 (1.9)	6 (1.9)	38 (2.0)

Reason for Discontinuation	BGF (N=639) n (%)	GFF (N=625) n (%)	BFF (N=314) n (%)	TBH (N=318) n (%)	Total (N=1896) n (%)
Investigator or designee considers it to be in subject's best interest	5 (0.8)	11 (1.8)	5 (1.6)	1 (0.3)	22 (1.2)
Major protocol deviation	3 (0.5)	4 (0.6)	4 (1.3)	4 (1.3)	15 (0.8)
Subject lost to follow-up	10 (1.6)	2 (0.3)	0	2 (0.6)	14 (0.7)
Protocol-specified discontinuation criteria a	3 (0.5)	1 (0.2)	3 (1.0)	1 (0.3)	8 (0.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate, BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; mITT = modified intent to treat
[a] Three treated patients participated in multiple studies and were excluded from the mITT population (2 patients in the GFF group and 1 patient in the BFF group) for a total of 1896
Source: PT010006 CSR Edition 1; Table 17; pg 98; confirmed by Clinical Reviewer

In Trial 08, the BGF safety extension trial, 627 patients signed the Trial 08 informed consent. Of these patients, 456 (72.7%) met eligibility criteria and were included in the Safety Population.

Frequency of discontinuation in Trial 08 was similar across groups, with subject discretion again being the most common reason (withdrawal of consent was the most common reason for discontinuation under subject discretion). These data are shown in Table 54.

Table 54. BGF Trial 08 Reasons for Discontinuation From Study Drug (Safety Population)

	BGF (N=194) n (%)	GFF (N=174) n (%)	BFF (N=88) n (%)	Total (N=456) n (%)
Discontinued from study drug	52 (26.8)	44 (25.3)	23 (26.1)	119 (26.1)
Subject discretion	18 (9.3)	13 (7.5)	7 (8.0)	38 (8.3)
Adverse events	14 (7.2)	13 (7.5)	6 (6.8)	33 (7.2)
Lack of efficacy	3 (1.5)	5 (2.9)	4 (4.5)	12 (2.6)
Investigator or designee considers it to be in subject's best interest	0	4 (2.3)	2 (2.3)	6 (1.3)
Major protocol deviation	2 (1.0)	2 (1.1)	2 (2.3)	6 (1.3)
Subject lost to follow-up	12 (6.2)	4 (2.3)	0	16 (3.5)
Protocol-specified discontinuation criteria[a]	3 (1.5)	2 (1.1)	2 (2.3)	7 (1.5)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate
[a] Includes subcategories of hepatic impairment, prescription of proh bited medication, other, and not eligible
Source: PT010008 CSR Edition 1; Table 9; pg 66; confirmed by Clinical Reviewer

In the BFF 24-week lung function trial, Trial 02, 2389 patients were randomized and 2370 were treated. Of the randomized patients, 2057 completed treatment. Patient disposition for Trial 02 is presented in Table 55.

Table 55. BFF Trial 02 Subject Disposition (All Subjects Randomized)

	BFF 320/9.6 N=664 n (%)	BFF 160/9.6 N=649 n (%)	FF N=648 n (%)	BD N=209 n (%)	TBH N=219 n (%)	Total N=2389 n (%)
Not treated	7 (1.1)	8 (1.2)	1 (0.2)	3 (1.4)	0	19 (0.8)
Treated	657 (98.9)	641 (98.8)	647 (99.8)	206 (98.6)	219 (100.0)	2370 (99.2)
Completed 24 weeks of treatment	576 (86.7)	568 (87.5)	554 (85.5)	169 (80.9)	190 (86.8)	2057 (86.1)
Discontinued from study drug	81 (12.2)	73 (11.2)	93 (14.4)	37 (17.7)	29 (13.2)	313 (13.1)
Withdrawn from study	45 (6.8)	44 (6.8)	48 (7.4)	17 (8.1)	19 (8.7)	173 (7.2)
Completed study	28 (4.2)	26 (4.0)	34 (5.2)	18 (8.6)	9 (4.1)	115 (4.8)
Number of subjects who completed the study overall	604 (91.0)	594 (91.5)	588 (90.7)	187 (89.5)	199 (90.9)	2172 (90.9)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler
Source: PT009002 CSR Edition 1; Table 17; pg 88; confirmed by Statistical Reviewer

Of the 2370 treated patients, 9 patients participated in multiple studies and were excluded from the mITT population (2 in the BFF 320/9.6 group, 4 in the BFF 160/9.6 group, and 3 in the FF group) for a total of 2361 patients. Regarding treatment discontinuation in Trial 02, for the mITT population, the BD group had the highest rate of discontinuation (18%). Otherwise, discontinuation rates were similar across groups. The most common reason for discontinuation was adverse events (AEs) (3.9%) followed by subject discretion (3.7%). A summary of discontinuations in Trial 02 is shown in Table 56.

Table 56. BFF Trial 02 Reasons for Discontinuation From Study Drug (mITT Population[a])

	BFF 320/9.6 N=655 n (%)	BFF 160/9.6 N=637 n (%)	FF N=644 n (%)	BD N=206 n (%)	TBH N=219 n (%)	Total N=2361 n (%)
Discontinued from study drug	79 (12.1)	70 (11.0)	90 (14.0)	37 (18.0)	29 (13.2)	305 (12.9)
Reasons for discontinuation from study drug						
Adverse events	27 (4.1)	22 (3.5)	17 (2.6)	13 (6.3)	12 (5.5)	91 (3.9)
Subject discretion	21 (3.2)	20 (3.1)	24 (3.7)	13 (6.3)	10 (4.6)	88 (3.7)
Lack of efficacy	16 (2.4)	15 (2.4)	32 (5.0)	8 (3.9)	2 (0.9)	73 (3.1)
Protocol-specified discontinuation criteria	3 (0.5)	3 (0.5)	4 (0.6)	0	0	10 (0.4)
Investigator or designee considers it to be in subject's best interest	3 (0.5)	2 (0.3)	3 (0.5)	1 (0.5)	2 (0.9)	11 (0.5)
Major protocol deviation	0	4 (0.6)	4 (0.6)	0	1 (0.5)	9 (0.4)
Administrative reason	3 (0.5)	1 (0.2)	1 (0.2)	0	0	5 (0.2)
Subject lost to follow-up	6 (0.9)	3 (0.5)	5 (0.8)	2 (1.0)	2 (0.9)	18 (0.8)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; mITT = modified intent to treat
[a] Nine treated patients participated in multiple studies and were excluded from the mITT population (2 in the BFF 320/9.6 group, 4 in the BFF 160/9.6 group, and 3 in the FF group) for a total of 2361 patients
Source: PT009002 CSR Edition 1; Table 18; pg 89; confirmed by Clinical Reviewer

In Trial 03, the BFF 12-week lung function trial, 1876 patients were randomized, 1864 were treated and 1625 (86.6%) patients completed 12-weeks of treatment. Trial 03 disposition is shown in Table 57.

Table 57. BFF Trial 03 Subject Disposition (All Subjects Randomized)

	BFF (N=629) n (%)	BFF (N=630) n (%)	FF (N=617) n (%)	All Subjects (N=1876) n (%)
Not treated	5 (0.8)	3 (0.5)	4 (0.6)	12 (0.6)
Treated	624 (99.2)	627 (99.5)	613 (99.4)	1864 (99.4)
Completed 12 weeks treatment	548 (87.1)	559 (88.7)	518 (84.0)	1625 (86.6)
Completed 24 weeks treatment	377 (59.9)	396 (62.9)	350 (56.7)	1123 (59.9)
Completed 52 weeks treatment	67 (10.7)	69 (11.0)	56 (9.1)	192 (10.2)
Discontinued from study drug	120 (19.1)	123 (19.5)	169 (27.4)	412 (22.0)
Withdrawn from study	71 (11.3)	87 (13.8)	101 (16.4)	259 (13.8)
Completed study	41 (6.5)	33 (5.2)	59 (9.6)	133 (7.1)
Number of subjects who completed the study overall	545 (86.6)	537 (85.2)	503 (81.5)	1585 (84.5)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate
Source: PT009003 CSR Edition 1; Table 15; pg 85; confirmed by Statistical Reviewer

Of the 1864 treated patients, 21 patients participated in multiple studies and were excluded from the mITT population (5 in the BFF 320/9.6 group, 10 in the BFF 160/9.6 group, and 6 in the FF group) for a total of 1843 patients. Regarding treatment discontinuation for Trial 03, in the mITT population, the FF group had the highest frequency of premature discontinuation (27.2%) and BFF 320/9.6 had the lowest (18.7%). The most common reason for discontinuation in Trial 03 was lack of efficacy (8.1%). Reasons for premature discontinuation for the mITT population for Trial 03 are shown in Table 58.

Table 58. BFF Trial 03 Reason for Discontinuation From Study Drug (mITT Population[a])

	BFF 320/9.6 (N=619) n (%)	BFF 160/9.6 (N=617) n (%)	FF 9.6 (N=607) n (%)	All Subjects (N=1843) n (%)
Premature discontinuation from study drug	116 (18.7)	116 (18.8)	165 (27.2)	397 (21.5)
Reasons for premature treatment Discontinuation				
AEs	28 (4.5)	21 (3.4)	32 (5.3)	81 (4.4)
Lack of efficacy	40 (6.5)	40 (6.5)	70 (11.5)	150 (8.1)
Protocol-specified discontinuation criteria	5 (0.8)	5 (0.8)	2 (0.3)	12 (0.7)
Investigator or designee considered it to be in subject's best interest	3 (0.5)	8 (1.3)	14 (2.3)	25 (1.4)
Subject discretion	26 (4.2)	25 (4.1)	30 (4.9)	81 (4.4)

	BFF 320/9.6 (N=619) n (%)	BFF 160/9.6 (N=617) n (%)	FF 9.6 (N=607) n (%)	All Subjects (N=1843) n (%)
Major protocol deviations	7 (1.1)	5 (0.8)	5 (0.8)	17 (0.9)
Administrative reasons	2 (0.3)	3 (0.5)	4 (0.7)	9 (0.5)
Subject lost to follow-up	5 (0.8)	9 (1.5)	8 (1.3)	22 (1.2)

Abbreviations: BFF = budesonide/formoterol fumarate, FF = formoterol fumarate; AE = adverse event; mITT = modified intent to treat
[a] twenty-one treated patients participated in multiple studies and were excluded from the mITT population (5 in the BFF 320/9.6 group, 10 in the BFF 160/9.6 group, and 6 in the FF group) for a total of 1843 patients
Source: PT009003 CSR Edition 1; Table 16; pg 86; confirmed by Statistical Reviewer

Overall, patient disposition and treatment discontinuation across the BGF and BFF programs are not likely to affect the interpretation of safety or efficacy results.

Protocol Violations/Deviations

Major protocol deviations included but were not limited to: non-compliance (<70% or >130% use), poor spirometry reproducibility, and using prohibited medication. In BGF efficacy Trial 06, there were 108 (5.7%) subjects with a major protocol deviation. The most common deviations were non-compliance (2.3%) and use of prohibited medications (2.0%). Rates were similar across treatment groups.

In BGF safety extension Trial 08, no subjects were excluded from the Safety Population due to a protocol violation. Trial 08 was not used in the analysis of efficacy.

In the BFF 24-week trial, Trial 02, there were 153 (6.5%) subjects with a major protocol deviation. The most common deviation was spirometry acceptability/repeatability (4.4%) followed by asthma diagnosis (1.4%). Frequency was similar between groups. In the BFF 12-week trial, Trial 03, the frequency of protocol deviations was similar between treatment groups. In Trial 03, there was no per-protocol analysis set and the ITT, mITT, and safety populations were identical.

Overall, in all trials the protocol violations were similar between treatment groups and not likely to affect the interpretation of results.

Table of Demographic Characteristics

Patient demographic characteristics for the 24-week BGF trial, Trial 06, are shown in Table 59. The average age was 65.2 years and the majority of patients were >65 years. There were more males than females and the most common race was White followed by Asian.

Table 59. BGF Trial 06 Demographics (mITT Population)

Demographic Parameters	BGF 320/18/9.6 µg (N=639)	GFF 18/9.6 µg (N=625)	BFF 320/9.6 µg (N=314)	Symbicort TBH 400/12 µg (N=318)	All Subjects (N=1896)
Age (Years)					
Mean (SD)	64.9 (7.8)	65.1 (7.7)	65.2 (7.2)	65.9 (7.7)	65.2 (7.7)
Median	65.0	66.0	65.0	66.0	65.5
Min, max	40, 80	42, 80	46, 80	45, 80	40, 80
Age Group, n (%)					
<65 years	296 (46.3)	272 (43.5)	146 (46.5)	132 (41.5)	846 (44.6)
≥65 years	343 (53.7)	353 (56.5)	168 (53.5)	186 (58.5)	1050 (55.4)
Gender, n (%)					
Male	460 (72.0)	430 (68.8)	224 (71.3)	236 (74.2)	1350 (71.2)
Female	179 (28.0)	195 (31.2)	90 (28.7)	82 (25.8)	546 (28.8)
Race, n (%)					
Black	23 (3.6)	38 (6.1)	15 (4.8)	14 (4.4)	90 (4.7)
White	329 (51.5)	301 (48.2)	157 (50.0)	163 (51.3)	950 (50.1)
Native Hawaiian or Pacific Islander	0	1 (0.2)	0	0	1 (0.1)
Native American or Alaska Native	1 (0.2)	0	0	0	1 (0.1)
Asian	284 (44.4)	285 (45.6)	142 (45.2)	141 (44.3)	852 (44.9)
Other	2 (0.3)	0	0	0	2 (0.1)
Ethnicity, n (%)					
Hispanic or Latino	16 (2.5)	14 (2.2)	7 (2.2)	4 (1.3)	41 (2.2)
Not Hispanic or Latino	623 (97.5)	611 (97.8)	305 (97.1)	312 (98.1)	1851 (97.6)
Unknown	0	0	1 (0.3)	2 (0.6)	3 (0.2)
Not reported	0	0	1 (0.3)	0	1 (0.1)
BMI, (kg/m²)					
Mean (SD)	26.1 (6.7)	26.3 (6.4)	26.1 (5.8)	26.2 (6.3)	26.2 (6.4)
Median	24.8	25.0	25.2	25.0	24.9
Min, max	13.5, 79.8	14.9, 65.2	15.1, 53.4	15.4, 50.0	13.5, 79.8

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; SD = standard deviation
Source: PT010006 CSR Edition 1; Table 20; pg 103-104, confirmed by Clinical Reviewer and identical to ITT population

The demographic characteristics of Trial 06 are similar across groups. The proportion males and of Asian patients in Trial 06 is notably higher than what is found in the United States COPD population. However, this is likely due to the global nature of this trial. Otherwise, the population of Trial 06 is a fair representation of the target population.

Patient demographic characteristics for the BGF safety extension trial, Trial 08, are shown in Table 60. The average age was 62.8 years, there were more males than females, and the most common race was White.

Table 60. BGF Trial 08 Demographics (Safety Population)

Demographic Parameters	BGF 320/18/9.6 µg (N=194)	GFF 18/9.6 µg (N=174)	BFF 320/9.6 µg (N=88)	All Subjects (N=456)
Age (Years)				
Mean (SD)	62.6 (7.9)	62.4 (7.8)	64.0 (7.2)	62.8 (7.7)
Median	63.0	62.5	64.0	63.0
Min, max	40, 78	46, 80	49, 79	40, 80
Age Group, n (%)				
<65 years	112 (57.7)	104 (59.8)	46 (52.3)	262 (57.5)
≥65 years	82 (42.3)	70 (40.2)	42 (47.7)	194 (42.5)
Gender, n (%)				
Male	102 (52.6)	87 (50.0)	53 (60.2)	242 (53.1)
Female	92 (47.4)	87 (50.0)	35 (39.8)	214 (46.9)
Race, n (%)				
Black	13 (6.7)	17 (9.8)	9 (10.2)	39 (8.6)
White	179 (92.3)	156 (89.7)	79 (89.8)	414 (90.8)
Asian	0	1 (0.6)	0	1 (0.2)
Other	2 (1.0)	0	0	2 (0.4)
Ethnicity, n (%)				
Hispanic or Latino	9 (4.6)	5 (2.9)	6 (6.8)	20 (4.4)
Not Hispanic or Latino	185 (95.4)	169 (97.1)	82 (93.2)	436 (95.6)
BMI, (kg/m²)				
Mean (SD)	29.0 (7.4)	29.0 (6.5)	29.0 (5.8)	29.0 (6.7)
Median	28.1	28.0	29.1	28.2
Min, max	17.3, 79.8	16.5, 65.2	18.3, 53.4	16.5, 79.8

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; SD = standard deviation
Source: PT010008 CSR Edition 1; Table 10; pg 68; confirmed by Clinical Reviewer

The demographics of Trial 08 are similar across groups and generally reflect the target population. Note that differences observed in the racial make-up of Trial 08 compared to Trial 06 is due to all Trial 08 sites being in the United States.

The demographic characteristics of the 24-week BFF trial, Trial 02, are shown in Table 61. The average age was 64.3 years and the majority of patients were male. The most common race was white. In 12-week BFF trial, Trial 03, the most common age was 64.9, the majority of patients were male (57.0%) and the majority of patients were White (83.2%) (data not shown).

Table 61. BFF Trial 02 Demographics (mITT Population)

Demographic Parameter	BFF 320/9.6 µg N=655	BFF 160/9.6 µg N=637	FF 9.6 µg N=644	BD 320 µg N=206	TBH 400/12 µg N=219	Total N=2361
Age (years)						
Mean (SD)	64.2 (7.7)	64.3 (7.6)	64.1 (8.0)	64.2 (7.4)	65.3 (7.0)	64.3 (7.7)
Median	65.0	65.0	65.0	65.0	66.0	65.0
Min, max	40, 81	42, 80	42, 80	44, 80	46, 80	40, 81
Age group, n (%)						
Age <65 years	322 (49.2)	298 (46.8)	313 (48.6)	101 (49.0)	98 (44.7)	1132 (47.9)
Age ≥65 years	333 (50.8)	339 (53.2)	331 (51.4)	105 (51.0)	121 (55.3)	1229 (52.1)

Demographic Parameter	BFF 320/9.6 µg N=655	BFF 160/9.6 µg N=637	FF 9.6 µg N=644	BD 320 µg N=206	TBH 400/12 µg N=219	Total N=2361
Gender, n (%)						
Male	402 (61.4)	377 (59.2)	383 (59.5)	125 (60.7)	141 (64.4)	1428 (60.5)
Female	253 (38.6)	260 (40.8)	261 (40.5)	81 (39.3)	78 (35.6)	933 (39.5)
Race, n (%)						
White	633 (96.6)	619 (97.2)	622 (96.6)	197 (95.6)	210 (95.9)	2281 (96.6)
Black	19 (2.9)	15 (2.4)	20 (3.1)	9 (4.4)	8 (3.7)	71 (3.0)
American Indian or Alaska Native	2 (0.3)	2 (0.3)	2 (0.3)	0	0	6 (0.3)
Asian	1 (0.2)	1 (0.2)	0	0	1 (0.5)	3 (0.1)
Ethnicity, n (%)						
Not Hispanic or Latino	637 (97.3)	616 (96.7)	623 (96.7)	198 (96.1)	212 (96.8)	2286 (96.8)
Hispanic or Latino	16 (2.4)	18 (2.8)	21 (3.3)	8 (3.9)	6 (2.7)	69 (2.9)
Not Reported	1 (0.2)	2 (0.3)	0	0	0	3 (0.1)
Unknown	1 (0.2)	1 (0.2)	0	0	1 (0.5)	3 (0.1)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler
Source: PT009002 CSR Edition 1; Table 21; pg 93-94; confirmed by Clinical Reviewer and identical to ITT population

The demographics of Trial 02 and Trial 03 in the BFF program are similar across groups and generally reflective of the United States COPD population. Overall, the demographic characteristics of the BGF and BFF programs were well-balanced and fairly representative of the COPD population.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

In the BGF program (Trial 06 and Trial 08) and the BFF program (Trial 02 and Trial 03), baseline pulmonary function, COPD severity, symptom scores, and smoking history were similar across groups. Background COPD medication use was also similar between groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In the BGF 24-week lung function trial, Trial 06, and the safety extension trial, Trial 08, treatment compliance was approximately 95% across groups. Compliance was defined as the total number of puffs per day divided by the total expected puffs per day averaged across all days of dosing multiplied by 100. Concomitant medication that were initiated after study entry were similar across groups in both rates and medication used. The most common concomitant non-COPD medications were aspirin, amlodipine, atorvastatin, and lisinopril. The most common COPD-related medications were ambroxol, budesonide, and oxygen. There were 164 subjects who received concomitant ICS and 132 of these subjects discontinued it at Visit 4 (randomization). The remainder either used ICS during study drug interruption, used ICS after permanent discontinuation of study drug, or were consider a protocol deviation.

In the BFF trials, Trial 02 and Trial 03, treatment compliance was above 90% in both studies with Trial 03 being slightly lower. The definition of compliance was the same as the BGF program. Concomitant medication that were initiated after trial entry were similar across

groups in both rates and medication used, with the most common non-COPD medications being aspirin and atorvastatin in both studies. The most common COPD-related medications were oxygen, theophylline, and salbutamol in both studies.

Efficacy Results – Primary Endpoint

BGF Phase 3 Trial:

Trial 06 – BGF 24-Week Lung Function Trial

For Trial 06, the co-primary endpoints were change from baseline in pre-dose trough FEV1 at Week 24 (BGF versus GFF) and change from baseline FEV1 AUC_{0-4} at Week 24 (BGF versus BFF).

To support the contribution of the ICS component (budesonide) to BGF, change from baseline in pre-dose trough FEV1 at Week 24 for BGF was compared to GFF. The use of trough FEV1 to assess for the ICS contribution to an inhaled COPD combination product is typical and acceptable. The difference in change from baseline in morning pre-dose trough FEV_1 at Week 24 between BGF and GFF was 13 ml (95% CI: -9, 36; p=0.2375) and was not statistically significant. This result is not supportive of the contribution of the ICS component to BGF in terms of lung function. These data are summarized in Table 62.

Table 62. BGF Trial 06 Treatment Comparisons for Change From Baseline in Morning Pre-Dose Trough FEV1 at Week 24 (BGF vs.GFF; mITT Population)

	BGF MDI 320/18/9.6 µg (N=639)	GFF MDI 18/9.6 µg (N=625)	BFF MDI 320/9.6 µg (N=314)
Mean change from baseline morning pre-dose trough FEV1 at Week 24: mL	122	109	44
Difference to BGF (SE): mL (95% CI)	n/a	13 (11) (-9, 36)	74(14) (47, 102)
p-value		0.2375	<0.0001

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler; CI = confidence interval; p-value = probability value
Source: Statistical Reviewer

While the ICS component does not appear to contribute to the trough-FEV1 effect of BGF, it is worth noting that based on the BGF to BFF comparison, that the LAMA component (glycopyrrolate) does appear to contribute to the trough effect with 95% confidence intervals excluding 0.

To assess for the contribution of the LAMA component (glycopyrrolate) to BGF, change from baseline in FEV1 AUC_{0-4} at Week 24 was compared between BGF and BFF. Typically, to assess for the LAMA contribution to an inhaled COPD combination product, this spirometric parameter is not used; more often, trough FEV1 is used. FEV1 assessed over the time period immediately following administration (e.g. FEV1 AUC_{0-4}) is more typically used to assess the contribution of the LABA component. However, as glycopyrrolate, like LABA, is a bronchodilator, it is not an

unreasonable choice. The difference in change from baseline in FEV1 AUC_{0-4} at Week 24 between BGF and BFF was 116 ml (95% CI: 80, 152; p<0.0001) and was statistically significant. These data demonstrate that the LAMA component of BGF does contribute to the FEV1 effect. These data are summarized in Table 63.

Table 63. BGF Trial 06 Treatment Comparisons for FEV1 AUC_{0-4} at Week 24 (BGF vs.BFF; mITT Population)

	BGF MDI 320/18/9.6 µg (N=639)	GFF MDI 18/9.6 µg (N=625)	BFF MDI 320/9.6 µg (N=314)
FEV1 AUC_{0-4} at Week 24: mL	290	284	178
Difference to BGF (SE): mL (95% CI)	n/a	5 (15) (-25, 34)	116(18) (80, 152)
p-value		0.7560	<0.0001

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; mITT = modified intent to treat; FEV_1 = forced expiratory volume in 1 second; AUC_{0-4} = area under the curve from zero to four hours; MDI = metered dose inhaler; p-value = probability value
Source: Statistical Reviewer

It is worth noting that for change from baseline in FEV1 AUC_{0-4} at Week 24, when comparing BGF to GFF and consistent with trough FEV1 for the same comparison, the results are not statistically significant. These data, taken with the trough FEV1 data, suggest that the ICS component of BGF does not contribute to the triple combination in terms of spirometric measurements.

These co-primary endpoint data suggest that BGF is superior to the unapproved product BFF, demonstrating contribution of the LAMA mono component. However, the comparison of BGF to GFF, the approved LAMA/LABA combination, does not support a conclusion that the ICS mono component contributes to the BGF effect. Therefore, these data do not demonstrate contribution of the relevant mono components and are insufficient to support efficacy.

Additionally, failure to meet statistical significance on both co-primary endpoints renders all subsequent efficacy endpoints in Trial 06 non-statistically significant due to hierarchical test procedures. As such, definitive determination of the ICS contribution to the benefit of BGF will not be possible based on data from this single trial, nor will definitive determination of the overall efficacy of BGF.

BFF Phase 3 Trials

Trial 02 – BFF 24-Week Lung Function Trial

For Trial 02, which compared BFF, the ICS/LABA portion of BGF, to BD (ICS) and FF (LABA), the co-primary endpoints were similar to the BGF Trial 06 and were change from baseline in pre-dose trough FEV1 at Week 24 (BFF vs. FF) and change from baseline in FEV1 AUC_{0-4} at Week 24 (BFF vs. BD).

Analysis results of change from baseline in pre-dose trough FEV1 at Week 24 is presented in Table 64. Contribution of ICS to BFF was assessed by comparing the treatment effect of BFF to FF. The difference of change from baseline in morning pre-dose trough FEV1 at Week 24 between these two treatment groups was 39 ml (95% CI: 15, 64; p=0.0018) and was statistically significant.

Table 64. BFF Trial 02 Treatment Comparisons for Change From Baseline in Morning Pre-Dose Trough FEV1 at Week 24 (BFF vs.FF; mITT Population)

	BFF MDI 320/9.6 µg (N=655)	FF MDI 9.6 µg (N=644)	BD MDI 320 µg (N=206)
Mean change from baseline morning pre-dose trough FEV1 at Week 24: mL	39	0	-27
Difference to BFF (SE): mL (95% CI)	n/a	39 (13) (15, 64)	65(18) (29, 101)
p-value		0.0018	0.0004

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; mITT = modified intent to treat; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler; p-value = probability value
Source: Statistical Reviewer

Analysis results of change from baseline in FEV1 AUC_{0-4} at Week 24 are presented in Table 65. Contribution of LABA to BFF was assessed by comparing the treatment effect of BFF to BD. The difference of change from baseline in FEV1 AUC_{0-4} at Week 24 between these two treatment groups was 173 ml (95% CI: 136, 210; p<0.0001) and was statistically significant.

Table 65. BFF Trial 02 Treatment Comparisons for FEV1 AUC_{0-4} at Week 24 (BFF vs.BD; mITT Population)

	BFF MDI 320/9.6 µg (N=655)	FF MDI 9.6 µg (N=644)	BD MDI 320 µg (N=206)
FEV1 AUC_{0-4} at Week 24: mL	200	160	25
Difference to BFF (SE): L (95% CI)	n/a	34 (13) (8, 59)	173(19) (136, 210)
p-value		0.0092	<0.0001

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; MDI = metered dose inhaler; FEV_1 = forced expiratory volume in 1 second; AUC_{0-4} = area under the curve from zero to four hours; CI = confidence interval; p-value = probability value
Source: Statistical Reviewer

Overall, the above primary endpoint results of BFF Trial 02 demonstrate the efficacy of BFF in COPD airflow obstruction and that each mono-component contributes to the bronchodilatory effect.

Trial 03 – BFF 12-Week Lung Function Trial

For Trial 03, which also compared BFF to FF, the primary endpoint was similar to Trial 02 and was change from baseline in pre-dose trough FEV1 at Week 12.

Analysis results of change from baseline in pre-dose trough FEV1 at Week 12 are presented in Table 66. Contribution of ICS to BFF was assessed by comparing the treatment effect of BFF to FF. The difference in change from baseline in morning pre-dose trough FEV1 at Week 12 between BFF and FF was 34 ml (95% CI: 9, 60; p=0.0081) and was statistically significant.

Table 66. BFF Trial 03 Treatment Comparisons for Change From Baseline in Morning Pre-Dose Trough FEV1 at Week 12 (BFF vs.FF; mITT Population)

	BFF MDI 320/9.6 µg (N=619)	FF MDI 9.6 µg (N=607)
Mean change from baseline morning pre-dose trough FEV1 at Week 12: mL	61	29
Difference to BFF (SE): L (95% CI)	n/a	34 (13) (9, 60)
p-value	n/a	0.0081

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; FEV_1 = forced expiratory volume in 1 second; CI = confidence interval; MDI = metered dose inhaler; mITT = modified intent to treat; p-value = probability value
Source: Statistical Reviewer

The primary endpoint result of Trial 03 demonstrates the efficacy of BFF in COPD airflow obstruction and that BD contributes to the bronchodilatory effect when added to FF.

Overall, the primary endpoints in the BFF development program (Trial 02 and Trial 03) demonstrate a contribution to the effectiveness of BFF from each mono-component in terms of lung function and support the efficacy of BFF in COPD.

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

BGF Phase 3 Trial

Trial 06 – BGF 24-Week Lung Function Trial

As Trial 06 failed on its co-primary endpoint, results for the secondary endpoints cannot be considered statistically significant. Therefore, no definitive conclusions regarding efficacy can be made based on these endpoints.

Secondary endpoints for Trial 06 are listed in order of testing hierarchy (see protocol review):

1. Change from baseline in morning pre-dose trough FEV1 over 24 weeks
2. Percentage of subjects achieving an MCID of ≥4 units in SGRQ total score at Week 24
3. Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
4. Peak change from baseline in FEV1 within 4 hours post-dosing at Week 24

5. Rate of moderate or severe COPD exacerbations over 24 weeks (BGF vs.BFF and GFF)
6. Time to onset of action on Day 1

For the analysis of change from baseline in pre-dose trough FEV1 over 24 weeks, contribution of ICS to BGF was assessed by comparing treatment effect of BGF to GFF. The difference of change from baseline in morning pre-dose trough FEV1 over 24 weeks between these two treatment groups was 22 ml (95% CI: 4, 39).

With regard to SGRQ, BGF demonstrated a numerically greater percentage of SGRQ responders at Week 24 compared with GFF (not statistically significant due to hierarchy). Similar trends were observed for the BGF to BFF comparison. SGRQ analysis results are presented in Table 67.

Table 67. BGF Trial 06 Treatment Comparisons for Percentage of Subjects Achieving an MCID of ≥4 Units in SGRQ Total Score at Week 24 (BGF vs.GFF, BGF vs.BFF, mITT Population)

	BGF MDI 320/18/9.6 µg (N=639)	GFF MDI 18/9.6 µg (N=625)	BFF MDI 320/9.6 µg (N=314)
Responder Rate in SGRQ total score at Week 24	49.7%	43.7%	43.3%
Difference of responder rate in SGRQ total score from BGF: (95% CI)	n/a	6.1% (0.3%, 11.8%)	6.4% (-0.6%, 13.5%)
Odds ratio: (95% CI)	n/a	1.28 (1.01, 1.61)	1.30 (0.97, 1.72)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; SGRQ = St. George's Respiratory Questionnaire; CI = confidence interval; MDI = metered dose inhaler; MCID = minimal clinically important difference
Source: Statistical Reviewer

For change from baseline in average daily rescue Ventolin HFA use over 24 weeks, BGF showed small numerical improvements in LS mean change from baseline compared with GFF (-0.25 puffs/day with 95% CI: -0.60, 0.09) and BFF (-0.24 puffs/day with 95% CI: -0.65, 0.18).

For peak change from baseline in FEV_1 within 4 hours post-dosing at Week 24, BGF demonstrated a numerical improvement in LS mean compared with BFF (118 mL; 95% CI: 80, 155), which was not statistically significant due to analysis hierarchy. Differences between BGF and GFF were negligible and not statistically significant (9 mL; 95% CI: -21, 40).

The rate of moderate or severe exacerbations was numerically lower during treatment with BGF relative to GFF (rate ratio [95% CI]: 0.48 [0.37, 0.64]) and numerically lower during treatment with BGF relative to BFF (rate ratio [95% CI]: 0.82 [0.58, 1.17]). While the 95% CI for the BGF to GFF comparison excluded null, the results are not statistically significant due to the comparisons position in the analysis hierarchy. Analysis results for rate of moderate or severe exacerbation are presented in Table 68.

Table 68. BGF Trial 06 Treatment Comparisons of Rate of Moderate or Severe COPD Exacerbations Over 24 Weeks (BGF vs.GFF, BGF vs.BFF; mITT Population)

	BGF MDI 320/18/9.6 µg (N=639)	GFF MDI 18/9.6 µg (N=625)	BFF MDI 320/9.6 µg (N=314)
Subjects with exacerbations, n (%)	108 (16.9)	157 (25.1)	65 (20.7)
Rate (per year) of moderate or severe COPD exacerbation over 24 weeks	0.49	0.89	0.57
Rate Ratio (SE): (95% CI)	n/a	0.48 (0.07) (0.37, 0.64)	0.82(0.15) (0.58, 1.17)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; COPD = chronic obstructive pulmonary disease; CI = confidence interval; mITT = modified intent to treat
Source: Statistical Reviewer

Time to onset is defined as the first post-dose time point where the mean change from baseline in FEV1 exceeded 100 mL. The time to onset of action on Day 1 was 5 minutes for BGF MDI (181 mL), GFF MDI (194 mL), and BFF MDI (167 mL). At 15 minutes, the change from baseline in FEV1 was 217 mL, 230 mL, and 197 mL for BGF, GFF and BFF, respectively.

Among the secondary endpoints in Trial 06, exacerbations and SGRQ are the most clinically relevant. For exacerbations and SGRQ, there were numerical trends favoring BGF compared to GFF, suggesting a therapeutic effect and a contribution of the ICS mono-component. However, because these results cannot be considered statistically significant, they do not alter the overall assessment for the efficacy of BGF gleaned from the primary endpoint results and do not rise to the level of substantial evidence of effectiveness. Overall, results for the secondary endpoints are not sufficient support for BGF efficacy or the contribution of BD to BGF.

BFF Phase 3 Trials

Trial 02 – BFF 24-Week Lung Function Trial

The secondary endpoints for Trial 02 are as follows (see protocol review for Type I error control strategy):

- Time to first moderate or severe COPD exacerbation (BFF vs.FF)
- Percentage of subjects achieving an MCID of ≥4 units in SGRQ total score at Week 24 (BFF vs.FF, BFF vs.BD)
- Change from baseline in morning pre-dose trough FEV1 at Week 24 (BFF vs.BD)
- Peak change from baseline in FEV1 post-dosing at Week 24 (BFF vs.BD)
- Change from Baseline in average daily Ventolin HFA use (puffs per day) over 24 weeks (BFF vs.BD)
- Time to onset of action as assessed by FEV1 on Day 1 (BFF vs.BD)

BFF 320/9.6 µg demonstrated a statistically significant improvement in time to first moderate or severe COPD exacerbation compared with FF (HR =0.675; p=0.0017). Results are presented in Table 69. Regarding annualized exacerbation rate, this was not included in the secondary

endpoints. The annualized exacerbation rate ratio for BFF 320/9.6 µg versus FF was 0.63 (p=0.0005) and for BFF 320/9.6 µg versus BD was 0.68 (p=0.0433).

Table 69. BFF Trial 02 Time to First Moderate or Severe COPD Exacerbation (BFF vs.FF; mITT Population)

	BFF MDI 320/9.6 µg (N=655)	FF MDI 9.6 µg (N=644)	BD MDI 320 µg (N=206)
Subjects with COPD exacerbation, n (%)	111 (16.9)	150 (23.3)	39 (18.9)
Time to first moderate or severe COPD exacerbation hazard ratio: (SE) (95% CI)	n/a	0.675 (0.528, 0.863)	0.806 (0.560, 1.162)
p-value		0.0017	0.2482

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; COPD = chronic obstructive pulmonary disease; CI = confidence interval; MDI = metered dose inhaler; mITT = modified intent to treat; p-value = probability value
Source: Statistical Reviewer

For time to first moderate or severe exacerbation and SGRQ, BFF 320/9.6 µg demonstrated effectiveness when compared to FF. Typically, annualized exacerbation rate is used as the endpoint to evaluate exacerbation. However, analysis of the annualized rate was supportive and the results from Trial 02 are still convincing evidence of effectiveness in terms of exacerbation.

For the percentage of subjects achieving an MCID of ≥4 units in SGRQ total score at Week 24, BFF 320/9.6 µg demonstrated a statistically significant greater percentage of SGRQ responders compared with FF, with an odds ratio of 1.3024 (p=0.0212). BFF 320/9.6 µg showed a numeric improvement in the percentage of SGRQ responders compared with BD, with an odds ratio of 1.1987 (p=0.2713). SGRQ results are presented Table 70.

Table 70. BFF Trial 02 Treatment Comparisons for Percent of Responders in SGRQ Total Score (Mean Improvement of ≥4.0 Units) at Week 24 (BFF vs.FF, BFF vs.BD; mITT Population)

	BFF MDI 320/9.6 µg (N=655)	FF MDI 9.6 µg (N=644)	BD MDI 320 µg (N=206)
Percentage of SGRQ responders at Week 24	48.12	41.59	43.62
Difference of % SGRQ responders compare to FF 9.6 or BD 320: (95% CI)	n/a	6.53 (0.99, 12.06)	4.50 (-3.48, 12.47)
Odds Ratio: (95% CI)	n/a	1.3024 (1.0402, 1.6306)	1.1987 (0.8679, 1.6557)
p-value		0.0212	0.2713

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; SGRQ = St. George's Respiratory Questionnaire; mITT = modified intent to treat; CI = confidence interval; p-value = probability value
Source: Statistical Reviewer

BFF 320/9.6 µg demonstrated a statistically significant improvement in change from baseline in morning pre-dose trough FEV1 at Week 24 compared to BD (Table 64 under Trial 02 primary endpoint).

BFF 320/9.6 µg demonstrated statistically significant improvements in LS mean peak change from baseline in FEV1 post-dosing at Week 24 compared with BD (157 mL; p<0.0001). Comparison to FF was not included in the secondary endpoints but did show a small increase (30 mL; p=0.0274).

BFF 320/9.6 µg also demonstrated statistically significant improvements in LS mean change from baseline in average daily rescue Ventolin HFA use over 24 weeks compared with BD (-0.70 puffs/day; p<0.0001). BFF 320/9.6 µg showed a smaller effect when compared to FF (-0.22 puffs/day; p=0.0610), and this comparison was not included in the secondary endpoints

The time to onset of action on Day 1 was 5 minutes for BFF 320/9.6 µg. BFF 320/9.6 µg demonstrated a 157 mL LS mean change from baseline in FEV1 at that timepoint with a statistically significant difference from BD of 132 mL (p<0.0001).

The secondary endpoint results in Trial 02 were generally consistent with the effectiveness of BFF 320/9.6 µg compared with the mono-components, FF and BD.

Trial 03 – BFF 12-Week Lung Function Trial

Secondary endpoints for Trial 03 included the following (see protocol review for statistical hierarchy):

- Time to first moderate or severe COPD exacerbation
- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score at Week 12
- Change from baseline in average daily rescue albuterol use over 12 weeks

For time to first moderate or severe COPD exacerbation, BFF 320/9.6 µg demonstrated a statistically significant improvement compared with FF (HR =0.827; p=0.0441). It should be noted that the exacerbation endpoint analysis includes data for patients who participated in the trial for as long as 52 weeks. Time to first exacerbation results are presented in Table 71. Annualized exacerbation rate was not included in the secondary endpoints, but BFF 320/9.6 µg did show improvement on annualized exacerbation rate with a rate ratio compared to FF of 0.67 (95% CI: 0.54, 0.82).

Table 71. BFF Trial 03 Time to First Moderate or Severe COPD Exacerbation (BFF vs.FF; mITT)

	BFF MDI 320/9.6 µg (N=619)	FF MDI 9.6 µg (N=607)
Subjects with COPD exacerbation: n (%)	220 (35.5)	241 (39.7)
Time to first moderate or severe COPD exacerbation hazard ratio: (95% CI)*	n/a	0.827 (0.688, 0.995)
p-value	n/a	0.0441

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; COPD = chronic obstructive pulmonary disease; mITT = modified intent to treat; CI = confidence interval; p-value = probability value
*95% CI and HR based on Cox regression, adjusting for baseline percent predicted FEV1 and baseline eosinophil count as continuous covariates and baseline COPD exacerbation history (Yes/No), country, and ICS use at Screening (yes/no) as categorical covariates.
Source: Statistical Reviewer

Taken together with the results from Trial 02, it is likely that the BFF 320/9.6 µg does add an exacerbation benefit over FF.

Regarding SGRQ, BFF 320/9.6 µg demonstrated a significantly greater percentage of SGRQ responders at Week 12 compared with FF, with a treatment difference of 7.55% (p=0.0121). SGRQ results are presented in Table 72.

Table 72. BFF Trial 03 Percentage of Subjects Achieving an MCID of ≥4 Units in SGRQ Total Score at Week 12 (BFF vs.FF; mITT Population)

	BFF MDI 320/9.6 µg (N=619)	FF MDI 9.6 µg (N=607)
SGRQ responders at Week 12: n (%)	315 (51.98)	262 (43.96)
SGRQ responders' difference: (95% CI)	n/a	7.55 (1.67, 13.43)
p-value	n/a	0.0121

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; MDI = metered dose inhaler; MCID = minimal clinically important difference; SGRQ = St. George's Respiratory Questionnaire; p-value = probability value; CI = confidence interval
Source: Statistical Reviewer

For rescue albuterol use, BFF 320/9.6 µg demonstrated a statistically significant improvement in LS mean change from baseline in average daily rescue Ventolin HFA use over 12 weeks compared with FF (-0.32 puffs/day; p=0.0097).

Overall, the results of secondary endpoints in Trial 03 provided additional evidence supporting the effectiveness of BFF 320/9.6 µg over FF. Importantly, this included effectiveness in exacerbation reduction and SGRQ.

Dose/Dose Response

The doses for GP and FF were established in the GFF program reviewed under NDA 208294 (see review by Dr. Stacy Chin dated March 21, 2016), so only the dose for BD needed to be established in this development program. In Trial 02, the BFF 24-week lung function trial BFF 320/9.6 µg showed a statistically significant improvement in change from baseline in morning

pre-dose trough FEV1 compared to FF whereas BFF 160/9.6 µg did not show a statistically significant improvement. Additionally, the magnitude of the effect was numerically larger for the 320/9.6 µg versus the 160/9.6 µg dose. These results are shown in Table 73.

Table 73. BFF Trial 02 Treatment Comparisons for Change From Baseline in Morning Pre-Dose Trough FEV1 at Week 24 (BFF 320/9.6 vs.FF 9.6 & BFF 160/9.6 vs.FF 9.6; Trial 02; mITT Population)

	BFF MDI 320/9.6 µg (N=655)	BFF MDI 160/9.6 µg (N=637)	FF MDI 9.6 µg (N=644)
Mean change from baseline morning pre-dose trough FEV1 at Week 24: mL	39	20	0
Difference to FF (SE): mL (95% CI)	39(13) (15, 64)	20(13) (-5, 44)	n/a
p-value	0.0018	0.1132	

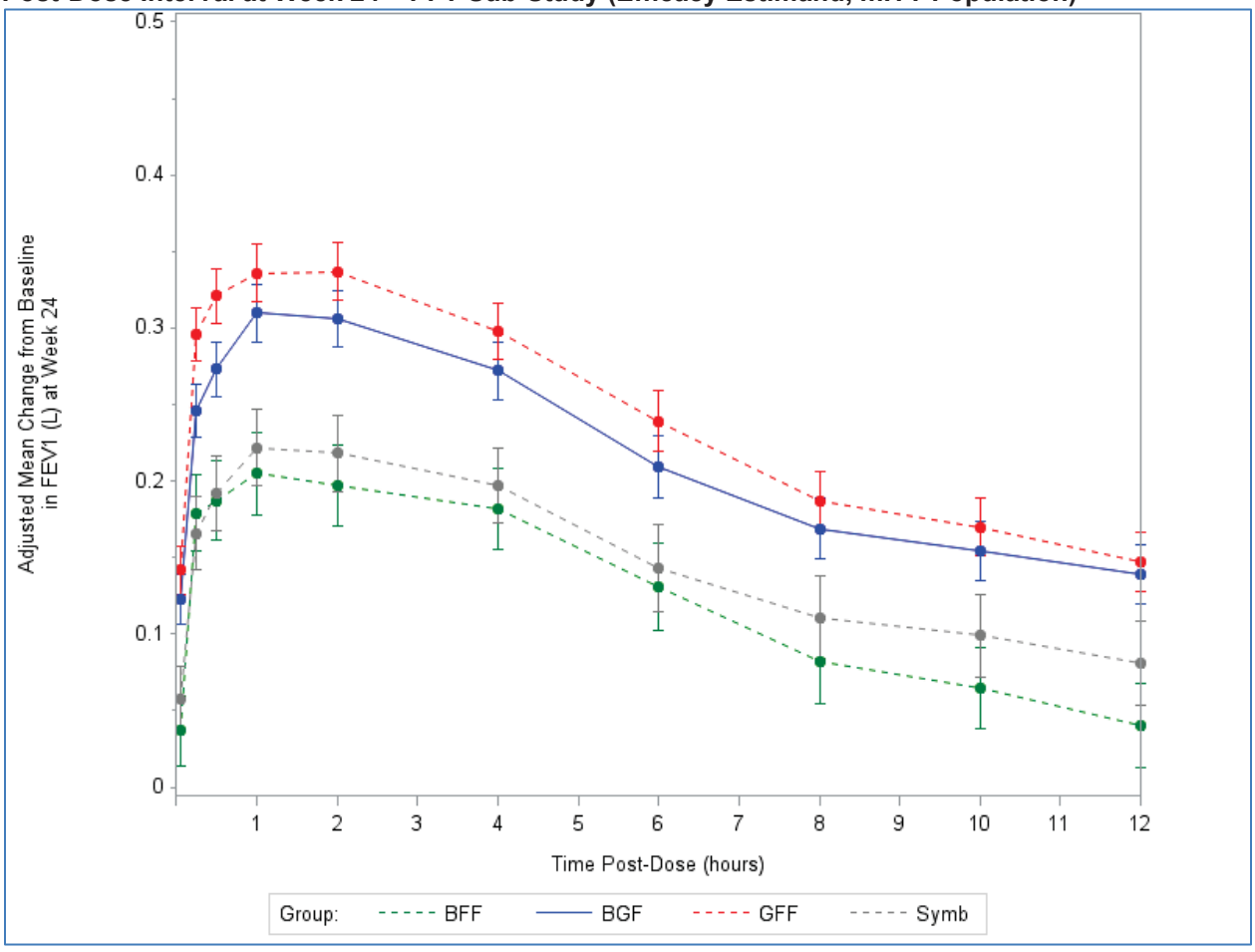
Abbreviations: BFF = budesonide/formoterol fumarate, FF = formoterol fumarate; mITT = modified intent to treat; MDI = metered dose inhaler; FF = formoterol fumarate; BFF = budesonide/formoterol fumarate; FEV_1 = forced expiratory volume in 1 second; p-value = probability value; SE = standard error
Source: Statistical Reviewer

Taken together with the results of BD dose-ranging (see section 6), the primary endpoint results of Trial 02 support the dose selection of BFF 320/9.6 µg over BFF 160/9.6 µg in the BGF combination.

Durability of Response

In the PFT sub-study of BGF lung function trial, Trial 06, the mean change from baseline in FEV1 over the 12-hour post-dose interval at Week 24 was assessed and showed durability of effect over the 12-hour period between doses for BGF. These results are shown in Figure 12.

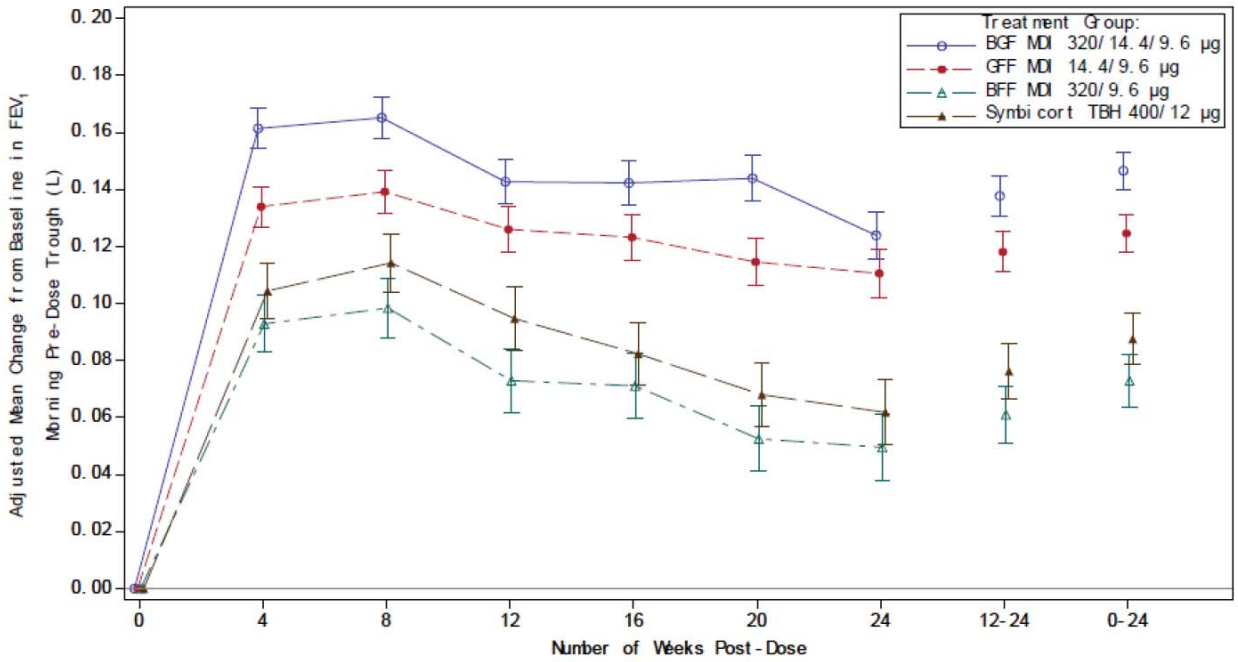
Figure 12. BGF Trial 06 Adjusted Mean Change From Baseline in FEV1 (L) ±SE Over the 12-Hour Post-Dose Interval at Week 24 – PFT Sub-Study (Efficacy Estimand, mITT Population)



Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Additionally, in Trial 06 the mean change from baseline in morning pre-dose trough FEV1 over time was assessed. BGF showed a durable response over the treatment period of 24-weeks. These results are shown in Figure 13.

Figure 13. BGF Trial 06 Adjusted Mean Change From Baseline in Morning Pre-Dose Trough FEV1 (L) ±SE Over Time (Efficacy Estimand, mITT Population)



Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH =Turbuhaler; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: PT010006 CSR Edition 1; Figure 3; pg 132

Overall, these results support the durability of effect for BGF.

Persistence of Effect

No analysis was performed to assess persistence of effect because the effects of BGF are not expected to persist following treatment discontinuation.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

In Trial 06 from the BGF program, SGRQ responder analysis of the percentage of patients achieving the MCID of ≥4 units in SGRQ total score revealed a numerical improvement for BGF over GFF and a numerical improvement over BFF (Table 67). Both comparisons were not statistically significant because failure of the primary endpoint and multiplicity control.

In Trial 02 from the BFF program, BFF 320/9.6 µg achieved a statistically significant improvement in SGRQ responder rate over FF and a numeric improvement over BD (Table 70). In Trial 03 from the BFF program, BFF 320/9.6 µg achieved a statistically significant improvement in SGRQ responder rate over FF (Table 72).

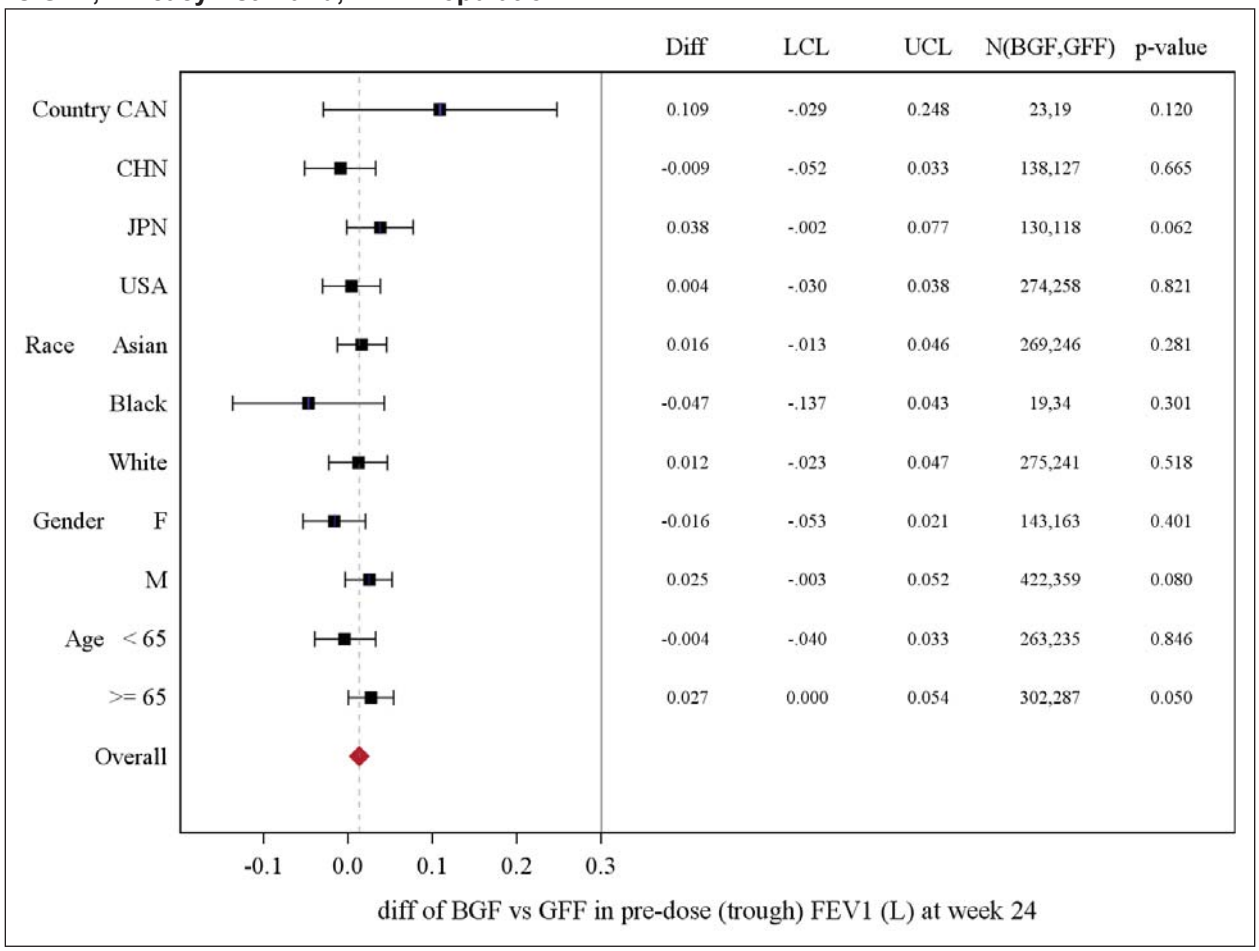
Additional Analyses Conducted on the Individual Trial

Traditional Subgroup Analysis

To examine whether the treatment effects vary among the levels of a baseline factor, such as age, gender, race or country (region), we conducted subgroup analyses on the primary endpoint(s) in these four factors. These subgroup analyses used the same analysis model, but a subset of the dataset used in the overall analyses.

Figure 14 presents the subgroup analysis results of co-primary endpoint pre-dose trough FEV1 of Trial 06. The overall result of this endpoint did not reach statistical significance. For all the subgroups considered, all the 95% CIs crossed zero, no subgroup reaches statistical significance. These results are consistent with the overall results.

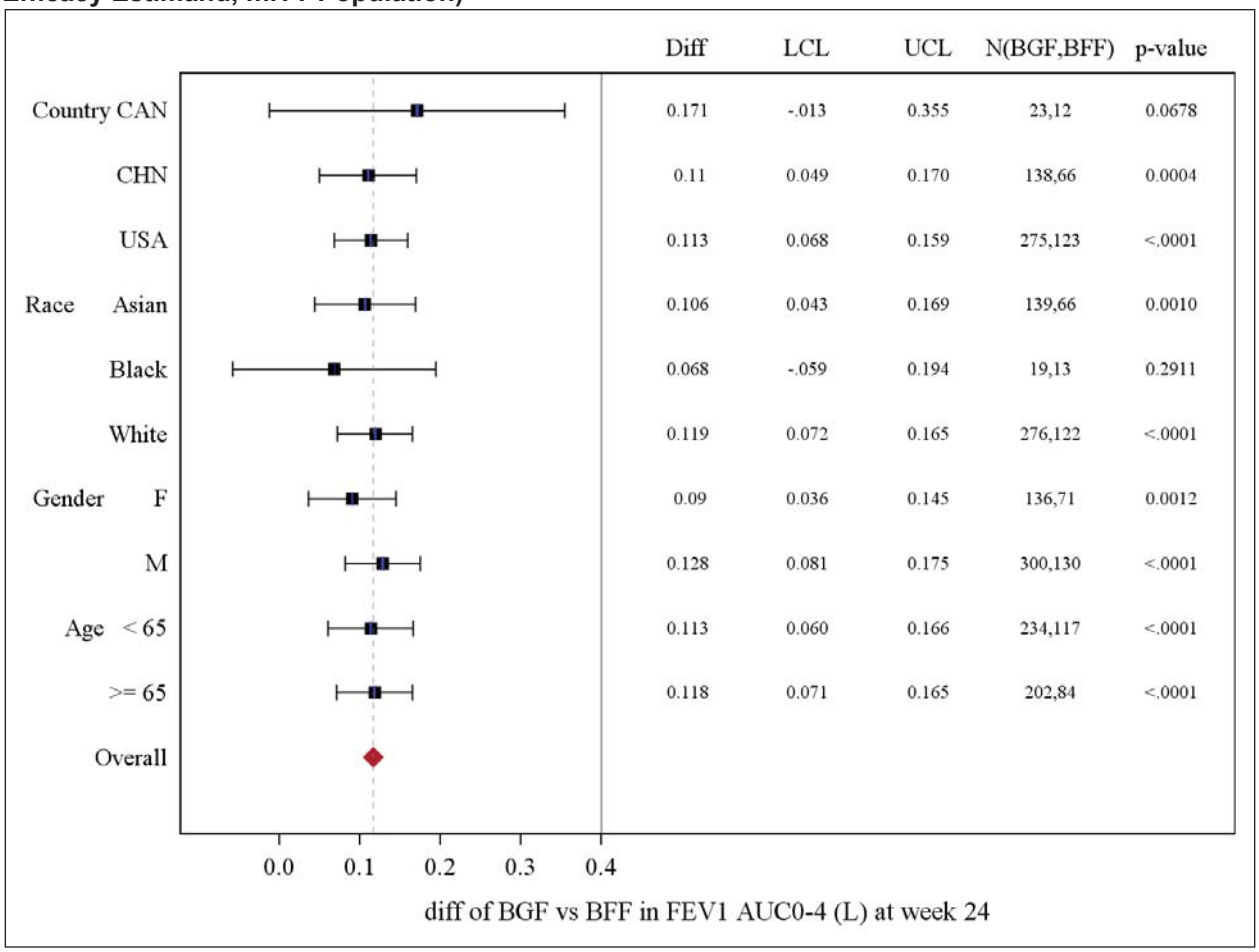
Figure 14. BGF Trial 06 Forest Plot of Pre-Dose Trough FEV_1 (L) (With 95% CI) by Subgroups (BGF vs.GFF, Efficacy Estimand, mITT Population



Abbreviations: CAN = Canada; CHN = China; JPN = Japan; Black = black or African American; F = female; M = male; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Figure 15 presents the subgroup analysis results of co-primary endpoint FEV1 AUC_{0-4} of Trial 06. The overall result of this endpoint reached statistical significance. For all the subgroups considered, almost all (except for subgroups of country Canada and race Black or African American), the lower bounds of 95% CIs were greater than zero, demonstrated statistically significant treatment effect. Due to small number of subjects in these two exceptional subgroups, the 95% CIs of treatment difference were wide. These results are considered consistent with the overall results.

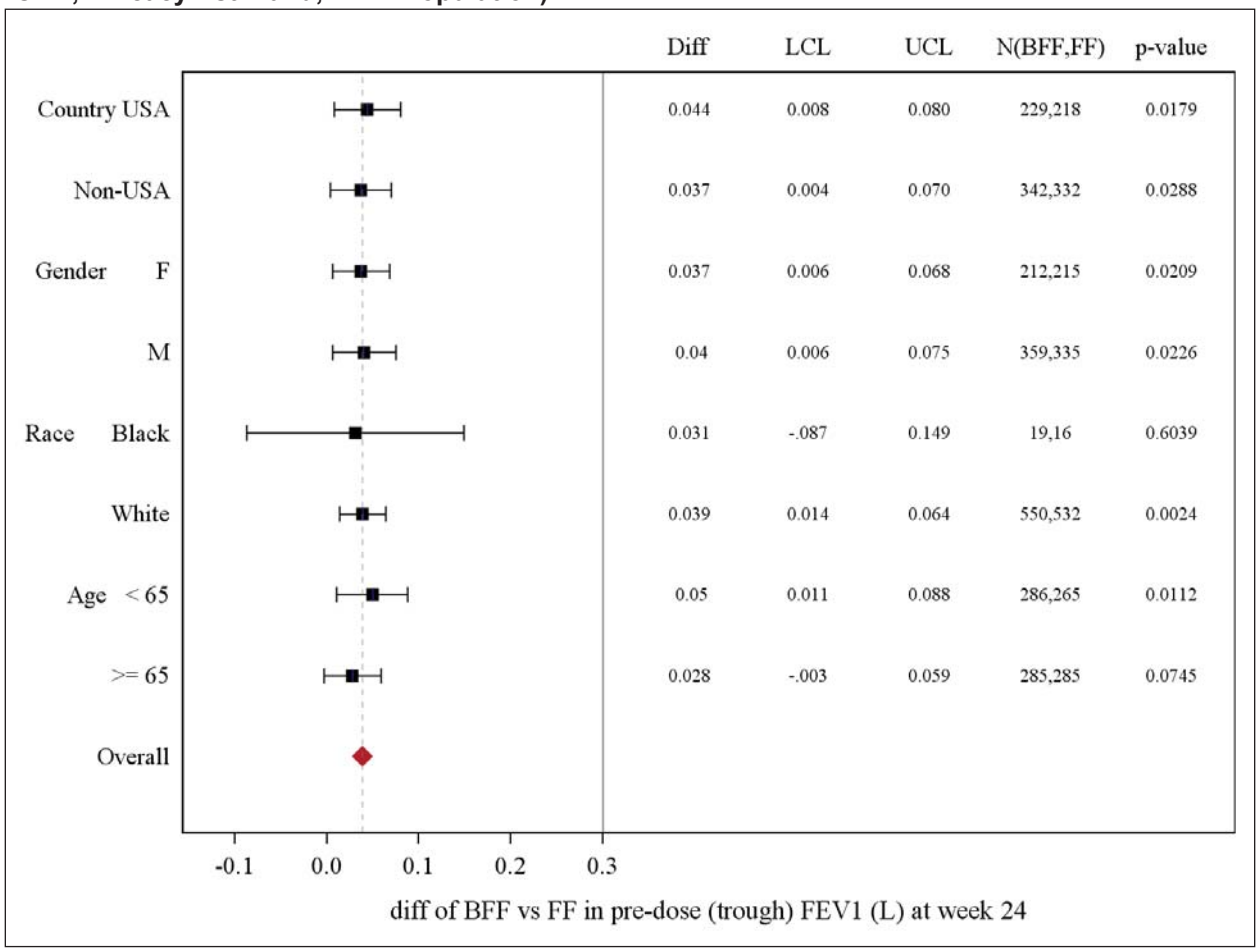
Figure 15. BGF Trial 06 Forest Plot of FEV1 AUC_{0-4} (L) (With 95% CI) by Subgroups (BGF vs.BFF, Efficacy Estimand, mITT Population)



Abbreviations: CAN = Canada; CHN = China; JPN = Japan; Black = black or African American; F = female; M = male; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Figure 16 presents the subgroup analysis results of co-primary endpoint pre-dose trough FEV1 of Trial 02. Subgroup of patients aged greater or equal to 65 years old did not reach statistical significance, although numerically better treatment effect. Subgroup of race Black or African American did not reach statistically significant treatment effect, this was due to large variability among the small number of subjects.

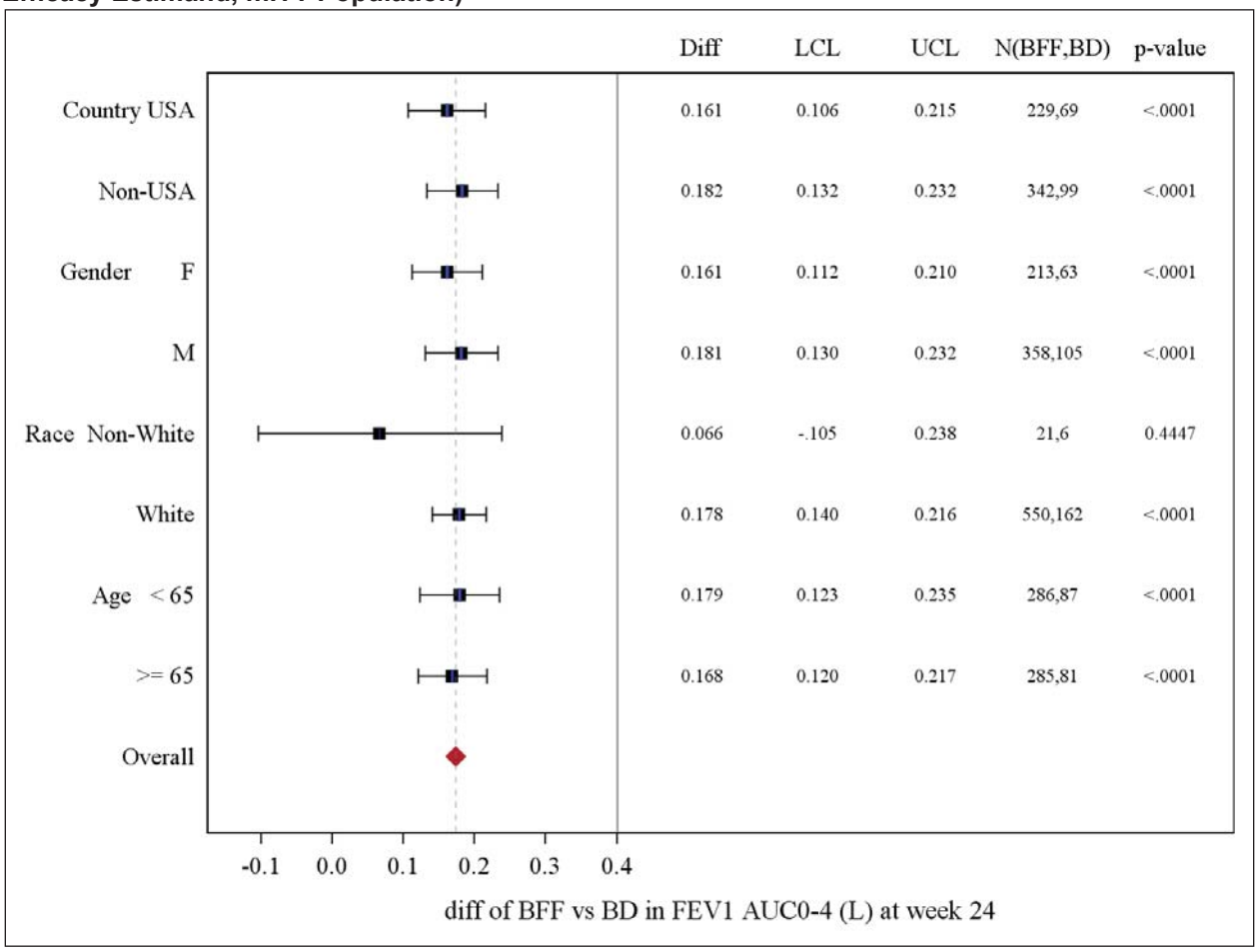
Figure 16. BFF Trial 02 Forest Plot of Pre-Dose Trough FEV1 (L) (With 95% CI) by Subgroups (BFF vs.FF, Efficacy Estimand, mITT Population)



Abbreviations: Black = black or African American; F = female; M = male; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Figure 17 presents the subgroup analysis results of co-primary endpoint FEV1 AUC_{0-4} of Trial 02. All the subgroups considered, except subgroup of race non-white (very small number of subjects in this subgroup), reached statistically significant treatment effect. These results are consistent with the overall analysis result of this endpoint.

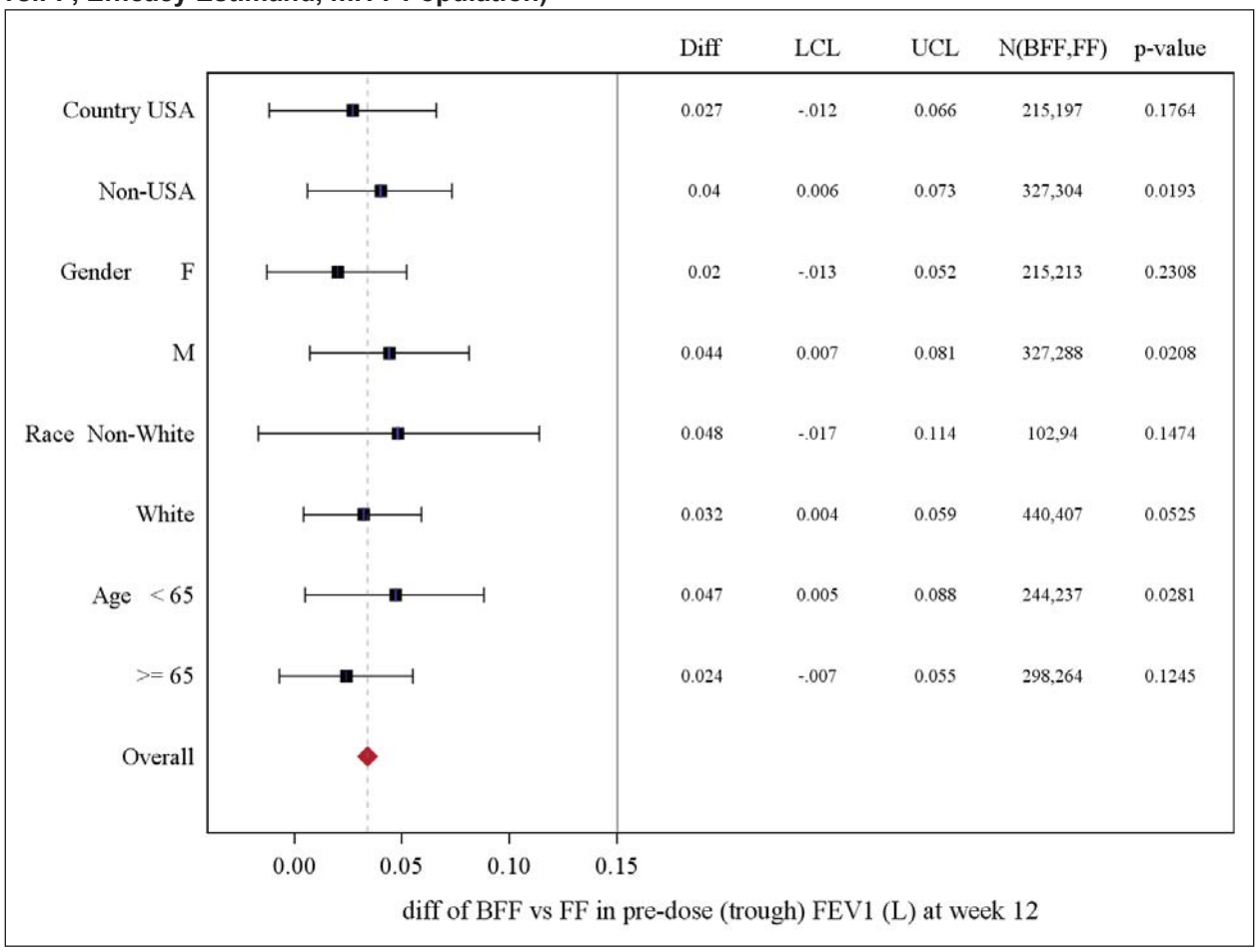
Figure 17. BFF Trial 02 Forest Plot of FEV1 AUC_{0-4} (L) (With 95% CI) by Subgroups (BFF vs.BD, Efficacy Estimand, mITT Population)



Abbreviations: F = female; M = male; BFF= budesonide/formoterol fumarate; FF = formoterol fumarate; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat; BD = budesonide; AUC_{0-4} = area under the curve from zero to four hours; LCL = lower confidence limit; UCL = upper confidence limit; p-value = probability value
Source: Statistical Reviewer

Figure 18 presents the subgroup analysis results of primary endpoint pre-dose trough FEV_1 of Trial 03. All the subgroups considered had numerically better treatment effect. However, the following subgroups did not reach statistically significant treatment effect, and they were not due to the small number of subjects in their subgroups: country of USA, gender of female, race of non-white, and age of equal or greater than 65 years.

Figure 18. BFF Trial 03Forest Plot of Pre-Dose Trough FEV1 (L) (With 95% CI) by Subgroups (BFF vs.FF, Efficacy Estimand, mITT Population)



Abbreviations: F = female; M = male; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat; LCL = lower confidence limit; UCL = upper confidence limit; p-value = probability value
Source: Statistical Reviewer

Bayesian Shrinkage Subgroup Analysis

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

In traditional subgroup analyses, there were some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size or large variability for some subgroups. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimates of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. With a shrinkage method, sample estimate is "shrunk" towards the overall estimate. The weights are

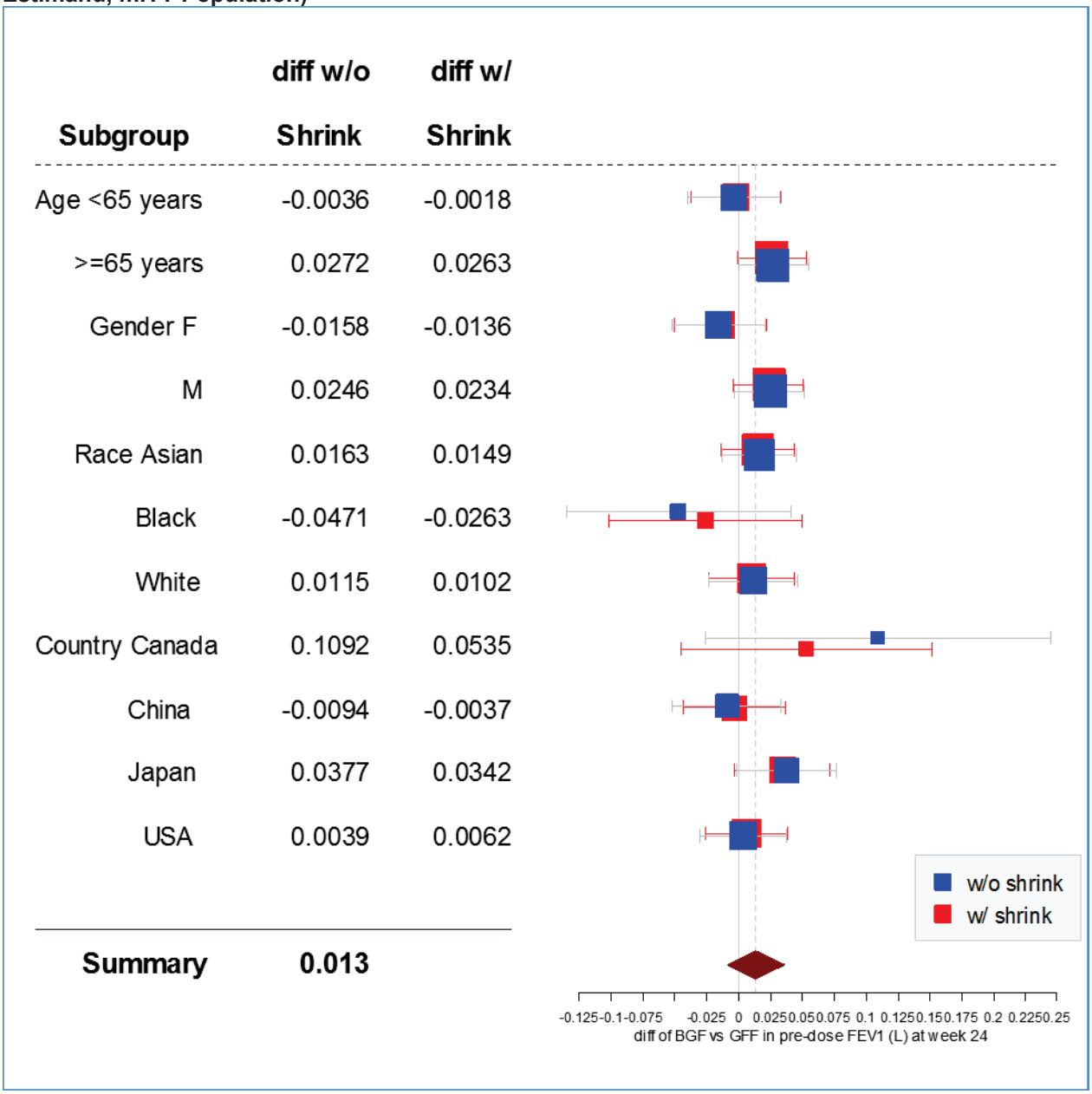
based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage).

The Bayesian hierarchical model was used in this review as a shrinkage method with sample estimates from the traditional subgroup analysis with the same flat prior to derive shrinkage estimates for all subgroups and assumptions as followings:
Y_i: the observed sample estimate of treatment effect in a subgroup level i (i =1,2, …, total number of subgroups), assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$ with $\mu \sim N(0, c^2)$, $1/\tau^2 \sim$ Gamma (0.001, 0.001) (noted as "shrinkage", c from patient-level standard deviation)

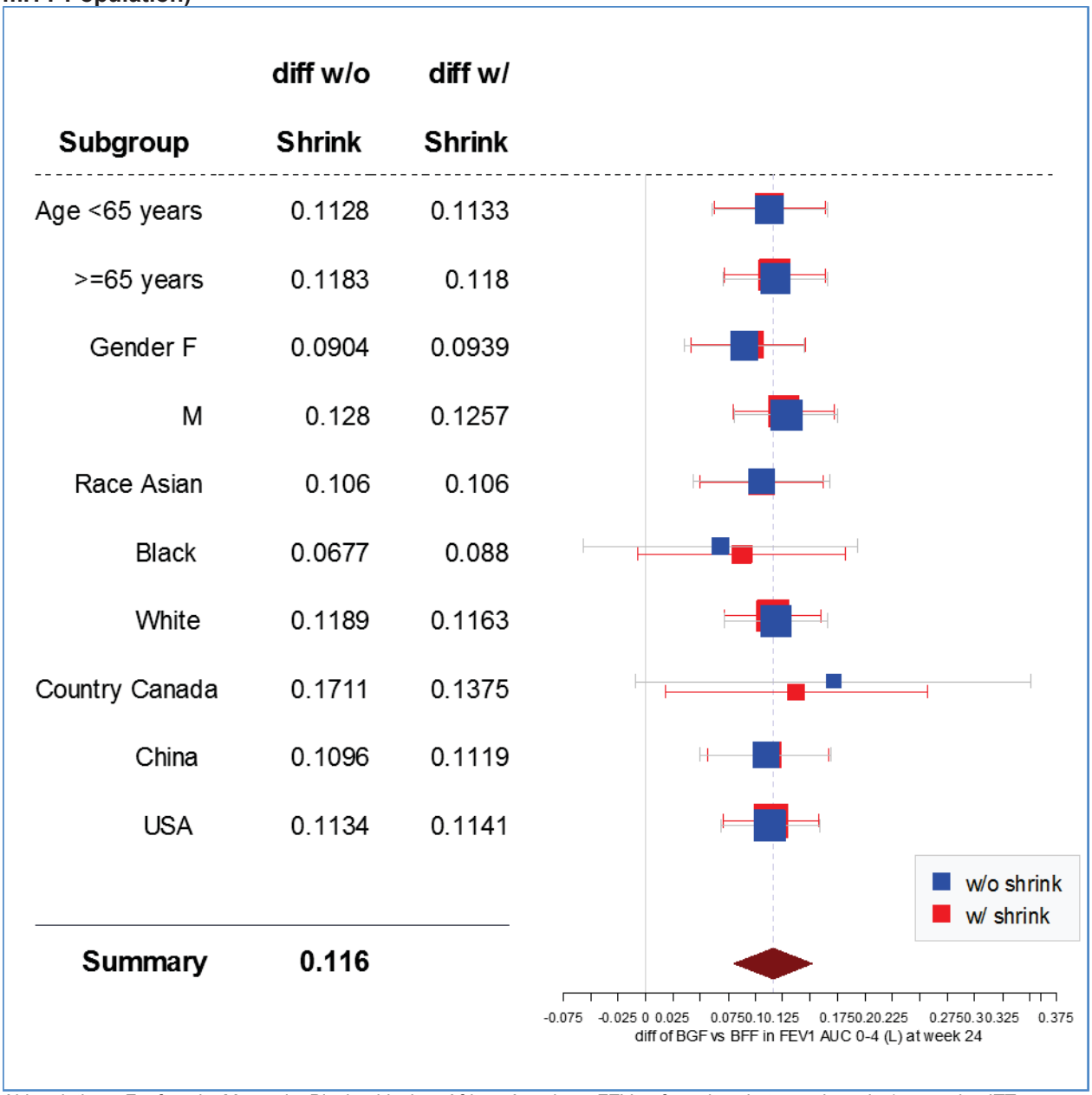
Shrunken estimates and 95% credible interval (equivalent to confidence interval of sample estimate) are calculated and depicted in the forest plot.

Figure 19. BGF Trial 06 Forest Plot of Bayesian Shrinkage Subgroup Analysis of Pre-Dose Trough FEV1 (L) (With 95% CI) With Comparison to Traditional Subgroup Analysis (BGF vs.GFF, Efficacy Estimand, mITT Population)



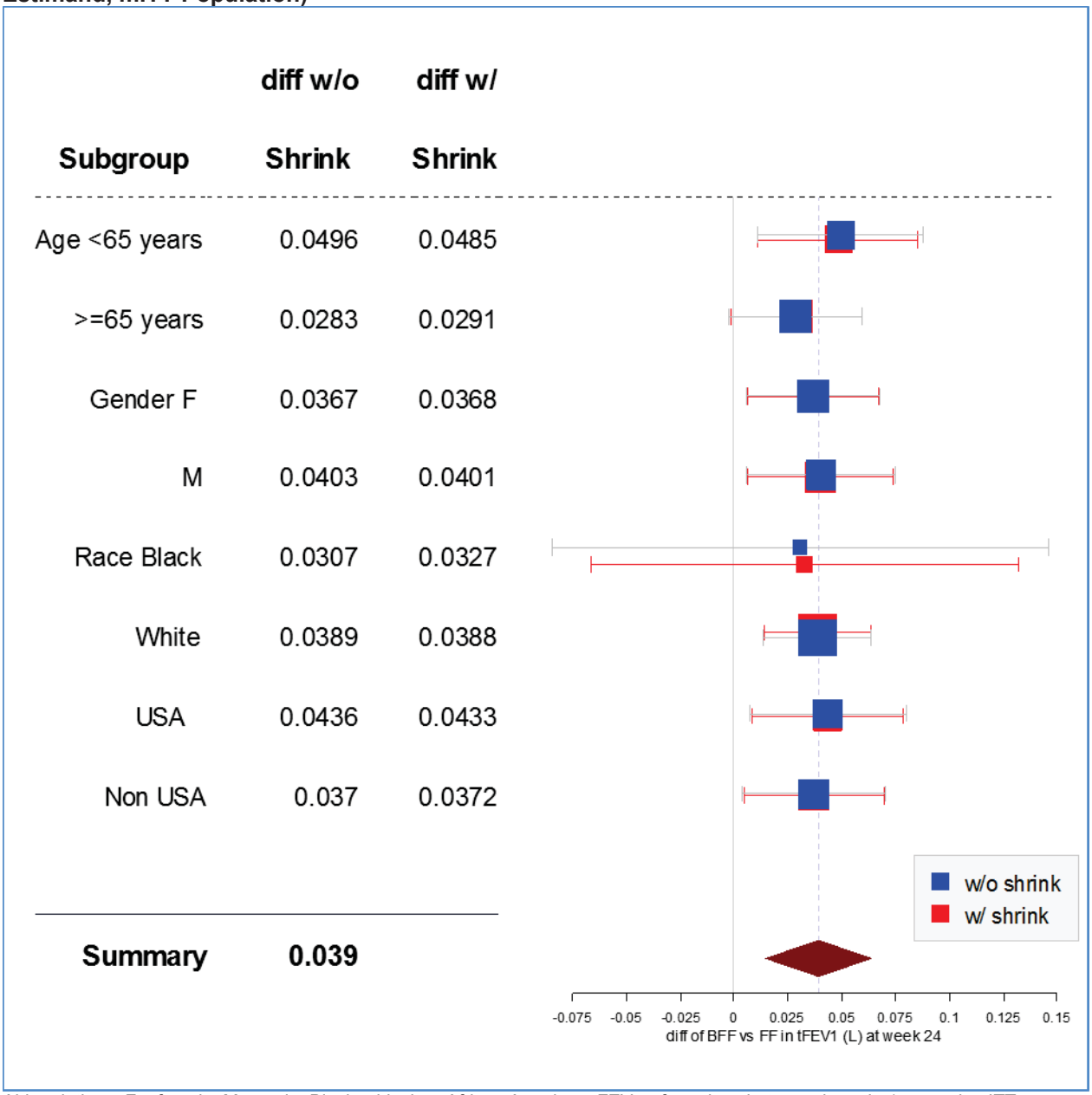
Abbreviations: F = female; M = male; Black = black or African American; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Figure 20. BGF Trial 06 Forest Plot of Bayesian Shrinkage Subgroup Analysis of FEV1 AUC_{0-4} (L) (With 95% CI) With Comparison to Traditional Subgroup Analysis (BGF vs.BFF, Efficacy Estimand, mITT Population)



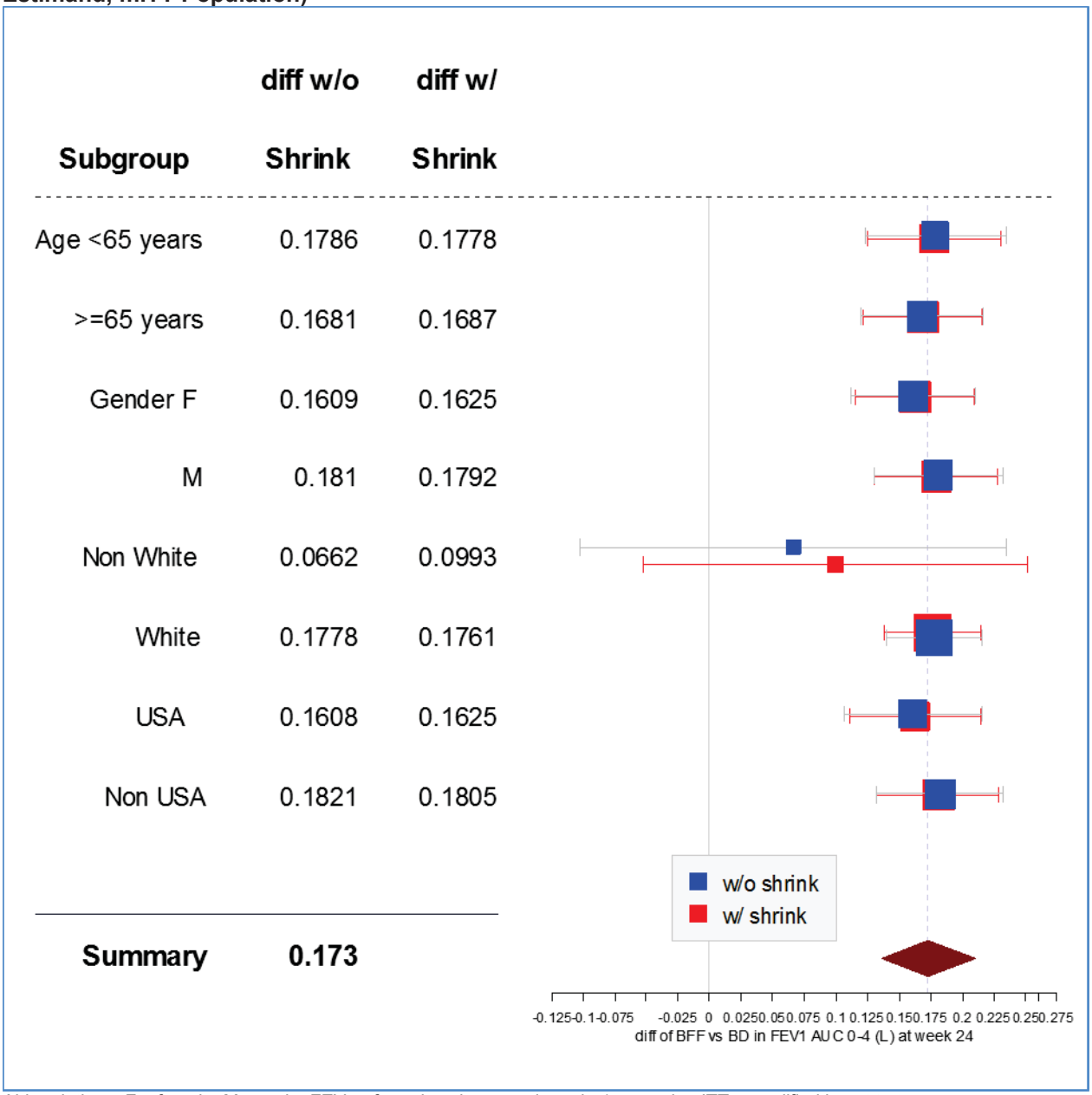
Abbreviations: F = female; M = male; Black = black or African American; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Figure 21. BFF Trial 02 Forest Plot of Bayesian Shrinkage Subgroup Analysis of Pre-Dose Trough FEV1 (L) (With 95% CI) With Comparison to Traditional Subgroup Analysis (BFF vs.FF, Efficacy Estimand, mITT Population)



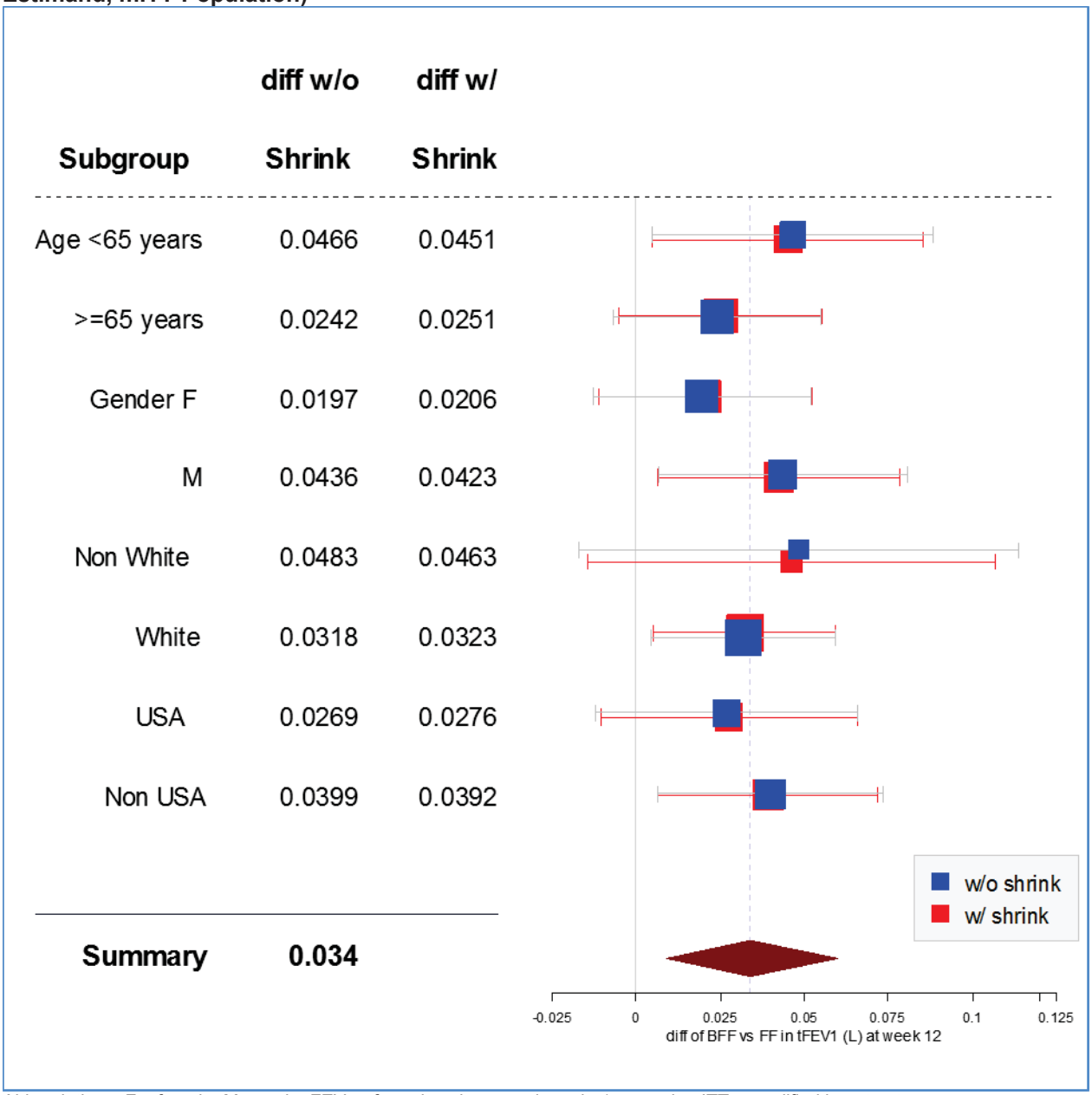
Abbreviations: F = female; M = male; Black = black or African American; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Figure 22. BFF Trial 02 Forest Plot of Bayesian Shrinkage Subgroup Analysis of FEV1 AUC_{0-4} (L) (With 95% CI) for With Comparison to Traditional Subgroup Analysis (BFF vs.BD, Efficacy Estimand, mITT Population)



Abbreviations: F = female; M = male; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Figure 23. BFF Trial 03 Forest Plot of Bayesian Shrinkage Subgroup Analysis of Pre-Dose Trough FEV1 (L) (With 95% CI) With Comparison to Traditional Subgroup Analysis (BFF vs.FF, Efficacy Estimand, mITT Population)



Abbreviations: F = female; M = male; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat
Source: Statistical Reviewer

Examining Figure 19 to Figure 23, we found that:

- All the subgroup means from the Bayesian shrinkage subgroup analysis shrunk to the overall mean
- All the 95% credible intervals of subgroup mean from Bayesian shrinkage subgroup analyses were narrower than the sample estimates' 95% confidence interval
- Although the Bayesian shrinkage subgroup analysis produced more accurate subgroup means and their credible intervals, the difference compared to the traditional subgroup analysis results were minimal.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Trial 06, the 24-week BGF lung function trial, had a co-primary endpoint of pre-dose trough FEV1 at Week 24 for the comparison of BGF to GFF and FEV1 AUC_{0-4} at Week 24 for the comparison of BGF to BFF. The results for pre-dose trough FEV1 at Week 24 for the comparison of BGF to GFF were not statistically significant (Table 62). Results for FEV1 AUC_{0-4} at Week 24 for the comparison of BGF to BFF showed a statistically significant improvement (Table 63). As such, Trial 06 only demonstrated the contribution of GP to BGF, but not the contribution of BD, and failed on its co-primary endpoint.

For the BFF program, in Trial 02, the 24-week lung function trial, the co-primary endpoints were similar to Trial 06. Pre-dose trough FEV1 at Week 24 was the primary endpoint for the BFF to FF comparison and FEV1 AUC_{0-4} at Week 24 was the primary endpoint for the BFF to BD comparison. Both co-primary endpoints showed a statistically significant improvement for the BFF 320/9.6 µg dose (Table 64 and Table 65). In BFF Trial 03, the 12-week BFF lung function trial, the primary endpoint was pre-dose trough FEV1 at Week 12 and the BFF 320/9.6 µg dose showed a statistically significant improvement over FF. The BFF primary endpoint data from these trials supports the efficacy of BFF, the contribution of components, and it use as a comparator arm for BGF Trial 06.

Overall, the BGF program does not show substantial evidence of effectiveness. This is primarily based on the failure in the co-primary endpoint of Trial 06, as well as the absence of replicate evidence for the efficacy of BGF.

Secondary and Other Endpoints

Exacerbation
In Trial 06, the 24-week BGF trial, the annualized rate of moderate or severe COPD exacerbations was a secondary endpoint and BGF was compared to both GFF and BFF. These results were not statistically significant because of failure of the primary endpoint and the testing hierarchy (Table 68).

For the BFF program, in Trial 02 and Trial 03, BFF 320/9.6 µg demonstrated a statistically significant improvement in time to first moderate or severe COPD exacerbation compared with FF (Table 69 and Table 71). The comparison with BD was not statistically significant in Trial 02 and Trial 03 did not have a BD arm. Moderate or severe exacerbation rate was assessed in Trial 02 and was supportive of BFF 320/9.6 µg when compared to both FF and BD. In Trial 03, BFF 320/9.6 µg had a favorable effect on moderate or severe exacerbation rate compared to FF.

SGRQ
In Trial 06, the 24-week BGF trial, the percentage of patients achieving the MCID of ≥4 units in SGRQ total score at Week 24 was included as a secondary endpoint (Table 67). These results were not statistically significant because of failure of the primary endpoint and multiplicity control.

For the BFF program, in both Trial 02 and Trial 03, BFF 320/9.6 µg demonstrated a statistically significant increase in SGRQ responders compared with FF (Table 70 and Table 72). In Trial 02, the comparison with BD was not significant, and in Trial 03 BD was not included as a treatment arm.

Subpopulations

For subgroup analyses, see the section entitled Additional Analyses Conducted on the Individual Trial. No notable differences were observed in comparison of subgroups and the subgroup analyses do not change the overall assessment of effectiveness.

Additional Efficacy Considerations

There are no additional efficacy considerations for this NDA.

8.1.5. Integrated Assessment of Effectiveness

To approve a combination product, evidence must support the efficacy of the overall combination, including the contribution of each active ingredient to the effectiveness of the combination. The Applicant submitted as the primary evidence of efficacy the results from a single phase 3, 24-week, randomized, placebo-controlled trial with the primary objective of assessing the effect of BGF compared to GFF and BFF on lung function (Trial 06). To support the proposed exacerbation claim, the Applicant referenced the secondary endpoints evaluating exacerbation in Trial 06. Trial 06 failed to demonstrate substantial evidence of efficacy as determined by the failure to achieve a statistically significant improvement for both co-primary endpoints. Trial 06 did show a statistically significant improvement in FEV_1 AUC_{0-4} for the BGF versus BFF comparison, one of the co-primary endpoints, demonstrating the contribution of GP to BGF. However, Trial 06 failed on the other co-primary endpoint: pre-dose trough FEV1 comparing BGF to GFF. Therefore, the contribution of BD to BGF was not demonstrated. Because of this failure on the co-primary endpoint and the hierarchical testing plan to control for multiplicity, all secondary endpoints comparing BGF to GFF or BFF, regardless of nominal p-

value, are not statistically significant, and cannot be used to make definitive efficacy conclusions. These failed secondary endpoints include the exacerbation endpoints referenced by the Applicant to support an exacerbation claim. Therefore, the Applicant has not presented substantial evidence to demonstrate BGF efficacy or contribution of all mono-components to the combination. Framed another way, the Applicant has not demonstrated that adding budesonide to the combination of glycopyrrolate/formoterol fumarate provides any additional benefit, thus failing to satisfy the combination rule for BGF.

In addition, the Applicant submitted only a single trial, Trial 06, to support BGF. As such, there could be no replicate evidence of efficacy of BGF. Overall, the evidence presented in this application does not support approval of BGF.

8.2. Review of Safety

8.2.1. Safety Review Approach

To support the safety of BGF, the Applicant submitted safety data from a single clinical trial of 24 weeks in duration (Trial 06) with a safety extension of an additional 28 weeks (Trial 08) in a subset of patients (see Section 8.1.1 for protocol review). The clinical assessment of safety primarily focuses on these trials, Trial 06 and its extension, Trial 08. These trials, along with supporting evidence from BFF Trial 02 and BFF Trial 03 and the known safety profile of GFF, are sufficient to characterize the safety profile of BGF. All studies utilized active controls, and the BGF studies included the approved dual-combination product GFF as a control. Safety analysis will be performed on the Safety Population, which is defined as all subjects who signed an informed consent and received any amount of study drug and will focus on the comparison of BGF to GFF, as GFF is an approved product with a well characterized safety profile.

Data for BGF Trial 06 and Trial 08 were not pooled because of the differing treatment durations and treatment arms and as all of the subjects in Trial 08 also participated in Trial 06. Therefore, each trial will be evaluated independently. It should be noted that any safety data from the first 24 weeks of Trial 08 is also included in the analysis of Trial 06. Data from BFF Trials 02 and 03 were also not be pooled as they were of differing lengths.

8.2.2. Review of the Safety Database

Overall Exposure

BGF Trials

Exposure data are taken from Trial 06 and its safety extension, Trial 08. In both Trial 06 and Trial 08, exposure was similar across treatment groups. In Trial 06, median exposure was 169 days in all groups and the majority of patients were exposed to treatment for at least 24 weeks (ranging from 73.9% to 78.7%%). Exposure data for Trial 06 are summarized in Table 74.

Exposure data for Trial 08 are summarized in Table 75. The exposure described for subjects in Trial 08 is cumulative and includes the time spent in Trial 06.

Table 74. BGF Trial 06 Exposure to Treatment (Safety Population)

	BGF 320/18/9.6 µg N=639	GFF 18/9.6 µg N=625	BFF 320/9.6 µg N=314	Symbicort TBH 400/12 µg N=318
Extent of exposure (days)				
Mean (SD)	158.5 (34.2)	154.5 (38.9)	153.8 (41.3)	156.8 (38.3)
Median	169	169	169	169
Min, max	5, 206	1, 204	1, 191	1, 184
Extent of exposure [N (%)]				
<24 weeks	136 (21.3)	163 (26.1)	75 (23.9)	72 (22.6)
≥24 weeks	503 (78.7)	462 (73.9)	239 (76.1)	246 (77.4)
≤4 weeks	14 (2.2)	17 (2.7)	9 (2.9)	12 (3.8)
≤8 weeks	31 (4.9)	37 (5.9)	25 (7.9)	19 (6.0)
≤12 weeks	41 (6.4)	61 (9.8)	35 (11.1)	25 (7.9)
≤16 weeks	57 (8.9)	77 (12.3)	42 (13.3)	29 (9.1)
≤20 weeks	67 (10.5)	88 (14.1)	45 (14.3)	34 (10.7)
≤24 weeks	223 (35.0)	241 (38.6)	113 (35.9)	109 (34.3)
≤28 weeks	638 (99.8)	624 (99.8)	315 (100)	318 (100)

Abbreviations: BGF= budesonide/glycopyrrolate/formoterol fumarate; GFF= glycopyrrolate/formoterol fumarate; BFF= budesonide/formoterol fumarate; TBH = Turbuhaler; SD = standard deviation
Source: Clinical Reviewer

Table 75. BGF Trial 08 Exposure to Treatment (Safety Population)*

	BGF 320/18/9.6 µg N=194	GFF 18/9.6 µg N=174	BFF 320/9.6 µg N=88
Extent of exposure (days)			
Mean (SD)	305.3 (110.0)	310.4 (109.5)	298.2 (120.8)
Median	364.0	363.0	364.0
Min, max	12,436	3,407	1,395
Extent of exposure [N (%)]			
<48 weeks	54 (27.8)	45 (25.9)	22 (25.0)
≥48 weeks	140 (72.2)	129 (74.1)	66 (75.0)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF= glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; SD = standard deviation
*Trial 08 exposure is cumulative and includes exposure from Trial 06
Source: CSR PT010008 Edition 1; Table 23; pg 84 and Clinical reviewer

BFF Trials

Exposure data for BFF comes from Trial 02 and Trial 03. In Trial 02, the majority of patients were exposed to treatment for at least 24-weeks and exposure was similar across treatment groups. A summary of exposure in Trial 02 is shown in Table 76. In Trial 03, which was a variable-length trial, the average length of exposure was not surprisingly longer at 202.9 days and exposure was similar across groups (data not shown).

Table 76. BFF Trial 02 Exposure to Treatment (Safety Population)

	BFF 320/9.6 µg N=655	BFF 160/9.6 µg N=637	FF 9.6 µg N=644	BD 320 µg N=206	TBH 400/12 µg N=219
Extent of exposure (days)					
Mean (SD)	157.1 (37.0)	158.5 (34.4)	154.0 (41.8)	149.2 (48.3)	155.7 (37.4)
Median	169.0	169.0	169.0	169.0	169.0
Min, max	1, 224	3, 208	1, 203	2, 191	1, 186
Extent of exposure [N(%)]					
<24 weeks	192 (29.3)	159 (25.0)	182 (28.3)	60 (29.1)	63 (28.8)
≥24 weeks	463 (70.7)	478 (75.0)	462 (71.7)	146 (70.9)	156 (71.2)

Abbreviations: BFF= budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; SD = standard deviation
Source: CSR PT009002 Edition 1; Table 58; pg 177; and Clinical reviewer

Adequacy of the Safety Database

The size of the trials for BGF are smaller than comparable combination products. Additionally, previously approved triple-combination products had their relevant subcomponents approved at the time of NDA submission. Despite this, the BGF safety database is adequate given the supportive data from the BFF studies, as well as the studies for GFF reviewed under NDA 208294 (see review by Dr. Stacy Chin dated March 21, 2016).

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. See Section 4.1 for additional details.

Categorization of Adverse Events

In all trials reviewed for safety, an AE was categorized as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE could be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE could arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. An AE was considered a treatment emergent adverse event (TEAE) if the event occurred on or after the first day of treatment and up to and including the last day of treatment (+1 day for subjects who permanently discontinued treatment before trial completion). Severity of AEs was graded as mild (no limitation in usual activity or only slight discomfort), moderate (limitation of usual activity or significant discomfort), or severe (inability to carry out usual activity or very marked discomfort).

Adverse events of special interest (AESI) were defined as LAMA/LABA class effects (potential anticholinergic events and β2-adrenergic agonist events), local steroid effects, pneumonia, and

paradoxical bronchospasm. Major Adverse Cardiovascular Events (MACE) were defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. All deaths and potential pneumonia events and MACE were reviewed by the CEC. The CEC was implemented to provide an independent, external, systematic, and unbiased assessment of investigator-reported events in the above categories. Review by the CEC was centralized and independent of the Applicant. The committee was comprised of individuals with experience and expertise in the clinical adjudication of pulmonary, neurological, mortality, and cardio- and cerebrovascular events. They were specifically trained in endpoint review and adjudication.

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

BGF Trials

In the BGF lung function trial, Trial 06, there was a total of 12 treatment-emergent deaths. There were six deaths in the BGF group compared to three deaths in the GFF group and two deaths in the BFF group. Though there were numerically more deaths in the BGF group, the overall number of deaths for all groups was small. There were no clear patterns in cause of death across treatment groups. These results are summarized in Table 77.

Table 77. BGF Trial 06 Treatment-Emergent Deaths (Safety Population)

Preferred Term	BGF 320/18/9.6 µg N=639 n (%)	GFF 18/9.6 µg N=625 n (%)	BFF 320/9.6 µg N=314 n (%)	TBH 400/12 µg N=318 n (%)	Total N=1899 n (%)
Patients with fatal outcomes	6 (0.9)	3 (0.5)	2 (0.6)	1 (0.3)	12 (0.6)
Acute myeloid leukemia	1 (0.2)	0	0	0	1 (0.1)
Acute myocardial infarction	1 (0.2)	0	0	0	1 (0.1)
Cardio-respiratory arrest	0	1 (0.2)	0	0	1 (0.1)
Brain cancer metastatic/central nervous system lesion	0	0	1 (0.3)	0	1 (0.1)
Metastases to spine	0	0	0	1 (0.3)	1 (0.1)
Squamous cell carcinoma of lung	0	0	1 (0.3)	0	1 (0.1)
Cerebral infarction	1 (0.2)	0	0	0	1 (0.1)
Pneumonia	0	1 (0.2)	0	0	1 (0.1)
Sepsis	1 (0.2)	0	0	0	1 (0.1)
Small cell lung cancer metastatic	1 (0.2)	0	0	0	1 (0.1)
Respiratory fume inhalation disorder	1 (0.2)	0	0	0	1 (0.1)
Death	0	1 (0.2)	0	0	1 (0.1)

Abbreviations: BGF= budesonide/glycopyrrolate/formoterol fumarate; BFF= budesonide/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; TBH = Turbuhaler
Source: PT010006 CSR Edition 1; Table 77; pg 244-245 and Clinical Reviewer

In Trial 08, the BGF safety extension trial, there was a total of 4 treatment-emergent deaths. There were three deaths in the BGF group compared to one death in the GFF group and zero deaths in the BFF group. Notably, all of the BGF deaths in Trial 08 were from the period overlapping with Trial 06. No new deaths occurred during the Trial 08 period following the completion of Trial 06. Though there were numerically more deaths in the BGF group, the overall number of deaths for all groups was small. There were no clear patterns in cause of death across treatment groups. These results are summarized in Table 78.

Table 78. BGF Trial 08 Treatment-Emergent Deaths (Safety Population)

Preferred Term	BGF 320/18/9.6 µg N=194 N (%)	GFF 18/9.6 µg N=174 N (%)	BFF 320/9.6 µg N=88 N (%)	Total N=456 n (%)
Patients with fatal outcomes	3 (1.5)	1 (0.6)	0	4 (0.9)
Myocardial ischemia	0	1	0	1 (0.2)
Right cerebral infarction	1	0	0	1 (0.2)
Sepsis	1	0	0	1 (0.2)
Smoke inhalation	1	0	0	1 (0.2)

Abbreviations: BGF= budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate
Source: Clinical Reviewer

Overall, the BGF studies had a low incidence of on-treatment death. Analysis of on study deaths in Trials 06 and 08 did not reveal additional deaths following the on-treatment period. While there were numerically more deaths in the BGF group in both Trial 06 and 08, there was no clear pattern in the cause of death and does not raise a safety concern.

BFF Trials

Treatment-emergent deaths in the BFF Trial 02 were similar across treatment groups and were infrequent. A summary of Trial 02 treatment-emergent deaths is shown in Table 79. Additionally, Trial 02 deaths that occurred during the post-treatment period were infrequent (overall: 0.1%) and did not change the assessment of safety.

Table 79. BFF Trial 02 Treatment-Emergent Deaths (Safety Population)

Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 320 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
Patients with fatal outcomes	3 (0.5)	2 (0.3)	2 (0.3)	0	2 (0.9)	9 (0.4)
Brain cancer metastatic	0	1 (0.2)	0	0	0	1 (0.0)
Cardiac arrest	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Cardiac failure	1 (0.2)	0	0	0	0	1 (0.0)
Death	0	0	0	0	1 (0.5)	1 (0.0)
Mesothelioma	1 (0.2)	0	0	0	0	1 (0.0)
Pancreatitis acute	0	0	0	0	1 (0.5)	1 (0.0)
Skull fractured base	0	0	1 (0.2)	0	0	1 (0.0)
Sudden cardiac death	0	0	1 (0.2)	0	0	1 (0.0)

Abbreviations: BFF = budesonide/formoterol fumarate; FF= formoterol fumarate; BD = budesonide; TBH = Turbuhaler
Source: PT009002 CSR Edition 1; Table 3.14.1; pg 916 and Clinical Reviewer

Regarding Trial 03, the BFF variable-length trial, on-study deaths (treatment emergent and post-treatment) were infrequent (overall: 0.8%), but more deaths were observed in the FF (1.3%) group than either BFF 320/9.6 µg (0.5%) or BFF 160/9.6 µg (0.6%). The Trial 03 deaths had no pattern that would raise a safety concern.

Overall, deaths were infrequent in the BGF and BFF programs. Analysis of treatment-emergent and post-treatment deaths did not reveal any substantial patterns or differences between treatment groups and no safety concerns were identified.

Serious Adverse Events

BGF Trials

In Trial 06, there were 173 (9.1%) patients who experienced at least one SAE. SAEs were numerically similar across treatment groups, ranging from 21 (6.7%) in the BFF group to 68 (10.9%) in the GFF group. SAEs were most commonly reported in the respiratory, thoracic and mediastinal disorders System Organ Class (SOC), with 78 (4.1%) patients affected. This was followed by the infections and infestations SOC with 38 (2.0%) patients, followed by cardiac disorders with 20 (1.1%) patients affected. COPD (i.e., COPD exacerbation) was the most common SAE Preferred Term (PT) across all treatment groups, and BGF had a numerically lower frequency of COPD SAEs than GFF. SAEs occurring in ≥2 patients in any treatment group are summarized in Table 80.

Table 80. BGF Trial 06 Serious Adverse Events Occurring in ≥2 Patients in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	BGF 320/18/9.6 µg (N=639) N (%)	GFF 18/9.6 µg (N=625) N (%)	BFF 320/9.6 µg (N=314) N (%)	TBH 400/12 µg (N=318) N (%)	Total (N=1896) N (%)
At least 1 SAE	55 (8.6)	68 (10.9)	21 (6.7)	29 (9.1)	173 (9.1)
Respiratory, thoracic and mediastinal disorders	20 (3.1)	33 (5.3)	10 (3.2)	15 (4.7)	78 (4.1)
Chronic obstructive pulmonary disease	17 (2.7)	32 (5.1)	8 (2.5)	13 (4.1)	70 (3.7)
Acute respiratory failure	4 (0.6)	1 (0.2)	0	1 (0.3)	6 (0.3)
Pneumothorax	2 (0.3)	1 (0.2)	1 (0.3)	1 (0.3)	5 (0.3)
Infections and infestations	16 (2.5)	14 (2.2)	3 (1.0)	5 (1.6)	38 (2.0)
Pneumonia	8 (1.3)	6 (1.0)	1 (0.3)	0	15 (0.8)
Cardiac disorders	5 (0.8)	8 (1.3)	4 (1.3)	3 (0.9)	20 (1.1)
Acute myocardial infarction	1 (0.2)	2 (0.3)	1 (0.3)	1 (0.3)	5 (0.3)
Atrial fibrillation	2 (0.3)	0	0	0	2 (0.1)
Gastrointestinal disorders	3 (0.5)	5 (0.8)	1 (0.3)	1 (0.3)	10 (0.5)
Inguinal hernia	0	2 (0.3)	0	0	2 (0.1)
Musculoskeletal and connective tissue disorders	3 (0.5)	0	0	2 (0.6)	5 (0.3)
Intervertebral disc disorder	2 (0.3)	0	0	0	2 (0.1)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; SAE = serious adverse event
Source: PT010006 CSR Edition 1; Table 78; pg 247; confirmed by Clinical Reviewer

In Trial 08, there were 62 (13.6) patients who experienced at least one SAE. SAEs were higher both numerically and percentage-wise in the BGF group. Overall, 33 (17%) of subjects in the BGF group experienced at least one SAE compared to 22 (12.6%) in the GFF group. In the BGF and GFF groups, SAEs were most commonly reported in the respiratory, thoracic and mediastinal disorders SOC, followed by the infections and infestations SOC. COPD was the most common SAE PT across all treatment groups, and BGF had a numerically lower frequency of COPD SAEs than GFF. SAEs occurring in ≥2 patients in any treatment group are summarized in Table 81.

Table 81. BGF Trial 08 SAEs Occurring in ≥2 Patients in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	BGF 320/18/9.6 µg (N=194) N (%)	GFF 18/9.6 µg (N=174) N (%)	BFF 320/9.6 µg (N=88) N (%)	Total N=456 N (%)
At least 1 SAE	33 (17.0)	22 (12.6)	7 (8.0)	62 (13.6)
Respiratory, thoracic and mediastinal disorders	14 (7.2)	9 (5.2)	2 (2.3)	25 (5.5)
Chronic obstructive pulmonary disease	12 (6.2)	9 (5.2)	1 (1.1)	22 (4.8)
Respiratory failure	1 (0.5)	2 (1.1)	1 (1.1)	4 (0.9)

System Organ Class Preferred Term	BGF 320/18/9.6 µg (N=194) N (%)	GFF 18/9.6 µg (N=174) N (%)	BFF 320/9.6 µg (N=88) N (%)	Total N=456 N (%)
Infections and infestations	6 (3.1)	6 (3.4)	2 (2.3)	14 (3.1)
Pneumonia	2 (1.0)	4 (2.3)	0	6 (1.3)
Cellulitis	1 (0.5)	0	1 (1.1)	2 (0.4)
Sepsis	1 (0.5)	0	1 (1.1)	2 (0.4)
Cardiac disorders	4 (2.1)	5 (2.9)	3 (3.4)	12 (2.6)
Myocardial infarction	2 (1.0)	2 (1.1)	0	4 (0.9)
Atrioventricular block complete	1 (0.5)	0	1 (1.1)	2 (0.4)
Gastrointestinal disorders	2 (1.0)	3 (1.7)	0	5 (1.1)
Pancreatitis acute	1 (0.5)	1 (0.6)	0	2 (0.4)
Nervous system disorders	3 (1.5)	0	0	3 (0.7)
Syncope	2 (1.0)	0	0	2 (0.4)
General disorders and administration site conditions	1 (0.5)	1 (0.6)	0	2 (0.4)
Non-cardiac chest pain	1 (0.5)	1 (0.6)	0	2 (0.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; SAE = serious adverse event
Source: PT010008 CSR Edition 1; Table 45; pg 118; Confirmed by Clinical Reviewer

Overall, the SAEs observed in Trial 06 and Trial 08 do not raise safety concerns. Interestingly, the smaller number of COPD SAEs for BGF compared to GFF observed in Trial 06 was not observed in Trial 08. It should be noted, however, that these COPD AEs were not protocol-defined and thus are different than the analyzed cases used for the exacerbation efficacy endpoints.

BFF Trials

In Trial 02 for BFF, there were more SAEs in the FF group compared to other treatments. This was driven primarily by an increased frequency of the COPD PT. A summary of SAEs occurring in Trial 02 is shown in Table 82. Trial 03 had similar results, with the FF group having a higher frequency of SAEs driven by an increased frequency of COPD (data not shown).

Table 82. BFF Trial 02 SAEs Occurring in ≥2 Patients in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 320 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
At least 1 SAE	42 (6.4)	45 (7.1)	72 (11.2)	15 (7.3)	20 (9.1)	194 (8.2)
Respiratory, thoracic and mediastinal disorders	17 (2.6)	11 (1.7)	32 (5.0)	2 (1.0)	7 (3.2)	69 (2.9)
COPD	15 (2.3)	10 (1.6)	29 (4.5)	2 (1.0)	6 (2.7)	62 (2.6)
Acute respiratory failure	2 (0.3)	2 (0.3)	4 (0.6)	0	1 (0.5)	9 (0.4)

System Organ Class Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 320 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
Cardiac disorders	6 (0.9)	17 (2.7)	11 (1.7)	8 (3.9)	1 (0.5)	43 (1.8)
Atrial fibrillation	1 (0.2)	5 (0.8)	2 (0.3)	1 (0.5)	0	9 (0.4)
Cardiac failure congestive	1 (0.2)	1 (0.2)	1 (0.2)	2 (1.0)	1 (0.5)	6 (0.3)
Acute myocardial infarction	0	2 (0.3)	2 (0.3)	0	0	4 (0.2)
Angina pectoris	1 (0.2)	2 (0.3)	1 (0.2)	0	0	4 (0.2)
Angina unstable	0	2 (0.3)	1 (0.2)	0	0	3 (0.1)
Cardiac failure	2 (0.3)	0	1 (0.2)	0	0	3 (0.1)
Cardiac failure chronic	0	2 (0.3)	1 (0.2)	0	0	3 (0.1)
Infections and infestations	4 (0.6)	7 (1.1)	9 (1.4)	0	4 (1.8)	24 (1.0)
Pneumonia	4 (0.6)	5 (0.8)	6 (0.9)	0	3 (1.4)	18 (0.8)
Nervous system disorders	1 (0.2)	5 (0.8)	6 (0.9)	1 (0.5)	2 (0.9)	15 (0.6)
Ischemic stroke	0	1 (0.2)	2 (0.3)	0	1 (0.5)	4 (0.2)
Gastrointestinal disorders	3 (0.5)	3 (0.5)	4 (0.6)	2 (1.0)	2 (0.9)	14 (0.6)
Small intestinal obstruction	0	1 (0.2)	2 (0.3)	0	0	3 (0.1)
Pancreatitis acute	0	0	0	0	2 (0.9)	2 (<0.1)

Abbreviations: BD = budesonide; BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; TBH = Turbuhaler; SAE = serious adverse event; COPD = chronic obstructive pulmonary disease
Source: PT009002 CSR Edition 1; Table 62; pg 184; confirmed by Clinical Reviewer

Overall, analysis of SAEs in the BGF and BFF programs did not raise any safety concerns.

Dropouts and/or Discontinuations Due to Adverse Effects

BGF Trials

In Trial 06, 82 (4.3%) of patients experienced an TEAE that lead to discontinuation of study drug, with the BGF and GFF treatment groups having slightly higher frequencies than BFF. The most common PT associated with discontinuation was COPD, which was higher in the GFF group than the BGF group. TEAEs leading to discontinuation of trial drug in Trial 06 are summarized in Table 83.

Table 83. BGF Trial 06 TEAEs Leading to Discontinuation of Study Drug in ≥2 Subjects in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
At least 1 TEAE leading to discontinuation of study drug	30 (4.7)	30 (4.8)	11 (3.5)	11 (3.5)	82 (4.3)
Respiratory, thoracic and mediastinal disorders	10 (1.6)	12 (1.9)	5 (1.6)	3 (0.9)	30 (1.6)
Chronic obstructive pulmonary disease	3 (0.5)	8 (1.3)	1 (0.3)	2 (0.6)	14 (0.7)
Dyspnea	1 (0.2)	2 (0.3)	1 (0.3)	0	4 (0.2)
Dysphonia	3 (0.5)	0	0	0	3 (0.2)
Pulmonary mass	0	0	2 (0.6)	0	2 (0.1)
Acute respiratory failure/respiratory failure	1 (0.2)	2 (0.3)	0	0	3 (0.2)

System Organ Class Preferred Term	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Infections and infestations	4 (0.6)	4 (0.6)	1 (0.3)	2 (0.6)	11 (0.6)
Pneumonia	1 (0.2)	2 (0.3)	0	0	3 (0.2)
Musculoskeletal and connective tissue disorders	2 (0.3)	0	1 (0.3)	0	3 (0.2)
Muscle spasms	2 (0.3)	0	1 (0.3)	0	3 (0.2)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; TEAE = treatment emergent adverse event
Source: PT010006 CSR Edition 1; Table 79; pg 248 and Clinical Reviewer

In Trial 08, 34 (7.5%) of patients experienced an TEAE that lead to discontinuation of study drug with the BGF group having a marginally higher frequency than GFF and BFF. This higher frequency in the BGF group was not driven by any particular SOC or PT and is not indicative of a safety signal. TEAEs leading to discontinuation of study drug in Trial 08 are summarized in Table 84.

Table 84. BGF Trial 08 TEAEs Leading to Discontinuation of Study Drug in ≥2 Subjects in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
At least 1 AE leading to discontinuation of study drug	16 (8.2)	12 (6.9)	6 (6.8)	34 (7.5)
Respiratory, thoracic and mediastinal disorders	2 (1.0)	5 (2.9)	2 (2.3)	9 (2.0)
Acute respiratory failure	0	2 (1.1)	0	2 (0.4)
Chronic obstructive pulmonary disease	0	2 (1.1)	0	2 (0.4)
Infections and infestations	2 (1.0)	2 (1.1)	1 (1.1)	5 (1.1)
Pneumonia	0	2 (1.1)	0	2 (0.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; AE = adverse event
Source: PT010008 CSR Edition 1; Table 47; pg 121; confirmed by Clinical Reviewer

BFF Trials

In Trial 02, 92 (3.9%) of patients experienced a TEAE that lead to discontinuation of study drug with similar frequencies and low frequency across treatment groups. The most common TEAE SOC leading to discontinuation in all groups was respiratory, thoracic, and mediastinal disorders, with dyspnea being the most common PT leading to discontinuation. TEAEs leading to discontinuation of study drug in Trial 02 are summarized in Table 85. In BFF Trial 03, similarly to Trial 02, TEAEs that lead to drug discontinuation were similar across groups, with the fewest discontinuations in the BFF 320/9.6 mcg treatment group (data not shown).

Table 85. BFF Trial 02 TEAEs Leading to Discontinuation of Study Drug in ≥1% of Subjects in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 320 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
At least 1 TEAE leading to discontinuation of study drug	28 (4.3)	23 (3.6)	17 (2.6)	12 (5.8)	12 (5.5)	92 (3.9)
Respiratory, thoracic and mediastinal disorders	9 (1.4)	14 (2.2)	9 (1.4)	4 (1.9)	2 (0.9)	38 (1.6)
Dyspnea	4 (0.6)	3 (0.5)	3 (0.5)	3 (1.5)	0	13 (0.6)
Cough	1 (0.2)	5 (0.8)	1 (0.2)	2 (1.0)	0	9 (0.4)
Musculoskeletal and connective tissue disorders	1 (0.2)	0	0	0	3 (1.4)	4 (0.2)
Muscle spasms	0	0	0	0	3 (1.4)	3 (0.1)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; TEAE = treatment emergent adverse event
Source: PT009002 CSR Edition 1; Table 63; pg 185; confirmed by Clinical Reviewer

Overall, dropouts and discontinuations due to AEs was uncommon across the BGF and BFF programs and do not indicate any safety signals.

Significant Adverse Events

In all BGF and BFF studies, a severe AE was defined as an inability to carry out usual activities, marked discomfort, life-threatening, resulting in significant capacity or disability, or requiring therapeutic intervention.

BGF Trials

The majority of TEAEs reported in Trial 06 were mild or moderate in severity. The number of patients with TEAEs of severe intensity was comparable across trial groups. The most common PT of severe intensity in Trial 06 was COPD (4.1%) and the number of patients was comparable across groups. Table 86 presents the AEs of severe intensity that occurred ≥2 patients in any trial group.

Table 86. BGF Trial 06 Severe TEAEs That Occurred in ≥2 Patients in Any Treatment Group (by PT) (Safety Population)

Preferred Term	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Patients with ≥1 severe TEAE	45 (7.0)	61 (9.8)	21 (6.7)	32 (10.1)	159 (8.4)
COPD	19 (3.0)	33 (5.3)	11 (3.5)	15 (4.7)	78 (4.1)
Pneumonia	5 (0.8)	5 (0.8)	1 (0.3)	1 (0.3)	12 (0.6)
Acute respiratory failure/respiratory failure	5 (0.8)	3 (0.5)	1 (0.3)	1 (0.3)	10 (0.5)
Acute myocardial infarction	1 (0.2)	2 (0.3)	1 (0.3)	0	4 (0.2)

Preferred Term	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Atrial fibrillation	2 (0.3)	0	0	0	2 (0.1)
Gastroenteritis	0	2 (0.3)	0	0	2 (0.1)
Migraine	0	0	0	2 (0.6)	2 (0.1)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease; PT = preferred term
Source: Clinical Reviewer

Similar to Trial 06, the majority of TEAEs reported in Trial 08 were mild or moderate in severity. The number of patients with TEAEs of severe intensity was greater in the BGF group compared to the GFF group. There was an increased frequency of pelvic pain in the BGF group compared to the GFF group, which partially accounts for the overall difference between BGF and GFF. The frequency of pelvic pain was still low in the BGF group (2.1%) and is unlikely to be related to treatment. The most common PT of severe intensity in Trial 08 was COPD (5.7%) and the number of patients was comparable between the BGF and GFF groups but lower in the BFF group. Table 87 presents the TEAEs of severe intensity that occurred ≥2 patients in any trial group.

Table 87. BGF Trial 08 Severe TEAEs That Occurred in ≥2 Patients in Any Treatment Group (by PT) (Safety Population)

Preferred Term	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
Patients with ≥1 severe TEAE	31 (16.0)	22 (12.6)	10 (11.4)	63 (13.8)
COPD	13 (6.7)	11 (6.3)	2 (2.3)	26 (5.7)
Pneumonia	1 (0.5)	4 (2.3)	1 (1.1)	6 (1.3)
Acute respiratory failure	0 (0)	2 (1.1)	2 (2.3)	4 (0.9)
Pelvic pain	4 (2.1)	0 (0)	0 (0)	4 (0.9)
Cellulitis	0 (0)	0 (0)	2 (2.3)	2 (0.4)
Hypoxia	0 (0)	2 (1.1)	0 (0)	2 (0.4)
Lymphadenopathy	2 (1.0)	0 (0)	0 (0)	2 (0.4)
Syncope	2 (1.0)	0 (0)	0 (0)	2 (0.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF= glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease; PT = preferred term
Source: Clinical Reviewer

BFF Trials

In the BFF studies, the majority of TEAEs were mild or moderate. Trial 02 severe TEAEs were highest in the FF and TBH groups compared to the BFF groups and BD group. The most common severe TEAE by PT was COPD by a wide margin and was highest in the FF group. The remaining severe TEAEs by PT occurred in 1% or fewer subjects in any treatment group. Severe TEAEs in Trial 02 are summarized in Table 88. Similarly, in Trial 03 the FF group had the highest

frequency of severe TEAEs with the most common severe TEAE by PT being COPD (data not shown).

Table 88. BFF Trial 02 Severe TEAEs That Occurred in ≥2 Patients in Any Treatment Group (by PT) (Safety Population)

Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 320 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
Patients with ≥1 severe TEAE	41 (6.3)	43 (6.8)	60 (9.3)	10 (4.9)	19 (8.7)	173 (7.3)
COPD	15 (2.3)	10 (1.6)	29 (4.5)	2 (1.0)	6 (2.7)	62 (2.6)
Pneumonia	3 (0.5)	5 (0.8)	4 (0.6)	0	2 (0.6)	14 (0.6)
Acute respiratory failure	2 (0.3)	2 (0.3)	4 (0.6)	0	0	8 (0.3)
Cardiac failure congestive	1 (0.2)	1 (0.2)	1 (0.2)	2 (1.0)	1 (0.5)	6 (0.3)
Back pain	2 (0.3)	1 (0.2)	1 (0.2)	0	0	4 (0.2)
Acute myocardial infarction	0	2 (0.3)	1 (0.2)	0	0	3 (0.1)
Cardiac failure	2 (0.3)	0	1 (0.2)	0	0	3 (0.1)
Small intestinal obstruction	0	1 (0.2)	2 (0.3)	0	0	3 (0.1)
Angina pectoris	0	2 (0.3)	0	0	0	2 (0.1)
Angina unstable	0	2 (0.3)	0	0	0	2 (0.1)
Pancreatitis acute	0	0	0	0	2 (0.9)	2 (0.1)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: Clinical Reviewer

Overall, analysis of severe TEAEs in the BGF and BFF programs did not identify any safety concerns.

Treatment Emergent Adverse Events and Adverse Reactions

BGF Trials

Table 89 summarizes TEAEs that occurred in at least 2% of patients in any treatment group in Trial 06. The proportion of patients with at least 1 TEAE was similar across treatment groups. The most common PTs were nasopharyngitis, upper respiratory tract infection (URTI), COPD, and bronchitis. There were more reports of URTI with BGF compared GFF (10.2% versus 6.1%). The majority of URTI cases were mild and do not cause a safety concern.

Table 89. BGF Trial 06 TEAEs Occurring in ≥2% of Patients in Any Treatment Group by PT (Safety Population)

Preferred Term	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Patients with ≥1 TEAE	396 (62.0)	387 (61.9)	183 (58.3)	189 (59.4)	1155 (60.9)
Nasopharyngitis	49 (7.7)	41 (6.6)	26 (8.3)	30 (9.4)	146 (7.7)
URTI	65 (10.2)	38 (6.1)	18 (5.7)	22 (6.9)	143 (7.5)
COPD	17 (2.7)	32 (5.1)	8 (2.5)	13 (4.1)	70 (3.7)
Bronchitis	20 (3.1)	15 (2.4)	12 (3.8)	9 (2.8)	56 (3.0)
Muscle spasms	21 (3.3)	8 (1.3)	17 (5.4)	6 (1.9)	52 (2.7)
Dysphonia	20 (3.1)	5 (0.8)	15 (4.8)	6 (1.9)	46 (2.4)
Hypertension	13 (2.0)	10 (1.6)	8 (2.5)	4 (1.3)	35 (1.8)

Preferred Term	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Dyspnea	9 (1.4)	9 (1.4)	8 (2.5)	8 (2.5)	34 (1.8)
Back pain	8 (1.3)	12 (1.9)	4 (1.3)	8 (2.5)	32 (1.7)
Nausea	7 (1.1)	3 (0.5)	4 (1.3)	7 (2.2)	21 (1.1)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease; URTI = upper respiratory tract infection
Source: PT010006 Production Run Tables Section 3 (Safety); Table 3.2.2.1; pg. 74 and Clinical Reviewer

Table 90 summarizes TEAEs that occurred in at least 2% of patients in any treatment group in Trial 08. The proportion of patients with at least 1 TEAE was similar in the across treatment groups. The most common PTs were URTI, bronchitis, COPD, and urinary tract infection. As opposed to the increased frequency of URTI seen with BGF versus GFF in Trial 06, in Trial 08 the frequencies are similar. However, there were more cases of viral URTI in the BGF group than the GFF group, but this was overall less common than the URTI PT.

Table 90. BGF Trial 08 TEAEs Occurring in ≥2% of Patients in Any Treatment Group by PT (Safety Population)

Preferred Term	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
Patients with ≥1 TEAE	145 (74.7)	133 (76.4)	64 (72.7)	342 (75.0)
Upper respiratory tract infection	18 (9.3)	18 (10.3)	6 (6.8)	42 (9.2)
Bronchitis	12 (6.2)	8 (4.6)	2 (2.3)	22 (4.8)
COPD	12 (6.2)	9 (5.2)	1 (1.1)	22 (4.8)
Urinary tract infection	10 (5.2)	10 (5.2)	5 (5.7)	21 (4.6)
Viral URTI	9 (4.6)	5 (2.9)	6 (6.8)	20 (4.4)
Muscle spasms	6 (3.1)	5 (2.9)	9 (10.2)	20 (4.4)
Sinusitis	11 (5.7)	6 (3.4)	2 (2.3)	19 (4.2)
Hypertension	8 (4.1)	6 (3.4)	4 (4.5)	18 (3.9)
Nasopharyngitis	7 (3.6)	6 (3.4)	4 (4.5)	17 (3.7)
Back pain	9 (4.6)	7 (4.0)	1 (1.1)	17 (3.7)
Diarrhea	5 (2.6)	9 (5.2)	2 (2.3)	16 (3.5)
Dyspnea	4 (2.1)	5 (2.9)	5 (5.7)	14 (3.1)
Pneumonia	5 (2.6)	8 (4.6)	1 (1.1)	14 (3.1)
Dysphonia	6 (3.1)	2 (1.1)	5 (5.7)	13 (2.9)
Cellulitis	5 (2.6)	4 (2.3)	2 (2.3)	11 (2.4)
Oral candidiasis	5 (2.6)	3 (1.7)	2 (2.3)	10 (2.2)
Gastroesophageal reflux disease	5 (2.6)	2 (1.1)	3 (3.4)	10 (2.2)
Oropharyngeal pain	4 (2.1)	5 (2.9)	1 (1.1)	10 (2.2)
Cough	5 (2.6)	4 (2.3)	0	9 (2.0)
Hyperglycemia	3 (1.5)	6 (3.4)	0	9 (2.0)
Nausea	3 (1.5)	4 (2.3)	2 (2.3)	9 (2.0)
Acute Sinusitis	3 (1.5)	4 (2.3)	2 (2.3)	9 (2.0)
Gastroenteritis	3 (1.5)	3 (1.7)	3 (3.4)	9 (2.0)
Arthralgia	4 (2.1)	4 (2.3)	0	8 (1.8)
Cataract	6 (3.1)	0	2 (2.3)	8 (1.8)

Preferred Term	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
Fatigue	5 (2.6)	5 (2.6)	0	8 (1.8)
Insomnia	4 (2.1)	4 (2.3)	0	8 (1.8)
Hypokalemia	3 (1.5)	1 (0.6)	3 (3.4)	7 (1.5)
Animal bite	5 (2.6)	1 (0.6)	1 (1.1)	7 (1.5)
Dyspepsia	3 (1.5)	4 (2.3)	0	7 (1.5)
Headache	2 (1.0)	4 (2.3)	1 (1.1)	7 (1.5)
Intraocular pressure increased	2 (1.0)	4 (2.3)	1 (1.1)	7 (1.5)
Bursitis	4 (2.1)	2 (1.1)	0	6 (1.3)
Non-cardiac chest pain	4 (2.1)	2 (1.1)	0	6 (1.3)
Seasonal allergy	1 (0.5)	2 (1.1)	3 (3.4)	6 (1.3)
Depression	2 (1.0)	2 (1.1)	2 (2.3)	6 (1.3)
Leukocytosis	4 (2.1)	1 (0.6)	1 (1.1)	6 (1.3)
Edema peripheral	4 (2.1)	2 (1.1)	0	6 (1.3)
Osteoarthritis	2 (1.0)	4 (2.3)	0	6 (1.3)
Vertigo	2 (1.0)	4 (2.3)	0	6 (1.3)
Fall	4 (2.1)	1 (0.6)	0	5 (1.1)
Candida infection	1 (0.5)	1 (0.6)	2 (2.3)	4 (0.9)
Cataract subcapsular	4 (2.1)	0	0	4 (0.9)
Skin abrasion	0	4 (2.3)	0	4 (0.9)
Tremor	4 (2.1)	0	0	4 (0.9)
Rhinitis	0	1 (0.6)	2 (2.3)	3 (0.7)
Blood pressure increased	0	0	2 (2.3)	2 (0.4)
Lenticular opacities	0	0	2 (2.3)	2 (0.4)
Ventricular extrasystoles	0	0	2 (2.3)	2 (0.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease; URTI = upper respiratory tract infection
Source: PT010008 Production Run Tables Section 4 (Safety); Table 4.1.4; pg. 184 and Clinical Reviewer

BFF Trials

In the BFF program, TEAEs were generally similar across groups. The most common TEAEs in Trial 02 were nasopharyngitis, URTI, COPD, and hypertension. One notable finding was that the frequency of COPD as an AE was higher in the FF group compared to all other groups in both Trial 02 and Trial 03 (data not shown). A summary of TEAEs for Trial 02 is shown in Table 91.

Table 91. BFF Trial 02 TEAEs Occurring in ≥2% of Patients in Any Treatment Group by PT (Safety Population)

Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 9.6 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
Patients with ≥1 TEAE	333 (50.8)	318 (49.9)	324 (50.3)	107 (51.9)	114 (52.1)	1196 (50.7)
Nasopharyngitis	40 (6.1)	40 (6.3)	43 (6.7)	17 (8.3)	14 (6.4)	154 (6.5)
Upper respiratory tract infection	25 (3.8)	21 (3.3)	20 (3.1)	5 (2.4)	3 (1.4)	74 (3.1)
COPD	16 (2.4)	10 (1.6)	30 (4.7)	2 (1.0)	6 (2.7)	64 (2.7)
Hypertension	14 (2.1)	22 (3.5)	15 (2.3)	5 (2.4)	4 (1.8)	60 (2.5)

Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 9.6 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
Back pain	18 (2.7)	13 (2.0)	18 (2.8)	3 (1.5)	2 (0.9)	54 (2.3)
Headache	19 (2.9)	8 (1.3)	15 (2.3)	3 (1.5)	1 (0.5)	46 (1.9)
Cough	7 (1.1)	15 (2.4)	15 (2.3)	7 (3.4)	0	44 (1.9)
Oral candidiasis	17 (2.6)	14 (2.2)	5 (0.8)	3 (1.5)	3 (1.4)	42 (1.8)
Dyspnea	12 (1.8)	11 (1.7)	9 (1.4)	7 (3.4)	3 (1.4)	42 (1.8)
Sinusitis	10 (1.5)	9 (1.4)	12 (1.9)	2 (1.0)	5 (2.3)	38 (1.6)
Bronchitis	16 (2.4)	7 (1.1)	10 (1.6)	4 (1.9)	2 (0.9)	39 (1.7)
Diarrhea	9 (1.4)	9 (1.4)	9 (1.4)	5 (2.4)	3 (1.4)	35 (1.5)
Muscle spasms	14 (2.1)	6 (0.9)	6 (0.9)	0	8 (3.7)	34 (1.4)
Dysphonia	16 (2.4)	13 (2.0)	3 (0.5)	2 (1.0)	1 (0.5)	35 (1.5)
Anxiety	6 (0.9)	2 (0.3)	4 (0.6)	5 (2.4)	1 (0.5)	18 (0.8)
Fatigue	1 (0.2)	1 (0.2)	5 (0.8)	5 (2.4)	1 (0.5)	13 (0.6)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; TEAE = treatment emergent adverse event; COPD = chronic obstructive pulmonary disease
Source: PT009002 Production Run Tables Section 3 (Safety); Table 3.2.2; pg. 84-85 and Clinical Reviewer

In the BGF and BFF programs, TEAEs occurred at similar frequencies across groups and the majority of events were mild or moderate. An increased frequency of dysphonia was consistently observed in treatment groups that included an ICS component, and this is consistent with other ICS programs. Overall, no safety concerns were identified in the analysis of TEAEs in the BGF and BFF programs.

Laboratory Findings

The Applicant conducted analyses of clinical laboratory results in the BGF and BFF phase 3 studies. Analyses included changes in mean values over time, changes in individual subjects over time, and in potentially clinically significant (PCS) values.

In the BGF studies, Trial 06 and its safety extension Trial 08, no clinically meaningful trends or mean changes from baseline were observed in parameters of hematology, clinical chemistry, kidney function, and urinalysis. Analysis of individual subjects showed that shifts of ≥2 Common Terminology Criteria for Adverse Event (CTCAE) grades was rare for hematology, clinical chemistry, and kidney function, and these occurrences were similar across groups. Post-baseline newly occurring or worsening PCS values for clinical chemistry, hematology, kidney function, and urinalysis were infrequent and similar across groups. Hy's law screening analysis by the Clinical Reviewer using JMP Clinical 7.0 revealed one possible case in the BGF program (the subject, (b) (6), was a participant in both Trial 06 and Trial 08 so the case is included in both analyses). The subject was in the BGF treatment group and the case occurred on-treatment. The cause of the liver function abnormality was determined to be cholecystitis and does not represent a safety concern. Time trends, box plots, and shift table analysis by the Clinical Reviewer using JMP Clinical 7.0 of hematology, clinical chemistry, kidney function, and urinalysis in Trial 06 and Trial 08 did not reveal any safety signals or notable differences between treatment groups.

In the BFF trials, Trial 02 and Trial 03, there were no clinically meaningful trends or mean changes from baseline observed in parameters of hematology, clinical chemistry, kidney function, and urinalysis. One possible Hy's law case in the BFF 320/9.6 mcg group in Trial 02 was identified by Clinical Reviewer analysis and resulted from metastatic pancreatic cancer and was unrelated to study treatment. No possible Hy's law cases were identified in Trial 03. Time trends, waterfall plots, box plots, and shift table analysis by the Clinical Reviewer using JMP Clinical 7.0 of hematology, clinical chemistry, kidney function, and urinalysis in Trial 02 and Trial 03 did not reveal any safety signals or notable differences between treatment groups.

Overall, no safety concerns were identified in the analysis of laboratory values in the BGF and BFF phase 3 studies.

Vital Signs

No clinically significant changes in vital signs were identified in BGF studies, Trial 06 and safety extension Trial 08. Similarly, no clinically significant changes in vital signs were identified in the BFF studies, 24-week Trial 02 and the variable length Trial 03. Time trend analysis, box plots, and waterfall plots (JMP Clinical 7.0) were used by the Clinical Reviewer to assess systolic and diastolic blood pressure, heart rate, temperature, and BMI. Overall, no safety concerns were identified in the analysis of vital signs in the BGF and BFF phase 3 studies.

Electrocardiograms

No clinically significant ECG trends were identified in BGF studies, Trial 06 and Trial 08. Similarly, no clinically significant changes in ECG parameters were identified in the BFF studies, 24-week Trial 02 and the variable length Trial 03. Time trend analysis, box plots, and waterfall plots (JMP Clinical 7.0) were used by the Clinical Reviewer to assess heart rate, PR interval, QRS interval, axis, and QTcF. Overall, no safety concerns were identified in the analysis of ECG parameters in the BGF and BFF phase 3 studies.

QT

See ECG section above. No TQT study was performed under this NDA submission. A TQT study was performed under NDA 208294 (GFF, Bevespi Aerosphere) and no significant QT prolongation was detected for GFF in that study.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Given specific safety concerns with products containing LABA, LAMA, and ICS components, the Applicant analyzed TEAEs of special interests (AESI). The AESIs were organized into medical

concepts with the operational definition of each concept based on a group of MedDRA PTs. PT groupings were reviewed and are adequate to identify AESIs for each medical concept. The most frequently occurring AESIs are discussed in this section.

In BGF Trial 06, the most common AESIs by medical concept were lower respiratory tract infection (other than pneumonia), dysphonia or aphonia, and hypertension. The frequency of these AESIs were all numerically higher in the BGF group compared to the GFF group, though similar to BFF. However, frequency was less than 4%, events were mild or moderate, and the differences between groups were numerically small. A summary of the most common AESIs in Trial 06 is shown in Table 92.

Table 92. BGF Trial 06 AESIs Occurring in ≥2% of Subjects in Any Treatment Group (Safety Population)

Medical Concept Preferred Term	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Lower respiratory tract infection (other than pneumonia)	21 (3.3)	15 (2.4)	13 (4.1)	10 (3.1)	59 (3.1)
Bronchitis	20 (3.1)	15 (2.4)	12 (3.8)	9 (2.8)	56 (3.0)
Dysphonia or aphonia	20 (3.1)	5 (0.8)	15 (4.8)	6 (1.9)	46 (2.4)
Dysphonia	20 (3.1)	5 (0.8)	15 (4.8)	6 (1.9)	46 (2.4)
Hypertension	15 (2.3)	10 (1.6)	9 (2.9)	5 (1.6)	39 (2.1)
Hypertension	13 (2.0)	10 (1.6)	8 (2.5)	4 (1.3)	35 (1.8)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; AESI = adverse event of special interest
Source: PT010006 CSR Edition 1; Table 80; pg 249; confirmed by Clinical Reviewer

In BGF Trial 08, the most common AESI by medical concept was cardiovascular conditions. Frequency of cardiovascular conditions was lowest in the BGF group. The next two most common AESIs, ocular effects and lower respiratory tract infections other than pneumonia, occurred more often in the BGF group compared to the GFF group. A summary of the most common AESIs in Trial 08 is shown in Table 93.

Table 93. BGF Trial 08 AESIs Occurring in ≥2% of Subjects in Any Treatment Group (Safety Population)

Medical Concept Preferred Term	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
Cardiovascular condition	10 (5.2)	12 (6.9)	8 (9.1)	30 (6.6)
Ventricular extrasystoles	0	0	2 (2.3)	2 (0.4)
Ocular effects	14 (7.2)	6 (3.4)	4 (4.5)	24 (5.3)
Cataract	6 (3.1)	0	2 (2.3)	8 (1.8)
Intraocular pressure increased	2 (1.0)	4 (2.3)	1 (1.1)	7 (1.5)
Cataract subcapsular	4 (2.1)	0	0	4 (0.9)

Medical Concept Preferred Term	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
Lower Respiratory tract infections other than pneumonia	12 (6.2)	8 (4.6)	2 (2.3)	22 (4.8)
Bronchitis	12 (6.2)	8 (4.6)	2 (2.3)	22 (4.8)
Hypertension	8 (4.1)	6 (3.4)	6 (6.8)	20 (4.4)
Hypertension	8 (4.1)	6 (3.4)	4 (4.5)	18 (3.9)
Blood pressure increased	0	0	2 (2.3)	2 (0.4)
Pneumonia	7 (3.6)	8 (4.6)	1 (1.1)	16 (3.5)
Pneumonia	5 (2.6)	8 (4.6)	1 (1.1)	14 (3.1)
Diabetes mellitus	6 (3.1)	6 (3.4)	2 (2.3)	14 (3.1)
Hyperglycemia	3 (1.5)	6 (3.4)	0	9 (2.0)
Psychiatric effects	6 (3.1)	6 (3.4)	2 (2.3)	14 (3.1)
Insomnia	4 (2.1)	4 (2.3)	0	8 (1.8)
Depression	2 (1.0)	2 (1.1)	2 (2.3)	6 (1.3)
Dysphonia or aphonia	6 (3.1)	2 (1.1)	5 (5.7)	13 (2.9)
Dysphonia	6 (3.1)	2 (1.1)	5 (5.7)	13 (2.9)
Candidiasis	6 (3.1)	3 (1.7)	2 (2.3)	11 (2.4)
Oral candidiasis	5 (2.6)	3 (1.7)	2 (2.3)	10 (2.2)
Hypokalemia	3 (1.5)	2 (1.1)	3 (3.4)	8 (1.8)
Hypokalemia	3 (1.5)	1 (0.6)	3 (3.4)	7 (1.5)
Headache	2 (1.0)	4 (2.3)	1 (1.1)	7 (1.5)
Headache	2 (1.0)	4 (2.3)	1 (1.1)	7 (1.5)
Tremor	4 (2.1)	0	0	4 (0.9)
Tremor	4 (2.1)	0	0	4 (0.9)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; AESI = adverse event of special interest
Source: PT010008 CSR Edition 1; Table 48; pg 122; Confirmed by Clinical Reviewer

In the BFF program, understandably, AESIs did not include AEs associated with LAMA effects. In BFF Trial 02, the most common medical concept was hypertension, followed by headache. Frequency of hypertension and headache were similar across groups. There were small but notable increases in oral candidiasis and dysphonia in the BFF products compared to FF. This is an expected effect from the inclusion of ICS. A summary of AESIs in Trial 02 is shown in Table 94. In Trial 03, the most common AESI was pneumonia, followed by headache and hypertension. Frequency of these most common AESIs were similar across groups (data not shown).

Table 94. BFF Trial 02 AESIs Occurring in ≥2% of Subjects in Any Treatment Group (Safety Population)

Medical Concept Preferred Term	BFF 320/9.6 µg N=655 n (%)	BFF 160/9.6 µg N=637 n (%)	FF 9.6 µg N=644 n (%)	BD 320 µg N=206 n (%)	TBH 400/12 µg N=219 n (%)	Total N=2361 n (%)
Hypertension	19 (2.9)	27 (4.2)	23 (3.6)	7 (3.4)	4 (1.8)	80 (3.4)
Hypertension	14 (2.1)	22 (3.5)	15 (2.3)	5 (2.4)	4 (1.8)	60 (2.5)
Headache	19 (2.9)	8 (1.3)	15 (2.3)	3 (1.5)	1 (0.5)	46 (1.9)
Headache	19 (2.9)	8 (1.3)	15 (2.3)	3 (1.5)	1 (0.5)	46 (1.9)
Lower respiratory tract infection other than pneumonia	18 (2.7)	9 (1.4)	11 (1.7)	4 (1.9)	2 (0.9)	44 (1.9)
Bronchitis	16 (2.4)	7 (1.1)	10 (1.6)	4 (1.9)	2 (0.9)	39 (1.7)
Candidiasis	17 (2.6)	14 (2.2)	5 (0.8)	3 (1.5)	3 (1.4)	42 (1.8)
Oral candidiasis	17 (2.6)	14 (2.2)	5 (0.8)	3 (1.5)	3 (1.4)	42 (1.8)
Dysphonia or Aphonia	16 (2.4)	13 (2.0)	3 (0.5)	2 (1.0)	1 (0.5)	35 (1.5)
Dysphonia	16 (2.4)	13 (2.0)	3 (0.5)	2 (1.0)	1 (0.5)	35 (1.5)
Agitation or Anxiety	6 (0.9)	2 (0.3)	5 (0.8)	5 (2.4)	1 (0.5)	19 (0.8)
Anxiety	6 (0.9)	2 (0.3)	4 (0.6)	5 (2.4)	1 (0.5)	18 (0.8)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; AESI = adverse event of special interest
Source: PT009002 CSR Edition 1; Table 64; pg 186; confirmed by Clinical Reviewer

Overall, analysis of AESIs in the BGF and BFF programs did not identify any safety concerns.

Respiratory Safety

The CEC reviewed and adjudicated TEAEs and SAEs with PTs that could relate to pneumonia and that occurred during the treatment period. In BGF Trial 06, the frequency of confirmed pneumonia events was similar across treatment groups. A summary of pneumonia events in Trial 06 is shown in Table 95.

Table 95. BGF Trial 06 Adjudicated Pneumonia as Determined by CEC (Safety Population)

	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Number of subjects with events submitted to CEC	16 (2.5)	11 (1.8)	7 (2.2)	6 (1.9)	40 (2.1)
Events submitted to CEC	16	13	7	6	42
Subjects with confirmed pneumonia as determined by CEC	12 (1.9)	10 (1.6)	6 (1.9)	4 (1.3)	32 (1.7)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; CEC = Clinical Endpoint Committee
Source: PT010006 CSR Edition 1; Table 82; pg 252; confirmed by Clinical Reviewer

In BGF Trial 08, the frequency of confirmed pneumonia events was similar between the BGF and GFF group, with a lower frequency in the BFF group. A summary of pneumonia events in Trial 08 is shown in Table 96.

Table 96. BGF Trial 08 Adjudicated Pneumonia as Determined by CEC (Safety Population)

	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
Number of subjects with events submitted to CEC	7 (3.6)	8 (4.6)	1 (1.1)	16 (3.5)
Events submitted to CEC	7	8	1	16
Subjects with confirmed pneumonia as determined by CEC	4 (2.1)	6 (3.4)	1 (1.1)	11 (2.4)

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; CEC = Clinical Endpoint Committee
Source: PT010008 CSR Edition 1; Table 50; pg 126; confirmed by Clinical Reviewer

In BFF Trial 02, the frequency of confirmed pneumonia was similar across groups. A summary of pneumonia events in Trial 02 is shown in Table 97. The results from BFF Trial 03 were similar with confirmed pneumonia occurring at the same frequency across groups (data not shown).

Table 97. BFF Trial 02 Adjudicated Pneumonia as Determined by CEC (Safety Population)

	BFF 320/9.6 µg N=655	BFF 160/9.6 µg N=637	FF 9.6 µg N=644	BD 320 µg N=206	TBH 400/12 µg N=219	Total N=2361
Number of subjects with events submitted to CEC, n (%)	7 (1.1)	9 (1.4)	11 (1.7)	1 (0.5)	4 (1.8)	32 (1.4)
Events submitted to CEC, events	7	9	13	1	4	34
Subjects with confirmed pneumonia as determined by CEC, n (%)	5 (0.8)	7 (1.1)	9 (1.4)	1 (0.5)	3 (1.4)	25 (1.1)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; CEC = Clinical Endpoint Committee
Source: PT009002 CSR Edition 1; Table 66; pg. 189; confirmed by Clinical Reviewer

Overall, no safety issues were identified in the BGF and BFF programs concerning respiratory safety.

Cardiovascular Safety

The CEC reviewed and adjudicated serious cardiovascular and cerebrovascular events that occurred during the treatment period as MACE. In both BGF Trial 06 and BGF Trial 08, the frequency of MACE was low and similar across groups. A summary of MACE events in Trial 06 is shown in Table 98. A summary of MACE events in Trial 08 is shown in Table 99.

Table 98. BGF Trial 06 Adjudicated MACE as Determined by CEC (Safety Population)

	BGF 320/18/9.6 µg (N=639) n (%)	GFF 18/9.6 µg (N=625) n (%)	BFF 320/9.6 µg (N=314) n (%)	TBH 400/12 µg (N=318) n (%)	Total (N=1896) n (%)
Number of subjects with events submitted to CEC	8 (1.3)	7 (1.1)	4 (1.3)	4 (1.3)	23 (1.2)
Number of events submitted to CEC	9	7	4	4	24
Subjects with MACE as determined by CEC	2 (0.3)	3 (0.5)	2 (0.6)	2 (0.6)	9 (0.5)
Non-fatal myocardial infarction	0	2 (0.3)	2 (0.6)	2 (0.6)	6 (0.3)
Cardiovascular death	2 (0.3)	1 (0.2)	0	0	3 (0.2)
Non-fatal stroke	0	0	0	0	0

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; TBH = Turbuhaler; CEC = Clinical Endpoint Committee; MACE = major adverse cardiovascular event
Source: PT010006 CSR Edition 1; Table 81; pg 251; confirmed by Clinical Reviewer

Table 99. BGF Trial 08 Adjudicated MACE as Determined by CEC (Safety Population)

	BGF 320/18/9.6 µg (N=194) n (%)	GFF 18/9.6 µg (N=174) n (%)	BFF 320/9.6 µg (N=88) n (%)	Total (N=456) n (%)
Number of subjects with events submitted to CEC	6 (3.1)	4 (2.3)	0	10 (2.2)
Number of events submitted to CEC	6	5	0	11
Subjects with MACE as determined by CEC	3 (1.5)	3 (1.7)	0	6 (1.3)
Non-fatal myocardial infarction	2 (1.0)	2 (1.1)	0	4 (0.9)
Cardiovascular death	1 (0.5)	1 (0.6)	0	2 (0.4)
Non-fatal stroke	0	0	0	0

Abbreviations: BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate; BFF = budesonide/formoterol fumarate; CEC = Clinical Endpoint Committee; MACE = major adverse cardiovascular event
Source: PT010008 CSR Edition 1; Table 49; pg 125; confirmed by Clinical Reviewer

In both BFF studies, Trial 02 and Trial 03, the frequency of MACE was low with no substantial difference between treatment groups. Adjudicated MACE for Trial 02 is shown in Table 100. Data is not shown for Trial 03.

Table 100. BFF Trial 02 Adjudicated MACE as Determined by CEC (Safety Population)

	BFF 320/9.6 µg N=655	BFF 160/9.6 µg N=637	FF 9.6 µg N=644	BD 320 µg N=206	TBH 400/12 µg N=219	Total N=2361
Number of subjects with events submitted to CEC, n (%)	4 (0.6)	9 (1.4)	10 (1.6)	2 (1.0)	4 (1.8)	29 (1.2)
Events submitted to CEC, events	4	9	11	2	4	30
Subjects with MACE as determined by CEC, n (%)	3 (0.5)	5 (0.8)	6 (0.9)	1 (0.5)	2 (0.9)	17 (0.7)
Cardiovascular death, n (%)	2 (0.3)	1 (0.2)	1 (0.2)	0	1 (0.5)	5 (0.2)
Non-fatal MI, n (%)	0	2 (0.3)	2 (0.3)	1 (0.5)	0	5 (0.2)
Non-fatal stroke, n (%)	1 (0.2)	2 (0.3)	3 (0.5)	0	1 (0.5)	7 (0.3)

Abbreviations: BFF = budesonide/formoterol fumarate; FF = formoterol fumarate; BD = budesonide; TBH = Turbuhaler; CEC = Clinical Endpoint Committee; MACE = major adverse cardiovascular event; MI = myocardial infarction
Source: PT009002 CSR Edition 1; Table 65; pg. 188; confirmed by Clinical Reviewer

Overall, analysis of AESIs in the BGF and BFF programs did not reveal any safety concerns. Specifically, adjudicated pneumonia and MACE occurrence was similar across treatment groups. Dysphonia was again identified as generally being more common groups treated with an ICS component, and this is consistent with other ICS-containing development programs.

Bone and Endocrine Safety

Corticosteroids, including ICS, are known to have effects on the HPA access and bone health, and the labels of ICS-containing products have statements regarding these effects in the Warnings and Precautions section. In the BGF program, sub-studies were performed to assess these effects. In BGF Trial 06, a subset of subjects participated in an HPA axis sub-study. The population consisted of 168 subjects and these subjects underwent adrenocorticoid testing over 24-hours prior to the first treatment and at Week 24. Serum cortisol curves showed normal diurnal variation over the 24-hour period and were similar between groups at both baseline and Week 24.

In BGF Trial 08, a BMD sub-study was performed in a subset of subjects (N=323). There was a small numerical decrease in BMD of the lumbar spine at Week 52 in the BGF group compared to the GFF group (-0.5% [-1.4, 0.5]) that was above the pre-specified non-inferiority margin of -2%. Similarly, BMD of the hip showed a small numerical decrease in the BGF group compared to the GFF group (-0.6% [-1.3, 0.2]). Frequencies of bone-related AEs, including osteoarthritis, osteoporosis, osteopenia, and bone fractures, was infrequent and similar across treatment groups.

Overall, the results of the HPA axis and BMD sub-studies do not raise any safety concerns.

Ocular Safety

In BGF safety extension Trial 08, ocular endpoints were evaluated and were consistent with increased frequency of lens opacification and cataract AEs in the ICS-containing groups. No

notable differences between treatment groups in intraocular pressure were observed. Cataracts and glaucoma are a recognized adverse effect of corticosteroids and is reflected in the Warnings and Precautions section of labels for ICS-containing 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 conducted demographic subgroup analyses on AEs in BGF Trial 06. Subgroup analyses were performed by country, age, gender, and race. Small numerical differences were identified between subgroups, but this is to be expected given the relatively small number of subjects within subgroups. Overall, demographic subgroup analysis of Trial 06 did not reveal any safety concerns.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant submitted a 120-day safety update that consisted of a CSR for trial PT010007, a 28-week extension trial to assess the safety and efficacy of BGF, GFF, and BFF in Japanese subjects (N=416) with moderate to very-severe COPD. One finding from this trial was a higher frequency of drug-related TEAEs in the BGF and BFF groups compared to GFF (24.5%, 22.9%, and 11.6%, respectively). The frequency of deaths, SAEs, and TEAEs leading to discontinuation were similar across groups and do not raise a safety concern. Regarding pneumonia, in PT010007 there was a higher frequency of adjudicated pneumonia events in the BGF group compared to the GFF and BFF groups (9.4%, 3.6%, and 5.7%, respectively). Pneumonia is a known risk of ICS, however, no safety signal for pneumonia was seen for BGF in Trial 06 or its extension Trial 08. Nonetheless, labeling for other ICS-containing products includes a warning for increased risk of pneumonia and the findings of PT010007 do not change the safety profile of BGF.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No human carcinogenicity studies have been conducted in this application.

Human Reproduction and Pregnancy

No studies in this application assessed pregnancy, lactation, or reproduction. No pregnancies were reported in BGF Trial 06 nor BGF safety extension Trial 08. No pregnancies were reported in the BFF phase 3 studies, Trial 02 and Trial 03.

Pediatrics and Assessment of Effects on Growth

BGF is not subject to PREA requirements due to the nature of COPD involving an older population group.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Given the nature of the drug components and delivery method, drug abuse, withdrawal, and rebound are not anticipated for this combination drug product. It is expected that overdose with BGF would produce typical class effects for LABA and anticholinergic agents. Theoretically, abrupt stoppage of excessive dosages of BGF may result in adrenal crisis. The product labels for other ICS-containing products contain warning language regarding this risk.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no post-market experience for BGF. No safety concerns have been identified through post-market experience with GFF (Bevespi Aerosphere).

Expectations on Safety in the Postmarket Setting

The BGF phase 3 program evaluated a moderate-severe COPD population already taking at least two maintenance therapies for COPD. Additionally, patients with certain respiratory comorbidities, chronic oxygen use, or recent exacerbations or infections were excluded from the clinical trials. Demographically, the BGF phase 3 program had some differences from the overall COPD population in the United States. Therefore, the COPD population exposed to BGF after marketing may experience other reactions not observed in the clinical trials. However, this is not expected given the extensive experience in the COPD population with this class of drugs and can be monitored for with standard post-marketing safety infrastructure.

8.2.11. Integrated Assessment of Safety

The safety data submitted with this application were sufficient for review. The data were derived primarily from a single phase 3 trial (BGF Trial 06) and its safety-extension (BGF Trial 08). Supportive data was derived from two phase 3 studies for the unapproved BFF combination product (24-week Trial 02 and variable-length Trial 03). Review of safety for the GFF (Bevespi Aerosphere) component was performed under NDA 208294.

Overall, the safety assessment, which included an evaluation of deaths, SAEs, all TEAEs, dropouts, AESIs, MACE, pneumonia events, laboratory findings, vital signs, ECGs, BMD, HPA axis, and ocular safety, was consistent with other products containing LAMA, LABA, or ICS alone or in combination. No new safety signals were revealed in this application. Overall, deaths,

SAEs, and TEAEs were generally similar across groups. BGF did show some numerical increases compared to GFF in URTIs, dysphonia, thrush and cataracts, which is consistent with the known adverse effects of ICS. Analysis of AE-related study discontinuations did not raise safety related concerns. Laboratory testing, vital signs, and ECG analysis did not show trends of concern for BGF.

In conclusion, BGF does not show significant safety concerns above the active comparators GFF and BFF. Identified numerical differences between BGF and GFF can be attributed to the ICS component and is already reflected in the Warnings and Precautions of other ICS-containing products. Overall, the BGF safety profile is consistent with other inhaled products containing drugs in these classes.

8.3. Statistical Issue

In the following, we will discuss the statistical issues in five categories: combination rule, substantial evidence of effectiveness, overall type I error control, estimand, and missing data and sensitivity analysis.

Combination Rule

First, BGF is a fixed-dose triple-combination products of ICS, LAMA and LABA. To assess the efficacy of this product, it is necessary to demonstrate the contribution of each mono component to the triple. Due to lack of treatment regimen of ICS and LAMA combo, it is only necessary to show the contribution of ICS and contribution of LAMA to the triple.

Contribution of ICS to the triple was assessed by comparison of BGF versus GFF on co-primary endpoint of morning trough FEV1 at Week 24.

Contribution of LAMA to the triple was assessed by comparison of BGF versus BFF on co-primary endpoint of FEV1 AUC_{0-4} at Week 24.

Trial 06 was the only trial in the program to study the triple versus doubles which assessed the contribution of ICS and LAMA to the triple. This trial failed to demonstrate the contribution of ICS to the triple (it failed on the co-primary endpoint of morning trough FEV1) although successfully demonstrated the contribution of LAMA to the triple (it won on the co-primary endpoint of FEV1 AUC_{0-4}). Thus, the combination rule was not satisfied in the BGF trial.

Second, BFF was a double combination of ICS and LABA. It was not an approved product. It is necessary to demonstrate the contribution of ICS and LABA to the double. This program included two phase 3 BFF trials: Trial 02 and Trial 03. Both served as supporting efficacy trials. Both trials won on all the co-primary endpoints or the primary endpoint and provided a qualification for BFF as an active comparator in Trial 06.

Overall, combination rule wasn't satisfied in the primary BGF efficacy trial, although it was satisfied in the supporting BFF efficacy trials.

Substantial Evidence of Effectiveness

Effectiveness of BGF was studied in Trial 06 which served as a primary efficacy trial, and effectiveness of BFF was studied in Trial 02 and Trial 03 which served as supporting efficacy trials. The primary endpoint(s) were the same in these three trials, while the secondary endpoints in these three trials were not all the same. In the following we only focus on the primary endpoint(s) and two secondary endpoints of SGRQ and exacerbation, which were considered clinically important endpoints among all the secondary endpoints.

In Trial 06, due to the failure on one of the co-primary endpoints, none of the secondary endpoints can be considered statistically significant. Any testing p-value less than 0.05 were considered nominally significant.

The effectiveness of BGF and BFF were assessed mainly in three categories: lung function benefit, SGRQ benefit and exacerbation benefit:

1. Lung Function Benefit

Lung function benefit were assessed by the co-primary endpoints or primary endpoint. Primary efficacy Trial 06 failed on one of the co-primary endpoints, therefore effectiveness of BGF in lung function wasn't demonstrated. Trial 02 and Trial 03 won on all primary endpoints, demonstrated the effectiveness of BFF in lung function, thereby implying that BFF was qualified as an active comparator to show contribution of LAMA to triple.

Overall, substantial evidence of effectiveness in lung function benefit wasn't demonstrated in BGF program.

2. SGRQ Benefit

For Trial 06, contribution of ICS to the triple in SGRQ benefit was assessed on responder rate in SGRQ total score at Week 24. The result reached nominal significant. Contribution of LAMA to the triple in SGRQ benefit was assessed on responder rate in SGRQ total score, the result only showed that BGF was numerically better than BFF but not nominally significant.

For Trial 02, contribution of ICS to BFF in SGRQ benefit was assessed on responder rate in SGRQ total score at Week 24. The result demonstrated that contribution of ICS to BFF is statistically significant. Contribution of LABA to BFF in SGRQ benefit was assessed on responder rate in SGRQ total score. The result demonstrated that LABA had some contribution to BFF, but not statistically significant.

For Trial 03, it only assessed the contribution of ICS to BFF in SGRQ benefit on the endpoint of SGRQ responder's rate at Week 12. The result showed that SGRQ benefit of BFF over FF was statistically significant.

Overall, BGF demonstrated some SGRQ improvement over GFF and BFF, but this was not statistically significant; BFF demonstrated a statistically significant SGRQ benefit over FF, but only a numerical improvement over BD.

3. Exacerbation Benefit

For Trial 06, contribution of ICS to the triple in exacerbation benefit was assessed on annual rate of moderate or severe COPD exacerbation over 24 weeks. The result was nominally significant. Contribution of LAMA to the triple in exacerbation benefit was assessed on annual rate of moderate or severe COPD exacerbation; the result showed that BGF had numerically less exacerbation than BFF but did not reach nominal significance.

For Trial 02, contribution of ICS to BFF in exacerbation benefit was assessed on time to first moderate or severe COPD exacerbation. The result was statistically significant. Contribution of LABA to BFF in exacerbation benefit was assessed on time to first moderate or severe COPD exacerbation. The result demonstrated that LABA had some contribution to BFF, but not statistically significant.

For Trial 03, it only assessed the contribution of ICS to BFF in exacerbation benefit on the endpoint of time to first moderate or severe COPD exacerbation. The result showed that exacerbation benefit of BFF over FF was statistically significant.

Overall, after considering important benefits including lung function, SGRQ and exacerbation, the substantial evidence of effectiveness of BGF was assessed. We conclude that overall the program failed to demonstrate substantial evidence of effectiveness of the study drug BGF. Mainly, this was due to the program failure on one of the co-primary endpoints in BGF trial, and there was only one BGF trial in the program.

Overall Type I Error Control

For all the trials in the program, overall type I error was controlled by performing graphical hierarchical testing among the primary endpoint(s) and secondary endpoints.

During the review, we found that there were two places where the overall type I error wasn't controlled in the strong sense, because the alpha wasn't split between the multiple outgoing tests from one test (the HD BFF test on efficacy estimand). These two places are in Figure 7 and Figure 10 (where the dotted lines led to one of the outgoing tests).

Because one of the outgoing tests was testing LD BFF which wasn't the proposed dose, also because all the subsequent test p-values in the hierarchy were far smaller than 0.025, or far

larger than 0.05, by splitting the alpha between the two outgoing tests will not change the conclusion in terms of statistical significance. Therefore, it was less of a concerned, but it was worthwhile to point out.

Estimand

In this program, all the primary efficacy analyses targeted efficacy estimand. All the data collected after discontinuing study treatment while on study (retrieved data) were excluded in the analysis. This estimand is a hypothetical estimand. It assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomized treatment had they remained on treatment. This estimand is not regulatory preferred estimand. The regulatory preferred estimand is treatment policy estimand; it targets the treatment effect over the trial period regardless of whether randomized treatment is continued. When estimating treatment policy estimand, all the retrieved data are included in the analysis.

In analysis targeting efficacy estimand, the data collected after subjects discontinued the study treatment while on study were considered missing at random. Often, subjects in active arm discontinue study treatment due to intolerability, therefore, the data collected after treatment discontinuation would reflect reduced effect compared to the on-treatment data. On the other hand, subjects in placebo arm often discontinue study treatment due to lack of efficacy, therefore, the data collected after treatment discontinuation would show similar effect compared to the on-treatment data. As a result, analysis targeting treatment policy estimand would show lower treatment effect for the study drug than analysis targeting efficacy estimand. In other words, analysis targeting efficacy estimand instead of treatment policy estimand would be favored by the Applicant without scientific justification as in this submission.

In this program, a single primary efficacy trial failed to show efficacy on efficacy estimand. Therefore, as expected, it also failed to show efficacy on treatment policy estimand which is considered more conservative.

Missing Data and Sensitivity Analyses

For the issue of missing data and sensitivity analyses, we focused on Trial 06 only, because this was the only trial studying the triple-combination products BGF.

In Trial 06, the rate of discontinuing from study drug is 11.4% in BGF 320/18/9.6 µg arm, 16.4% in GFF 18/9.6 µg arm and 15.6% in BFF 320/9.6 µg arm.

Missing rate over 10% usually warrants a sensitivity analysis to check the robustness of the efficacy result seen in the primary analysis.

Since Trial 06 failed on pre-dose trough morning $FEV_{1,}$ sensitivity analysis under more conservative approach would not change the conclusion of non-statistically significant result.

Thus, it was not the focus of this review. Instead, we focused on checking the robustness of efficacy result seen in FEV_1 AUC_{0-4}.

Sensitivity analysis was conducted on FEV1 AUC_{0-4} by the Applicant using pattern mixture model and tipping point analysis. Both analyses showed that the primary efficacy analysis was robust to the departure of missing at random assumption. Therefore, the contribution of LAMA to the triple combination BGF was re-assured in terms of lung function benefit.

8.4. Conclusions and Recommendations

The recommended regulatory action for BGF 320/18/9.6 µg is Complete Response.

The Applicant submitted results from a single phase 3 trial, Trial 06, as the primary evidence of efficacy to support a lung function and exacerbation claim. Trial 06 was a 24-week lung function trial that failed to show a statistically significant improvement for one of its co-primary endpoints, pre-dose trough FEV1 at Week 24 for BGF versus GFF, thus not demonstrating the contribution of BD to BGF. However, Trial 06 did show a statistically significant improvement for the other co-primary endpoint of FEV1 AUC_{0-4} at Week 24 for BGF versus BFF, demonstrating the contribution of GP to BGF. As such, the co-primary endpoint results are insufficient to support the efficacy of BGF and the contribution of the BD component. Because of the Type I error control strategy, all subsequent pairwise comparisons for BGF were not statistically significant, including exacerbation rate and SGRQ. As such, results from the secondary endpoints could not be used to support efficacy or the contribution of BD to BGF. Therefore, the BGF program failed to show any contribution of BD to the effectiveness of the triple combination. Furthermore, the Applicant did not provide replicate evidence of effectiveness for BGF as the results of only one trial were submitted.

With regard to BFF, in both BFF trials, statistically significant improvements for the spirometric primary endpoint were demonstrated when comparing BFF 320/9.6 µg to its relevant mono-components. For the exacerbation-related secondary endpoints, BFF 320/9.6 µg demonstrated superiority to both FF and BD in Trial 02, and FF in Trial 03. The results of the BFF program supported the efficacy of BFF 320/9.6 µg, demonstrated the contribution of BD and FF to the BFF 320/9.6 µg combination, and supported the use of BFF as an active comparator in the BGF program.

Regarding safety, assessment of BGF focused on Trial 06 and the safety extension Trial 08. Assessment of BFF focused on Trial 02 and Trial 03. No large imbalance of safety signals was observed across treatment groups in the BGF and BFF programs. Safety signals identified were consistent with drugs in this class, and no new concerns were identified.

Overall, while the safety assessment of BGF was consistent with other products on this class, due the issues outlined with the BGF trial, there was insufficient evidence to conclude that BGF was effective and that the BD component contributed to the combination. Therefore, the

benefit-risk assessment is not favorable, and the recommendation is a Complete Response Action.

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, a disease that rarely or never occurs in pediatric patients. A Pediatric Research Equity Act (PREA) waiver was requested and granted.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Not applicable.

12. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13. Postmarketing Requirements and Commitment

Not applicable.

14. Division Director (Clinical, Designated Signatory Authority) Comments

This 505(b)(2) NDA is for a new triple therapy (ICS/LABA/LAMA) fixed-dose combination (FDC) of budesonide (BD), glycopyrrolate (GP), and formoterol fumarate (FF) inhalation aerosol (BGF) proposed for the (b) (4)b) (4), maintenance treatment of (b) (4) patients with COPD (b) (4) BGF is delivered by a pressurized MDI. Each inhalation contains budesonide 160 µg, glycopyrrolate (glycopyrronium bromide) 9 µg, and formoterol fumarate 4.8 µg. The proposed dose is 2 inhalations for a total dose of 320, 18, and 9.6 µg of each component, respectively, and it is taken twice daily. The proposed trade name is Breztri Aerosphere.

There is currently one approved triple therapy inhalation product for patients with COPD, Trelegy Ellipta, which contains fluticasone furoate (ICS), vilanterol (LABA), and umeclidinium (LAMA). The Trelegy Ellipta program was quite large and was supported by development programs for two combination products, Breo Ellipta (ICS/LABA) and Anoro Ellipta (LABA/LAMA) as well as the LAMA single ingredient (Incruse Ellipta), all of which were approved in the US.

The FDC of glycopyrrolate and formoterol fumarate (GFF) is approved in the United States under the tradename Bevespi Aerosphere using the same delivery device. The FDC of budesonide and formoterol fumarate (BFF) is not approved, nor are the mono-components, budesonide (BD), glycopyrrolate (GP), and formoterol fumarate (FF) in this delivery device.

The development of a combination MDI needs to address relevant CMC and clinical pharmacology considerations, including the potential for interactions between components and pharmaceutical equivalence between the combination product and comparators in the clinical trials. The CMC and clinical pharmacology issues were adequately addressed in this program, so the focus of this summary is the clinical program.

To support this application, Astra Zeneca submitted the results of one pivotal phase 3 trial (Trial 06) comparing the BGF combination product to BFF and GFF. Since BFF is not an approved product, AZ also submitted the results of 2 additional supportive trials (Trial 02 and Trial 03) to support the efficacy and safety of BFF. AZ also had one additional phase 3 trial (Trial 05) that was ongoing at the time of submission of the NDA but was recently completed. Trial 05 compared 2 doses of BGF (320/18/9.6 µg and 160/18/9.6 µg) to GFF and BFF.

BFF Combination
Trial 02 was a 24 week, randomized, double-blind trial in 2361 patients with COPD. Patients were randomized to one of 2 doses of BFF (320/9.6 µg BID or 160/9.6 µg BID), FF 9.6 µg BID, or BD 320 µg BID. Co-primary endpoints were change from baseline trough FEV_1 at week 24 (BFF vs. FF) to show the contribution of BD and change from baseline FEV_1 AUC_{0-4} at week 24 (BFF 320/9.6 µg vs. BD 320 µg) to show the contribution of FF. Results showed a statistically

significant improvement in both co-primary endpoints for the BFF 320/9.6 µg dose, demonstrating a contribution of each component to the BFF combination.

Trial 03 was a randomized, double-blind trial in 1843 patients with COPD. This trial was initially designed as a 52-week exacerbation trial but was subsequently amended to a be a 12-week bronchodilator trial. As such, all patients received at least 12-weeks of treatment, but some received treatment for longer. Patients were randomized to one of 2 doses of BFF (320/9.6 µg BID or 160/9.6 µg BID) or FF 9.6 µg BID. The primary endpoint was the change from baseline in trough FEV_1 at 12 weeks (BFF 320/9.6 µg vs. FF) to show the contribution of BD. Results showed a statistically significant improvement in change from baseline in trough FEV_1 at Week 12 for BFF 320/9.6 µg compared to FF.

In both trials, statistically significant improvements in time to first exacerbation were shown for BFF 320/9.6 µg compared to FF. The results of Trials 02 and 03 demonstrate the contribution of BD and FF to the BFF combination and support the use of BFF as a comparator in the BGF program.

BGF Combination
Trial 06 was a 24 week, randomized, double-blind, trial in 1896 patients with COPD designed to show the benefit of BGF over the two double combinations (BFF and GFF). Patients were randomized to BGF 320/14.4/9.6 µg, GFF 14.4/9.6 µg, BFF 320/9.6 µg BID, or open label Symbicort Turbuhaler 400/12 µg BID. The co-primary endpoints were change from baseline in FEV_1 AUC_{0-4} (BGF vs. BFF) at week 24 to show the contribution of GP and change from baseline in trough FEV_1 (BGF vs. GFF) at week 24 to show the contribution of BD. The results of Trial 06 showed a statistically significant increase in FEV_1 AUC_{0-4} for BGF vs. BFF, but results did not show a statistically significant increase in trough FEV_1 for BGF vs. GFF. Thus, Trial 06 failed to demonstrate the contribution of BD in the BGF combination product based on the results of the co-primary endpoint. Because of the failure to achieve statistical significance in the co-primary endpoint, all secondary endpoints are considered not statistically significant, including exacerbation rate and SGRQ. I note that the exacerbation rate for comparison of BGF vs. GFF (contribution of BD) was numerically favorable.

Review of the safety data from this development program did not identify a new safety signal. ICS, LABA, and LAMA are well-established therapeutic classes in patients with COPD. The safety findings were consistent with the known safety profile of these therapeutic classes.

Overall, the single pivotal trial with BGF failed to show the contribution of BD in the BGF combination product and thus substantial evidence of effectiveness of BGF has not been established. The program (Trials 02 and 03) did provide support for the efficacy and safety of BFF.

Clinical Deficiency

The submitted data do not provide substantial evidence of the efficacy and safety of the use of BGF for the proposed indication - the (b) (4), maintenance treatment of (b) (4) (b) (4) patients with COPD (b) (4). The single pivotal trial failed on the co-primary endpoint of change from baseline in trough FEV_1 for the comparison between BGF and GF. Therefore, the submitted data do not establish the contribution of budesonide in the BGF combination product. Failure of the co-primary endpoint limits interpretation of the secondary endpoints. Given that a single phase 3 study was submitted with this application, additional data were not available to directly support the efficacy and safety of BGF.

The Applicant should conduct an additional trial or trials to provide data to demonstrate the efficacy of BGF and the contribution of budesonide to the BGF combination product.

15. Appendices

15.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): PT010006

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1471		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PT009002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1138		
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: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PT009003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1162		
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: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT H LIM
09/26/2019 12:28:10 PM

SALLY M SEYMOUR
09/30/2019 07:28:26 AM

MEMORANDUM	DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH
DATE:	8/15/2019
TO:	File for NDA 212122
THROUGH:	Bhawana Saluja, Ph.D.
FROM:	Yunzhao Ren, M.D. Ph.D.
SUBJECT:	**Clinical Pharmacology Primary Review**
APPLICATION/DRUG:	**NDA 212122 Breztri Aerosphere (budesonide, glycopyrronium bromide, and formoterol fumarate inhalation aerosol)**

AstraZeneca submitted NDA 212122 for a fixed-dose triple combination of budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol on 11/30/2018 for the (b) (4) (b) (4), maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4).

AstraZeneca submitted study reports for 8 clinical pharmacology studies and a population PK analysis report.

The Office of Clinical Pharmacology (OCP) finds the application acceptable from a clinical pharmacology perspective.

A multi-disciplinary unireview has been used for this application, and the clinical pharmacology review will be submitted as part of this unireview.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YUNZHAO REN
08/21/2019 09:46:48 AM

BHAWANA SALUJA
08/21/2019 09:49:56 AM

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212122
Supporting document/s:	SDN# 1, 5, 10
Applicant's letter date:	November 30, 2018
CDER stamp date:	November 30, 2018
Product:	Budesonide, Formoterol Fumarate, Glycopyrrolate (BGF) pMDI
Indication:	COPD
Applicant:	AstraZeneca
Review Division:	Division of Pulmonary Allergy and Rheumatology Products
Reviewer:	Ijeoma Uzoma, PhD
Supervisor/Team Leader:	Timothy Robison, PhD, DABT
Division Director:	Sally Seymour, MD
Project Manager:	Linda Ebonine, PA

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 212122 are owned by AstraZeneca or are data for which AstraZeneca has obtained a written right of reference. Any information or data necessary for approval of NDA 212122 that AstraZeneca does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 212122.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

The Sponsor has submitted a marketing application for the inhaled triple combination product composed of glycopyrrolate (G), budesonide (B), and formoterol fumarate (F or FF) as a treatment for COPD. The Sponsor currently markets the combination of glycopyrrolate and formoterol under the tradename of Bevespi Aerosphere™ (NDA 208294) as a treatment for COPD. The inhaled triple combination product represents the addition of budesonide to the approved combination of glycopyrrolate and formoterol. The Sponsor also markets the combination of formoterol and budesonide under the tradename of Symbicort (NDA 21929) for the treatment of asthma and COPD.

During the IND development phase for the inhaled triple combination product, the Sponsor was requested to conduct only one nonclinical study, a 90-day inhalation toxicology study in dogs with the combination of BGF.

The Sponsor has complete nonclinical programs for formoterol and budesonide, which were reviewed under the NDA 21929 for Symbicort (Budesonide and Formoterol Fumarate) and NDA 20929 for Pulmicort Respules (Budesonide).

In an attempt to support a 505b1 application for the inhaled triple combination, the Sponsor provided a complete nonclinical program for glycopyrrolate. In the current application, the Sponsor provided a 90-day inhalation toxicology study with BGF in dogs, complete reproductive toxicity studies with glycopyrrolate, and 2-year inhalation carcinogenicity studies with glycopyrrolate in Sprague-Dawley rats and B6C3F1 mice. The Sponsor had previously submitted 6-month inhalation toxicology studies with glycopyrrolate in rats and dogs, a 90-day inhalation toxicology study in dogs with the combination of glycopyrrolate and formoterol, and a complete battery of genetic toxicity studies with glycopyrrolate that were reviewed under NDA 208294 for Bevespi Aerosphere. The Sponsor never conducted their own pharmacology studies with glycopyrrolate, but rather relied on the published literature. It is noted that NDA 208294 for Bevespi Aerosphere used the 505b2 pathway, which relied on reproductive toxicity studies conducted with glycopyrrolate that are described in the label for the reference listed drug, ROBINUL Injection (NDA 17558) as well as published literature for the pharmacology of glycopyrrolate.

This review evaluated the 2-year inhalation carcinogenicity studies in rats and mouse with glycopyrrolate. As described below, the Sponsor's 505b1 approach was determined to not be viable given that 2-year inhalation carcinogenicity study in rats was considered invalid. As a path forward to avoid repeating the 2-year carcinogenicity study with rats, the Sponsor administratively changed the application to the 505(b)(2) pathway in order to rely on the Agency's previous findings of safety for glycopyrrolate with the reference listed drug, ROBINUL Injection (NDA 17558) and published literature on the pharmacology of glycopyrrolate.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor conducted two-year inhalation carcinogenicity studies with glycopyrrolate in Sprague-Dawley rats and B6C3F1 mice. Prior concurrence for doses used in these studies was not obtained from the Executive Carcinogenicity Assessment Committee (ECAC). Final results of these studies were presented to the ECAC on April 16, 2019.

In the 2-year carcinogenicity study, Sprague Dawley rats received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 151.7/165.93 (LD, M/F), 302.9/330.66 (MD, M/F), and 620.45/684.14 (HD, M/F) µg/kg/day. Treatment with glycopyrrolate had no effects on survival of male or female rats. The Sponsor elected to terminate the entire study early (starting at Week 82) for all male and female groups due to low survival (22 of 60 [37%] females remaining) in the female air-control group at week 82. According to ECAC criteria for study termination, if the number of animals of a sex within the control group declines to 20, then all groups of that sex including drug-treated should be terminated. Based on these criteria, it was inappropriate to terminate female groups at that time. Further, in the male air-control and vehicle-control groups, 37 of 60 (62%) and 27 of 60 (45%) animals, respectively, were alive at week 82. Male groups were also inappropriately terminated per ECAC criteria for study termination. The study duration was potentially inadequate to assess drug-induced tumor development. The ECAC concluded that the carcinogenicity study was inadequate in male and female rats due to early termination of the study. The label will provide a description of the 2-year carcinogenicity study with glycopyrrolate administered by oral gavage to rats that can be found in the label for the referenced listed drug, CUVPOSA® (pending).

In a 2-year carcinogenicity study, B6C3F1 mice received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 0.347/0.335 (LD, M/F), 0.705/0.7 (MD, M/F), and 1.46/1.42 (HD, M/F) mg/kg/day. Treatment with glycopyrrolate had no effects on survival of male or female mice up to 104 weeks. Dose-related decreases of absolute body weights were observed in males and females beginning around Week 3 and Week 11, respectively, and continuing over the course of study. Decreases of absolute body weights at the end of the study appeared to be potentially excessive (>10%) for MD Females (-15.9%), HD males (-15%), and HD females (-27.7%). The Sponsor did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights. There were no statistically significant test article-related tumor findings in male mice in the LD and MD groups or female mice in the LD group. The Committee concluded that body weight decreases in high dose males and mid and high dose females could confound interpretation. The ECAC concluded that no drug-related neoplasms were observed at the low dose in females and the mid and low dose in males.

Refer to the unireview for a discussion of the Sponsor's nonclinical program for glycopyrrolate. A detailed discussion of the Sponsor's nonclinical program for glycopyrrolate is also provided in the Summary and Evaluation section of the current review. The nonclinical programs for budesonide and formoterol fumarate are also briefly discussed in the unireview and the Summary and Evaluation section of the current review.

2 Drug Information

2.1 Drug

Generic Name: Budesonide, Glycopyrrolate, and Formoterol Fumarate Inhalation Aerosol, 120 Inhalations for Budesonide, Glycopyrrolate, and Formoterol Fumarate metered dose inhaler, 120 Inhalations (BGF MDI)

Individual Components

Budesonide

CAS Registry Number: 51333-22-3

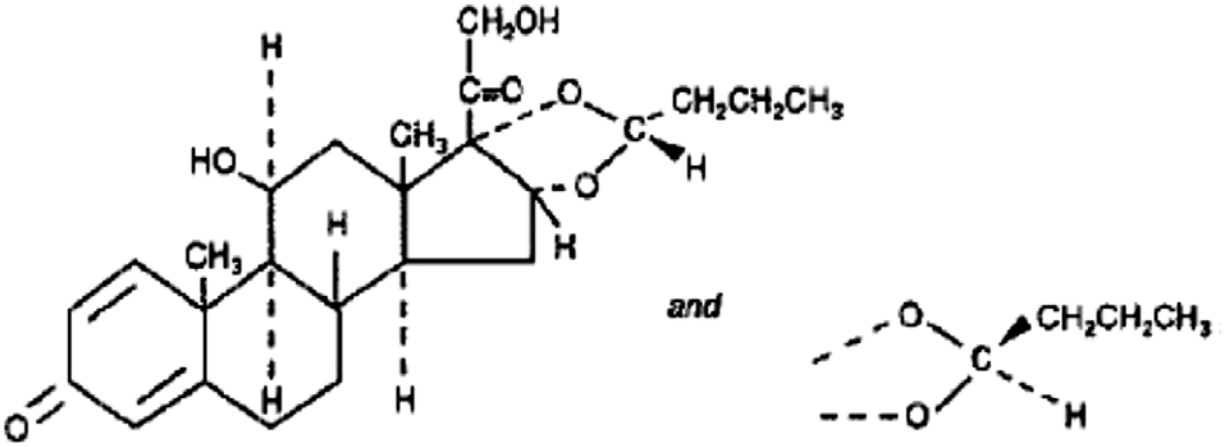
Generic Name: Budesonide

Code Name: NA

Chemical Name: (RS)-11b, 16a, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde

Molecular Formula/Molecular Weight: $C_{25}H_{34}O_6$ / 430.5 g/mol

Structure or Biochemical Description: Budesonide is provided as a mixture of two epimers (22R and 22S).



Pharmacologic Class: Corticosteroid

Glycopyrrolate

CAS Registry Number (Optional): 596-51-0

Generic Name: Glycopyrrolate (or Glycopyrronium Bromide)

Code Name: NA

Chemical Name: Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, Bromide or 3-Hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate

Molecular Formula/Molecular Weight: $C_{19}H_{28}BrNO_3$/ 398.33 g/mol

Structure or Biochemical Description: (b) (4) The product is a 50/50% mixture of three enantiomers i.e., racemate of the (R,S) and (S,R) enantiomeric pair. The product is not optically active.

Pharmacologic Class: Anticholinergic

Formoterol Fumarate

CAS Registry Number: 43229-80-7

Generic Name: Formoterol Fumarate

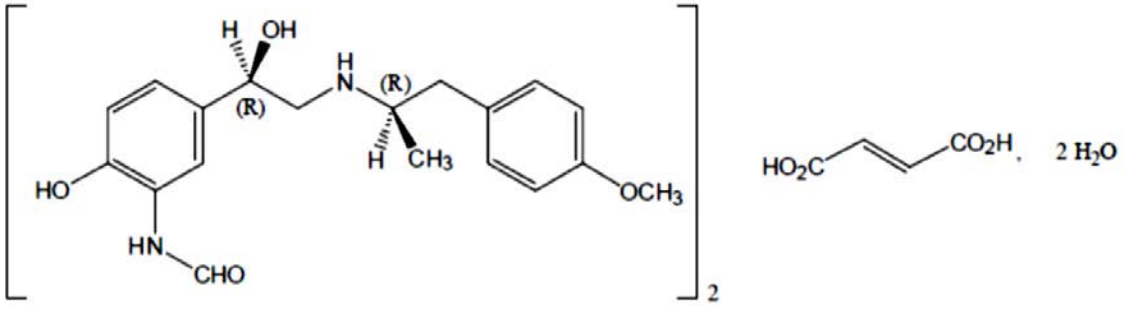
Code Name: NA

Chemical Name: N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino] ethyl]phenyl] formamide, (E)-2-butenedioate dihydrate

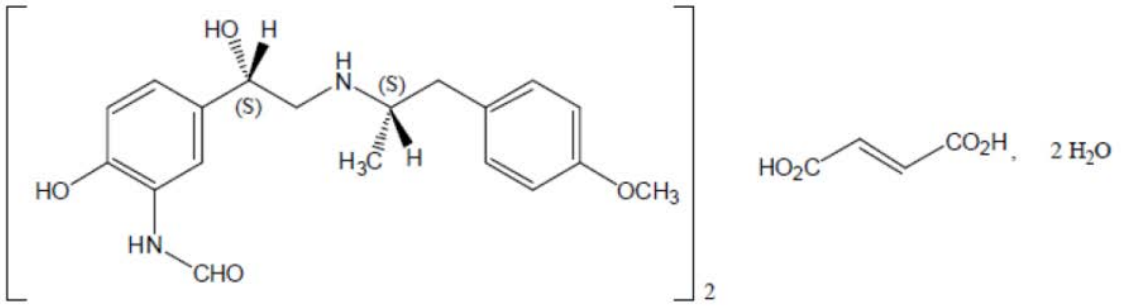
Molecular Formula/Molecular Weight: $(C_{19}H_{24}N_2O_4)2.C_4H_4O_4.2H_2O$/ 840.91 g/mol

Structure or Biochemical Description: Formoterol fumarate (FF) has two chiral centers. The active ingredient is an equimolar mixture of (R,R) and (S,S) enantiomers as shown below. (b) (4)

ENANTIOMER (R,R)



ENANTIOMER (S,S)



Pharmacologic Class: Long-acting β_2-adrenergic agonist [LABA]

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 21929: Symbicort® MDI (budesonide/formoterol) Inhalation Aerosol

NDA 208294: Bevespi Aerosphere® (formoterol fumarate/glycopyrrolate)

IND 118313: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI)

IND 101,985: Glycopyrrolate Inhalation Aerosol (GP MDI) as a monoproduct

IND 105,586: Formoterol Fumarate Inhalation Aerosol (FF MDI) as a monoproduct

IND 107,739: Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol (GFF MDI) as a dual combination product

(b) (4)

2.3 Drug Formulation

BGF MDI 160 product is 160 µg micronized budesonide, 7.2 µg micronized glycopyrronium, and 4.8 µg micronized formoterol fumarate per actuation. In addition to the drug substances, each actuation delivers approximately (b) (4) of porous particles and (b) (4) of HFA-134a from the actuator. One dose is two actuations from the MDI. It is noted that 7.2 µg of glycopyrronium is equivalent to 9.0 µg glycopyrronium bromide or glycopyrrolate (quaternary ammonium bromide salt form of the drug substance). Throughout the review, the drug substance will be referred to as glycopyrrolate and concentrations of the drug substance also reflect the glycopyrrolate form. The MDI is manufactured at 120, (b) (4) and 28 inhalations. The quantity of the drug substances varies based on the number of inhalations per MDI, but the metered and delivered dose per actuation are identical across all MDIs.

Composition of BGF MDI 120/(b) (4)/28 inhalations, 160/9/4.8 µg per actuation

Component	Quantity per canister (120/(b) (4)/28 inhalations)	Metered dose (ex-valve)	Delivered dose (ex-actuator)	Function	Reference to Standard
Budesonide, micronised	(b) (4)	(b) (4)	160 µg	Active ingredient	USP / AstraZeneca
Glycopyrrolate, micronised			9 µg	Active ingredient	USP / AstraZeneca
Formoterol fumarate, micronised			4.8 µg	Active ingredient	USP / AstraZeneca
Porous particles					(b) (4)
HFA-134a					
					(b) (4)

2.4 Comments on Novel Excipients

This product contains no novel excipients. BGF contains HFA-134a as the propellant and porous particles (PP) as an excipient. Both materials are present in approved and currently marketed products including Bevespi Aerosphere (NDA 208294). Porous particles (PP) are comprised of (b) (4) DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and (b) (4) $CaCl_2$ (calcium chloride). The Sponsor has rights of reference to the safety data for HFA-134a through DMF (b) (4) from (b) (4) (b) (4)

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

Adult COPD patients will use BGF pMDI twice daily. Each dose consists of two actuations. Each actuation of Bevespi releases 9 µg glycopyrrolate, 4.8 µg formoterol fumarate, and 160 µg budesonide. This dosing regimen corresponds to the maximum recommended human daily inhalation dose (MRHDID) of 36 µg glycopyrrolate, 19.2 µg formoterol fumarate, and 640 µg budesonide, respectively. These inhaled doses correspond to nominal doses of 0.6 µg/kg/day glycopyrrolate, 0.32 µg/kg/day formoterol fumarate, and 10.7 µg/kg/day budesonide on a unit bodyweight basis for a 60-kg patient.

2.7 Regulatory Background

The Sponsor submitted NDA 212122 as a 505b1 application. The Sponsor owns complete nonclinical programs for formoterol fumarate and budesonide. The Sponsor completed the nonclinical program for glycopyrrolate in the present application in order to file a 505b1 application. The Sponsor currently markets the combination of formoterol and budesonide under the tradename of Symbicort® (NDA 21929). The Sponsor also markets the combination of glycopyrrolate and formoterol fumarate under the tradename of Bevespi Aerosphere (NDA 208294), although it was approved as a 505b2 application. The Reviewer referenced FDA PharmTox NDA reviews of studies owned by the Sponsor for budesonide and formoterol fumarate.

3 Studies Submitted

3.1 Studies Reviewed

CARCINOGENICITY:
1. Glycopyrrolate pMDI: Up to 104 Week Nose-Only Inhalation Toxicology Study in Sprague Dawley Rats (Study: FY12-072)
2. Glycopyrrolate pMDI: Up to 104 Week Nose-Only Inhalation Toxicology Study in B6C3F1 Mice (Study: FY14-128)

3.3 Previous Reviews Referenced

1. Pharmacology and Toxicology Review of NDA 21929 for Symbicort (Combination of Budesonide and Formoterol) dated May 22, 2006.

2. Pharmacology and Toxicology Review of NDA 208294 for Bevespi Aerosphere (Combination of Formoterol and Glycopyrrolate) dated March 10, 2016.

3. Pharmacology and Toxicology Review of IND 118313 for the Combination of Budesonide, Formoterol, and Glycopyrrolate) dated November 7, 2013.

8 Carcinogenicity

Study title: Glycopyrrolate pMDI: Up to 104 Week Nose-Only Inhalation Toxicology Study in Sprague Dawley Rats

Study no.:	FY12-072
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 13, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Glycopyrronium bromide, Lot # N-1304-001A and N-13005-001A CMC reviewer, Dr. Craig Bertha, estimates the purity is > 99.97% for each lot based on COAs
CAC concurrence:	No

Key Study Findings

- In the 2-year carcinogenicity study, Sprague Dawley rats received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 151.7/165.93 (LD, M/F), 302.9/330.66 (MD, M/F), and 620.45/684.14 (HD, M/F) µg/kg/day. The study included an interim sacrifice of 10 rats/sex/group after 52 weeks of treatment.

- Doses are represented as the estimated achieved pulmonary doses with the quaternary ammonium bromide salt form of the drug substance (glycopyrrolate)

- Prior concurrence for doses used in this study was not obtained from the Executive Carcinogenicity Assessment Committee.

- Treatment with glycopyrrolate had no effects on survival of male or female rats. The Sponsor elected to terminate the entire study early (starting at Week 82) for all male and female groups due to low survival (22 of 60 [37%] females remaining) in the female air-control group at week 82. According to ECAC criteria for study termination, if the number of animals of a sex within the control group declines to 20, then all groups of that sex including drug-treated should be terminated. Based on these criteria, it was inappropriate to terminate female groups at that time. Further, in the male air-control and vehicle-control groups, 37 of 60 (62%) and 27 of 60 (45%) animals, respectively, were alive at week 82. Male groups were inappropriately terminated per ECAC criteria for study

termination. The study duration was potentially inadequate to assess drug-induced tumor development.

- Sacrifice of female and male groups was prolonged and extended from week 82 into week 83.

- Dose-related decreases of absolute body weights were observed in male and female rats beginning at approximately week 12 and continuing over the course of study. At Week 81, absolute body weights were reduced for drug-treated male groups by 11.8% (LD), 19.9% (MD), and 20% (HD) and for female drug-treated groups by 16% (LD), 11.4% (MD), and 23.4% (HD), relative to air-control groups. Decreases of absolute body weights appeared to be potentially excessive (>10%). The Sponsor did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights.

- There were no statistically significant test article-related tumor findings in male or female rats.

- Test article related non-neoplastic findings were identified in the larynx, lungs, and nasal turbinates. In the larynx, incidences of squamous metaplasia were increased in all male and female glycopyrrolate-treated groups. In the lung, alveolar macrophage aggregates generally increased in incidence with the dose in males and were higher in females receiving treatment. In the nasal turbinates, findings included dose-dependent increased incidences of neutrophilic inflammation and infiltration, hyaline degeneration of the olfactory epithelium, and squamous metaplasia of the respiratory epithelium.

- Toxicokinetic analysis was not conducted; however, histopathological findings in the nose/turbinates, larynx, and lungs demonstrated exposure to glycopyrrolate in the respiratory tract. Decreased body weights in drug-treated groups were considered indicative of systemic drug exposure.

- Final results of this study were presented to the ECAC on April 16, 2019. The Committee concluded that the carcinogenicity study was inadequate in male and female rats due to early termination of the study.

Adequacy of Carcinogenicity Study

- Prior concurrence for doses used in this study was not obtained from the Executive Carcinogenicity Assessment Committee.

- Sacrifice of the male and female air-control, vehicle-control, and drug-treated groups did not appear to be appropriate as survival in the air-control and vehicle-control groups were >20 per group.

- The duration of the rat carcinogenicity study at 82-83 weeks was potentially insufficient to assess drug-induced tumor development.

- Doses of glycopyrrolate used in the study may have been excessive as reductions of absolute body weights in dose groups exceeded 10%, relative to the air control groups. No dose reductions were implemented during the course of the study to reduce decreases of absolute body weight gains.

- Sacrifice of female and male groups was prolonged and extended from week 82 into week 83.

- Systemic drug exposures in male and female rats were not verified by toxicokinetic analysis; however, histopathological findings in the nose/turbinates, larynx, and lungs demonstrated exposure to glycopyrrolate in the respiratory tract. Decreased body weights in drug-treated groups were suggestive of systemic drug exposure.

Appropriateness of Test Models

- Sprague Dawley rats are a standard model for assessment of carcinogenic potential.

- Evaluation of Tumor Findings: There were no treatment-related neoplastic findings based on the lack of statistical significance for both trend and pair-wise statistical analysis; however, the ECAC concluded that the carcinogenicity study was inadequate in male and female rats due to early termination of the study.

- There were no apparent tumor findings in rats associated with glycopyrrolate (glycopyrronium bromide) treatment; however, the duration of the study at 82-83 weeks may have been inadequate for the development of drug-related tumors in rat. Excessive decreases of body weight gain for male and female glycopyrrolate-treated groups also confounded any interpretation of the study results.

Methods

Doses:	(M/F) LD 151.7/165.93, MD 302.92/330.66, and HD 620.45/684.14 µg/kg/day
Frequency of dosing:	Up to 120 minutes per day for up to 83 weeks
Dose volume:	Group 1 air control: 120 min Group 2 placebo pMDI: 120 min Group 3 Low Dose pMDI: 30 min Group 4 Mid Dose pMDI: 60 min Group 5 High Dose pMDI: 120 min
Route of administration:	Nose only Inhalation - use of pressurized metered dose inhalers (pMDIs)
Formulation/Vehicle:	Calcium Chloride Dihydrate ($CaCl_2$) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC) (Vehicle-control)

Basis of dose selection: Doses used in the 14-Day Rat Study (FY08-076) and 6-Month Rat Study (FY10-120) were used as the basis for dose selection. The Sponsor did not submit a SPA for ECAC dose selection concurrence.

Estimated Doses

Estimated Doses	14-day study FY08-076		6-month study FY10-120	
µg/kg/day	Males	Females	Males	Females
Low Exposure	46	49	65	70
Mid Exposure	254	279	264	286
High Exposure	514	555	523	572

In the 14-day rat study (FY08-076), all animals survived and there were no effects on survival. At Day 14, BW gains (BWG) were significantly decreased in treatment groups relative to air controls. In males, BWG reductions were 35% (LD), 10.7% (MD), and 26.8% (HD). In females, BWG reductions were 33% (LD), 47% (MD), and 43% (HD).

In the 26-week rat study (FY10-120), rats received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 65/70 (LD, M/F), 264/286 (MD, M/F), and 523/572 (HD, M/F) µg/kg/day. There were no test article related deaths during the study. At week 26, BW reductions in MD and HD males were 14% and 6%, respectively, relative to the air-control group. For HD females, the BW reduction was 7.5% relative to the air-control group. Microscopic findings in the nasal turbinates showed hyaline degeneration of the respiratory and olfactory epithelium, which generally increased in incidence with dose.

The Sponsor elected to increase the doses for the 2-year carcinogenicity study relative to the 26-week study. The doses used in the 2-year study led to potentially excessive reductions of absolute body weights (see below).

Species/Strain:	Sprague Dawley (CD)
Number/Sex/Group:	70/sex/group
Age:	Animals were approximately 5-6 weeks old at arrival.
Animal housing:	Housed with up to 2 animals per cage in polycarbonate shoebox cages on racks with Alpha-dri- or Sani-Chip bedding changed once or twice weekly
Paradigm for dietary restriction:	None. Rats had unlimited access to chow diet,
Dual control employed:	No
Interim sacrifice:	Yes, 10/sex/group at Week 52
Satellite groups:	No
Deviation from study protocol:	Deviations were presented in the study report. There were no deviations that affected the overall integrity of the study or interpretation of the study results. The Reviewer noted the following deviations that potentially impacted the conduct of the study: All surviving animals on-study were terminated at 82-83 weeks. This study duration was potentially insufficient to assess drug-induced tumor development. Doses of glycopyrrolate used in the study were excessive as reductions of absolute body weights in dose groups exceeded 10%, relative to the air control groups. No dose reductions were implemented during the course of the study to reduce decreases of absolute body weight gains. Sacrifice of female and male groups was prolonged and extended from weeks 82 to 83.

Inhalation Exposure

Exposure durations and animal assignment numbers are shown in the table below. Animals were exposed to glycopyrrolate aerosol at Low (30 minutes), Mid (60 minutes), or High dose (120 minutes) levels using a pre-qualified inhalation expsosure system. The vehicle-control (120 minutes) and air-control (120 minutes) groups were exposed on separate, but identical systems.

Table 1: Experimental Design

Exposure	Animal IDs	Sex	Exposure Duration (min)	N	52 Week Nx	104 Week Nx*
Air Control	1001-1070	M	120	70	10	20
Air Control	1071-1140	F	120	70	10	20
Placebo pMDI	2001-2070	M	120	70	10	20
Placebo pMDI	2071-2140	F	120	70	10	20
Low Dose pMDI	3001-3070	M	30	70	10	20
Low Dose pMDI	3071-3140	F	30	70	10	20
Mid Dose pMDI	4001-4070	M	60	70	10	20
Mid Dose pMDI	4071-4140	F	60	70	10	20
High Dose pMDI	5001-5070	M	120	70	10	20
High Dose pMDI	5071-5140	F	120	70	10	20

(Excerpted from Study Report)

Exposure System

The exposure system schematic was excerpted from the study report and shown below. The aerosol generation system coupled glycopyrrolate pMDIs to an expansion chamber that allowed the propellant to expand and evaporate prior to transitioning into the exposure plenum. pMDIs were actuated directly into the expansion chamber. In the expansion chamber, 25±3 L/min forced air dilution was mixed into the air inside of the chamber which was fitted with 5 pMDI actuators. The actuation of each pMDI was controlled by a two-way pneumatic valve. Identical aerosol generation systems were used for the vehicle-control and air-control groups. It is noted that only 48 ports (3-tiers) are shown in the schematic; however, the actual system that was utilized on study had 80 ports (5-tiers).

The pMDIs were actuated at a rate of 75 shots/min (15 shots/vial/min). The pMDIs were changed every 15 minutes for 19 mL cans or every 10 minutes for 14 mL cans.

The expansion chamber utilized 25 ± 3 L/min of forced air dilution to mix the air inside of the chamber. From the expansion chamber, the aerosols transitioned into an 80-port nose-only inhalation chamber. For personnel protection, the test article exposure chambers were placed inside a secondary containment box. The exhaust flow through the system was maintained at 24 ± 3 L/min, when the exhaust flow was within these specified limits, the port flow met the required minimum of 1.5 times the respiratory minute volume for an 80-port exposure system (port flow approximated based on total chamber exhaust flow).

Animals were placed in nose-only restraint tubes connected to the exposure chamber. Daily exposures to aerosol and the test article was determined from samples collected on (b) (4) 47-mm membrane filters during the entire exposure period. Samples were

collected at a flow rate of 0.5 L/min. Samples from the test article and vehicle-control systems were collected for a target of 30 minutes (±15 minutes). Samples from the air-control were collected for a target of 120 minutes (± 60 minutes). Aerosol concentrations were measured gravimetrically by weighing the samples on the filter. Glycopyrrolate concentrations were measured chemically by extracting samples from filters followed by analysis using a HPLC-UV method.

Figure 1: Schematic of (b) (4) pMDI Aerosol Generator coupled to a rodent exposure system

The average total aerosol concentrations for the air-control and vehicle-control groups were 0.00 mg/L and 0.15 mg/L, respectively. The average aerosol concentration for the glycopyrrolate LD, MD, and HD treatment groups was 0.12 mg/L (Table 2). The average

glycopyrronium bromide (glycopyrrolate) concentrations for the LD, MD, and HD groups were 8.88 µg/L, 8.83 µg/L, and 9.04 µg/L, respectively. Glycopyrrolate concentrations were below the limit of detection in the air-control and vehicle-control groups.

Table 2: Average Total Aerosol and Glycopyrronium Bromide (glycopyrrolate) concentrations

Group	Total Aerosol Conc. Average (SD) (mg/L)	Glycopyrronium Bromide Aerosol Conc. Average (SD) (µg/L)
Air Control	0.00 (0.00)	<LOD
Placebo	0.15 (0.03)	<LOD
Gly Low	0.12 (0.04)	8.88 (3.01)
Gly Mid	0.12 (0.04)	8.83 (2.77)
Gly High	0.12 (0.04)	9.04 (2.62)

(Excerpted from Study Report)

Table 3: Doses of Glycopyrronium Bromide (µg/kg/day) based upon Chemical Analysis of Filters

	Glycopyrronium Bromide Dose (µg/kg/day)	
Group	Male	Female
Air Control	NA	NA
Placebo	NA	NA
Gly Low	151.70	165.93
Gly Mid	302.92	330.66
Gly High	620.45	684.14

Table 4: Group Average Pulmonary Doses of Excipients, DSPC and $CaCl_2$

	DSPC Dose (mg/kg/day)		CaCl2 Dose (mg/kg/day)	
Group	Male	Female	Male	Female
Air	NA	NA	NA	NA
Placebo	2.363	2.609	0.167	0.184
Gly Low	1.915	2.094	0.135	0.148
Gly Mid	3.790	4.197	0.268	0.297
Gly High	7.693	8.482	0.544	0.599

Particle size

Particle size was determined for each exposure atmosphere (except air) at least once per month throughout the study using a [redacted] (b) (4) Impactor. The aerosol particle size was determined using representative samples collected from each exposure system except Air. The mass median aerodynamic diameters (MMADs) and geometric standard deviations (GSDs) were 3.64 (1.91) µm for glycopyrrolate-treated groups and 4.20 (1.68) µm for the vehicle-control (placebo) group.

Table 5: MMADs and GSDs for each aerosol impactor

Aerosol	MMAD (µm)	GSD
Placebo	4.20	1.68
Glycopyrrolate	3.64	1.91

Observations and Results

Mortality

During the study period, mortality checks were performed on all animals at a minimum of twice daily.

At Week 52, the scheduled interim sacrifice was conducted and 10 males and females per group were sacrificed for histopathological analysis. These animals (10/sex/group) were not included in the survival analysis table below (Table 6).

The Sponsor elected to terminate the entire study early for all male and female groups due to low survival (22 of 60 [37%] animals remaining) in the female air-control group at week 82. According to ECAC criteria for study termination, if the number of animals of a sex within the control group declines to 20, then all groups of that sex, including drug-treated should be terminated. Based on these criteria, it was inappropriate to terminate female groups at that time. Further, in the male air-control and vehicle-control groups, 37 of 60 (62%) and 27 of 60 (45%) animals, respectively, were alive at week 82. Male groups were inappropriately terminated per ECAC criteria for study termination.

There were no test article related effects on male or female survival relative to air-control and vehicle-control groups (Table 6). For males, survival was relatively comparable in the air-control and glycopyrrolate-treated groups; however, survival was slightly reduced for the vehicle-control group. For females, survival was comparable in the vehicle-control and glycopyrrolate-treated groups; however, survival was reduced for the air-control group. The sacrifice periods were prolonged as conduct extended over approximately two weeks (Week 82 and 83) and animals died naturally during this period. Natural deaths during the sacrifice periods were noted as footnotes in the Survival table and included in the number of animals at terminal necropsy rather than as early deaths. The statistical reviewer conducted a survival analysis and generated Kaplan-Meier survival curves (below) for male and female animals up to 83 weeks.

Table 6: Rat Carcinogenicity Study: Survival Analysis

Rat Study Glycopyrrolate µg/kg/day	**Males**		**Females**	
Males/Females (interim sacrifice	# of EarlyDeaths	# At terminal necropsy	# of Natural Deaths	# At terminal necropsy
Air Control	23 (38%)	37 (62%)	38 (63%)	22 (37%)
Placebo	33 (55%)	27 (45%)	34 (57%)	26 (44%)*
Low Dose	25 (42%)	35 (58%)	31 (52%)	29 (48%)
Mid Dose	25 (42%)	35 (58%)**	35 (58%)	25 (42%)***
High Dose	22 (37%)	38 (63%)****	31 (52%)	29 (48%)
* 1 animal died during sacrifice period				
** 3 animals died during the sacrifice period				
*** 3 animals died during the sacrifice period				
**** 1 animal died during the sacrifice period				

Number of early deaths = unscheduled necropsy + found dead + accidental deaths

Numbers in parentheses represent the percent when compared to the number of main study animals at the start of the study (i.e., 60 animals/sex/group)

Figure 2: FDA Statistical Reviewer Kaplan-Meier Survival Curves for Male Rats

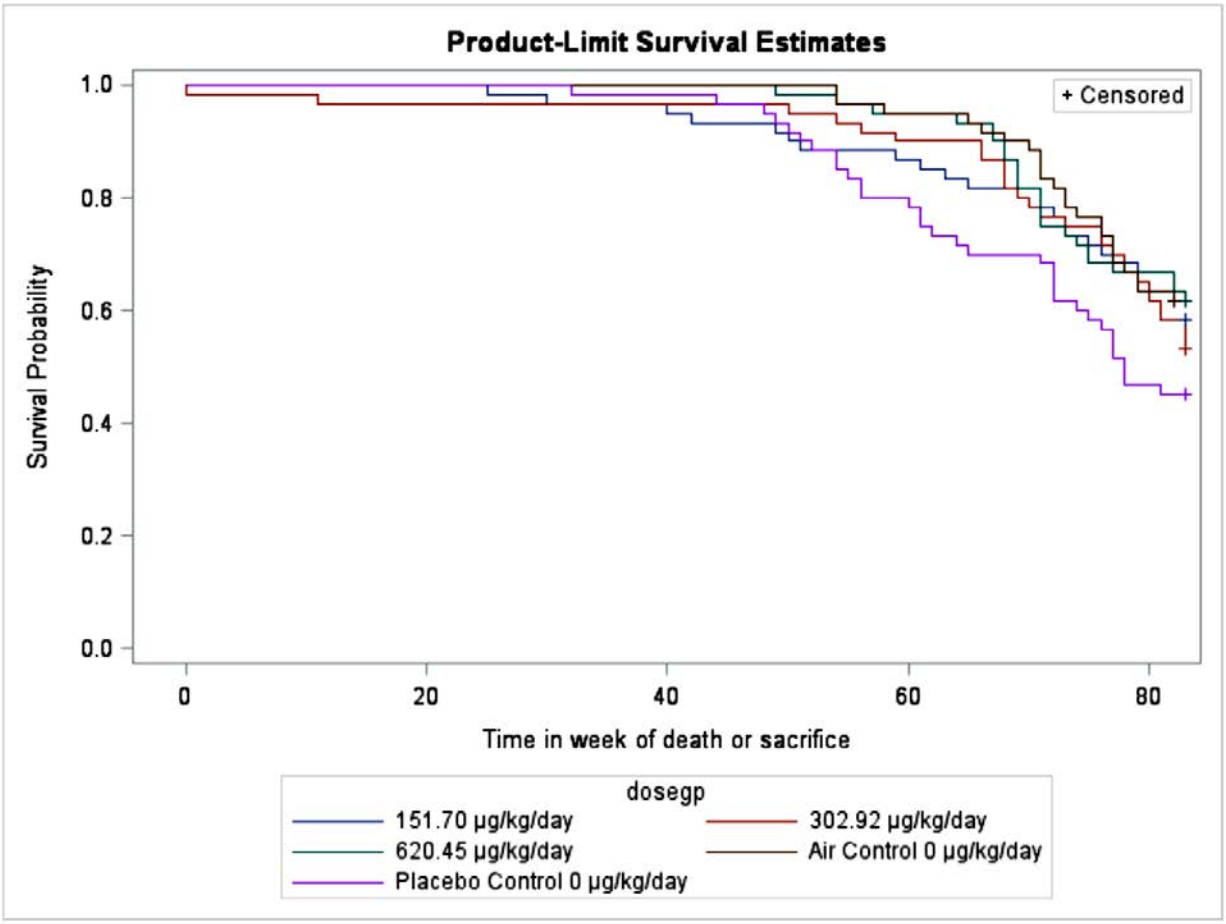
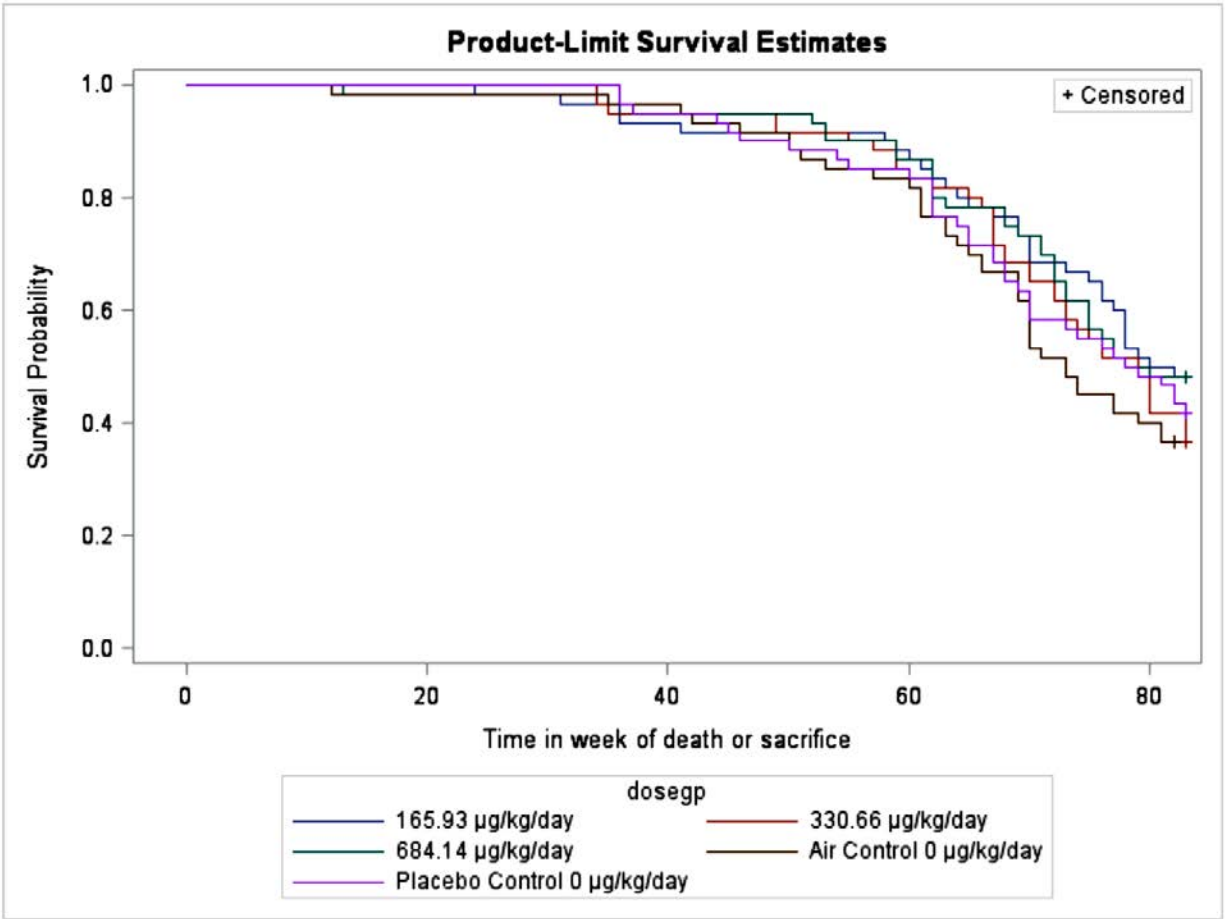


Figure 3: FDA Statistical Reviewer Kaplan-Meier Survival Curves for Female Rats



Clinical Signs

During the study period, twice daily cage-side or detailed observations and morbidity/mortality checks were performed on all animals. Observations included but were not limited to reactivity to general stimuli and description of any abnormal behaviors, lesions, or appearances. Clinical signs associated with the respiratory tract (e.g. apnea, labored breathing, rapid breathing, malaise, marked nasal discharge, etc).

No treatment-related clinical signs were noted during the treatment period.

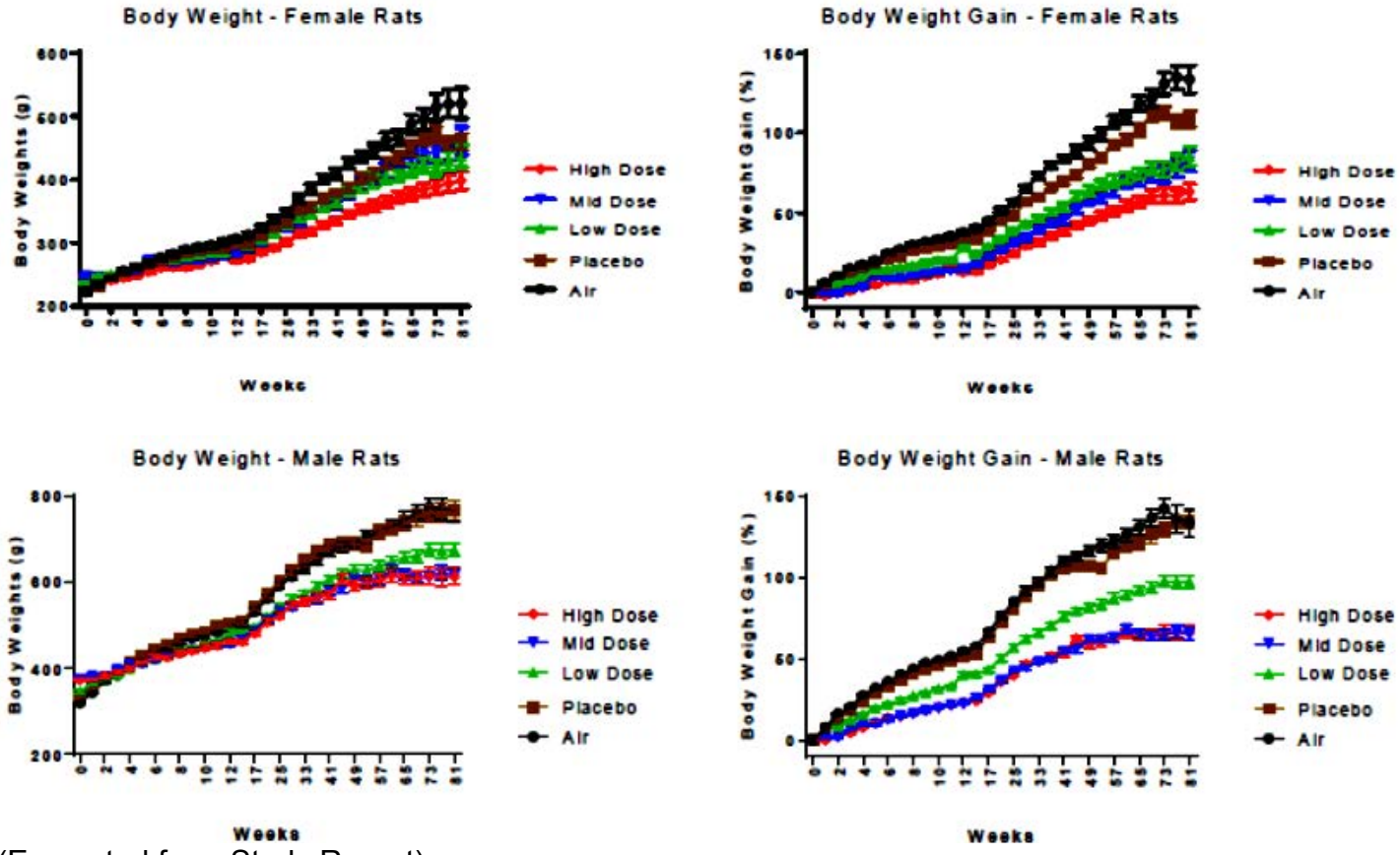
Body Weights

All animals on-study were weighed prior to randomization and then weekly for the first 13 Weeks of the treatment period, then monthly until the time of necropsy. Fasted body weights were measured at necropsy.

In general, there were dose-dependent decreases of absolute body weights for male and female drug-treated groups. Examinations of body weight curves indicated that air-control groups separated from drug-treated groups beginning at approximately week 12 (see below). Body weight changes at weeks 0, 25, 53, and 81, relative to the air- control groups are shown in the table. At the end of the study, decreases of absolute body weight exceeded 10% for all male drug-treated groups (i.e., 11.8%, 19.9%, and 20% decreases of absolute body weights for males in the LD, MD, and HD groups, respectively, relative to the air control group). Similarly, for females at week 81, decreases of absolute body weights exceeded 10% for all female drug-treated groups (i.e., 16%, 11.4%, and 23.4% decreases of absolute body weights for females in the LD, MD, and HD groups, respectively, relative to the air-control group).

Reductions in BW of greater than 10% relative to air-control groups for the male and female LD, MD, and HD groups suggested the MTD was exceeded at all doses in males and females. The Sponsor never implemented any dose reductions during the course of the study to minimize decreases of absolute body weights.

Figure 4: Body Weights of Female and Male Rats in the 83-Week Carcinogenicity Study



(Excerpted from Study Report)

Table 7: Body Weight Changes in 83 Week Inhalation Carcinogenicity Study in Rats

Body Weight	Males					Females				
	Air control	Placebo	Low Dose	Mid Dose	High Dose	Air control	Placebo	Low Dose	Mid Dose	High Dose
Week 0	319.7	331.9	345.3	374.2	372.9	223.0	223.4	236.4	247.8	243.3
Week 25	591.0	600.0	541.7	532.9	521.1	348.7	330.8	328.1	325.3	302.2
Absolute BW, % Contro	0.0	1.5	-8.3	-9.8	-11.8	0.0	-5.1	-5.9	-6.7	-13.3
Δ, g	271.3	268.1	196.4	158.7	148.2	125.7	107.4	91.7	77.5	58.9
BW gain, % control	0.0	-1.2	-27.6	-41.5	-45.4	0.0	-14.6	-27.0	-38.3	-53.1
Week 53	705.4	685.0	626.5	602.9	597.6	445.0	409.8	399.0	402.4	357.1
Absolute BW, % Contro	0.0	-2.9	-11.2	-14.5	-15.3	0.0	-7.9	-10.3	-9.6	-19.8
Δ, g	385.7	353.1	281.2	228.7	224.7	222.0	186.4	162.6	154.6	113.8
BW gain, % control	0.0	-8.5	-27.1	-40.7	-41.7	0.0	-16.0	-26.8	-30.4	-48.7
Week 81	764.8	765.9	674.4	612.9	612.2	520.5	459.8	437.3	461.4	398.7
Absolute BW, % Contro	0.0	0.1	-11.8	-19.9	-20.0	0.0	-11.7	-16.0	-11.4	-23.4
Δ, g	445.1	434.0	329.1	238.7	239.3	297.5	236.4	200.9	213.6	155.4
BW gain, % control	0.0	-2.5	-26.1	-46.4	-46.2	0.0	-20.5	-32.5	-28.2	-47.8

Feed Consumption

During the study period, animals had unlimited access to chow diet (2016C Harlan Global Certified Rodent Chow).

Feed consumption monitoring was not conducted.

Ophthalmology: All rats except the serology animals were examined by a board-certified veterinary ophthalmologist prior to exposure. No post-exposure examination was performed due to the early ending (82 weeks) of the study and schedule conflict.

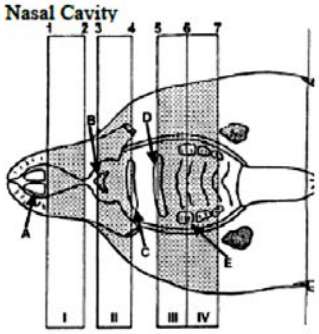
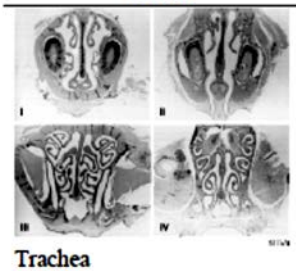
Gross Pathology

Detailed gross necropsies were performed on all animals (found dead, moribund, sentinel/serology, scheduled necropsy or early termination) and consisted of a complete external and internal examination including body orifices (ears, nostrils, mouth, anus, etc.) and cranial, thoracic, and abdominal organs and tissues. All gross findings were recorded in descriptive terms, typically including location(s), size (in mm), shape, color, consistency, and number.

Tissues in Table 8 below were collected, and grossly examined from all animals. The organs in Table 8 were weighed at scheduled sacrifice or moribund euthanasia; paired organs were weighed together. Eyes and optic nerves, testes and epididymides were fixed in Bouin's solution. Other tissues were fixed in 10% neutral buffered formalin.

Table 8 Routine Organs Collected for the Rat Carcinogenicity Study

Tissues	Weigh	Examine	Comments
Abnormal Tissue		X	Representative examples. Redundant changes within an animal may be preserved at the discretion of the Study Pathologist
Adrenal × 2	X	X	
Aorta (thoracic)		X	
Brain	X	X	Seven levels
Epididymis (Male) × 2	X	X	Fixed in Bouin's fluid
Eye × 2 (+ Optic Nerve)		X	Fixed in Bouin's fluid. At least one optic nerve should be present on the slide.
Femur (including bone marrow for smear)		X	
Gastrointestinal tract:			
Stomach		X	
Duodenum		X	
Jejunum		X	
Ileum		X	
Cecum		X	
Colon		X	
Rectum		X	
Harderian Gland × 2		X	
Heart	X	X	Sections including all four chambers
ID (microchip)			Retained for identification purposes
Kidney × 2	X	X	
Lacrimal Glands × 2		X	
Liver	X	X	Samples from two lobes
Mammary Gland		X	Histopathology on males only if present in routine skin section
Mesenteric Lymph Nodes		X	
Esophagus		X	
Ovary (Female)× 2	X	X	
Pancreas		X	
Parathyroid × 2		X	At least one parathyroid should be present on the slide
Pituitary		X	
Prostate (Male)		X	
Sciatic Nerve		X	
Skin		X	Caudoventral abdomen
Seminal Vesicles (Male)		X	(+coagulating gland)

Tissues	Weigh	Examine	Comments
Spinal Cord		X	Cervical, midthoracic and lumbar
Spleen	X	X	
Sternum (including Bone Marrow)		X	
Mandibular Lymph Node		X	
Submandibular Salivary Gland × 2		X	
Testis (Male) × 2	X	X	Fixed in Bouin's
Thigh Muscle		X	
Thymus	X	X	
Thyroid × 2		X	Left attached to the trachea for tracheal trimming and gland sampling
Tongue		X	
Urinary Bladder		X	
Uterus (Female)	X	X	Body and horns
Vagina (Female)		X	
Tracheobronchial Lymph Node		X	
Larynx		X	
Lungs	X	X	Whole lung was harvested, weighed, perfused with 10% NBF via tracheal cannula until pleura was tense
Nasal Cavity 		X	After dissection from the carcass, the nasal cavity was gently flushed with 10% NBF in order to ensure removal of air pockets from within the nasal cavity. Decalcification was undertaken using formic acid. Four transverse sections of the nasal cavity were produced and evaluated. Sections were taken from approximate areas as follows: (I) caudal surface of upper incisor (II) between the incisive papilla and the first palatal ridge (III) between last palatal ridge and mid-point of first molar (IV) 2nd molar
Tissues	Weigh	Examine	Comments
			
Trachea		X	Two sections at level of thyroid and carina.

(Excerpted from Study Report)

Gross pathology examination of animals on study from Days 0 to 365 (interim sacrifice and early deaths) found slight increased incidences of irregular white discoloration (0-2 mm) in the lungs for males and females in the mid and high dose group.

Gross pathology examination of animals on study from Day 366 to end of the study found irregular white discoloration (0-2 mm) in the lungs that generally increased in incidence with the dose. These gross findings correlated with histopathological findings of aggregates of alveolar macrophages. In males, this gross finding was present in 16/60 air-control, 8/53 vehicle-control, 15/52 LD, 11/44 MD, and 20/57 HD animals. In females, this gross finding was present in 8/52 air-control, 4/52 vehicle-control, 13/53 LD, 12/54 MD, and 16/56 HD animals. It is noted that gross pathological examinations of the lungs were limited to only 44 MD males, which was low compared to other groups.

Table 9: Gross Pathology Findings in the Inhalation Carcinogenicity Study in Rats On-study from Day 366 to the End of Study

Gross Pathology Findings	**Males (µg/kg/day)**					**Females (µg/kg/day)**				
Organ/Tissue	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose
	NA	NA	151.7	302.92	620.45	NA	NA	165.93	330.66	684.14
# of animals on Study	60	53	53	57	59	52	53	55	55	56
# of animals completed	59	53	52	56	58	52	52	53	54	56
Lungs										
total examined	60	53	52	44	57	48	51	53	53	54
Discoloration; white , All, Irregular; Multiple; 0 - 2 mm	16	8	15	11	20	8	4	13	12	16

Organ weights: Absolute weights were measured for the organs listed in the Table 8 and relative weights were calculated. Organ weight data was not reviewed as it was not critical to the evaluation of neoplastic findings.

Histopathology

Adequate battery: Yes. Fixed tissues were sent to (b) (4) for histologic processing where they were trimmed for placement into tissue cassettes and submitted for histology. Tissues were processed routinely, paraffin embedded, sectioned, and stained with hematoxylin and eosin for microscopic examination.

Histopathologic examination was initially conducted in a “read down” fashion: i.e. all tissues and gross lesions were examined for Groups 1-Air Control, 2-Placebo (Vehicle-control) pMDI Control, and 5-‘High Dose Glycopyrrolate pMDI’, whereas respiratory and related tissues plus gross lesions were initially examined for remaining groups (3-‘Low Dose Glycopyrrolate pMDI’, and 4-‘Mid Dose Glycopyrrolate pMDI’). For the initial histopathology read, two board certified veterinary pathologists collaborated on the study, with each reading the same tissue set in all groups to ensure consistent interpretation. The principal pathologist, ((b) (4)) read primarily respiratory tissues

and major organs while the contributing pathologist ((b) (4)) read other organs/tissues to divide the histopathology read approximately in half. Specifically, (b) (4) read nose/turbinates, larynx, trachea, lung, and tracheobronchial lymph node, as well as thyroid glands, parathyroid glands, brain, spinal cord, spleen, liver, heart, aorta, kidneys, thymus and gross lesions of those tissues. Dr. (b) (4) read gastrointestinal tract and mesenteric lymph nodes, tongue, salivary glands, mandibular lymph nodes, pituitary glands, adrenal glands, skin with mammary glands, reproductive tract, peripheral nerve, skeletal muscle, eye and optic nerve, bones with marrow and gross lesions of those tissues. The pathologists were in frequent contact regarding histopathology terminology and diagnostic criteria of various changes such that both pathologists reviewed examples of all tissues and characteristic or unusual lesions. On sponsor request for this report, all remaining fixed tissues were trimmed and examined to yield a full tissue set histopathologic examination from all animals on study (the additional tissues including a full tissue set from all Found Dead and Moribund animals, and all remaining tissues from the Low and Mid dose groups were examined microscopically by Dr. (b) (4)).

Peer Review
A peer review of the microscopic findings was conducted by Dr. (b) (4) of (b) (4)

Neoplastic
Tumors were analyzed by organ, systemic tumors were analyzed on a whole-body basis, and tumors were combined per McConnell *et al.* (Evaluation of Rodent Carcinogenesis Studies in Cancer Risk Assessment Chapter 28, Pages 699-715, John Wiley & Sons, Inc. 2010). In the Sponsor's histopathology tables, animals designated for the interim sacrifice were grouped with animals that died on study up to Day 365. Animals on-study from Day 366 through the terminal sacrifice (End of Study) were grouped together.

There were no statistically significant treatment-related increases of tumor incidences for male or female rats treated from Days 0 to 365 or Days 366 to the end of the study. Neoplastic findings from Day 0 to 365 and Days 366 to the end of the study are combined and represented together in the table below. Male and female rats in the interim sacrifice conducted at week 52 were not included.

Table 10: Neoplastic Findings in Inhalation Carcinogenicity Study in Rats On-study from Day 0 to the End of Study

Organ/Tissue (Neoplastic findings)	Males (µg/kg/day)					Females (µg/kg/day)				
Mammary Gland	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose
	NA	NA	151.7	302.92	620.45	NA	NA	165.93	330.66	684.14
total examined	35	37	41	38	35	59	60	60	60	60
Fibroadenoma, Benign; Primary	0	0	0	0	0	11	14	19	17	12
Fibroadenoma (2nd), Benign; Primary	0	0	0	0	0	2	1	1	0	3
Benign Fibroadenoma Tumor Number						**11**	**14**	**19**	**17**	**12**
Adenoma, Mammary Gland; Benign Primary	0	0	0	0	0	0	2	10	1	0
Adenoma, Mammary Gland (2nd); Benign Primary	0	0	0	0	0	0	0	2	0	0
Adenoma, Mammary Gland (3rd); Benign; Primary	0	0	0	0	0	0	0	1	0	0
Adenocarcinoma; Mammary Gland; Malignant Primary	0	0	0	0	0	10	13	9	7	7
Adenocarcinoma; Mammary Gland (2nd); Malignant Primary	0	0	0	0	0	2	3	1	1	2
Adenocarcinoma, Mammary Gland (3rd); Malignant; Primary	0	0	0	0	0	2	0	0	0	0
Adenocarcinoma, Mammary Gland (4th); Malignant; Primary	0	0	0	0	0	1	0	0	0	0
Adenocarcinoma, Mammary Gland (5th); Malignant; Primary	0	0	0	0	0	1	0	0	0	0
Adenoma tumor number	0	0	0	0	0	0	2	10	1	0
Adenocarcinoma tumor number	0	0	0	0	0	10	13	9	7	7
Adenoma and Adenocarcinoma tumor number	0	0	0	0	0	**10**	**14**	**17**	**8**	**7**

Non-neoplastic

Days 0 to 365: Treatment-related non-neoplastic findings in rats from study days 0 to 365 were evident in the larynx and nasal turbinates.

In the larynx, incidences of squamous metaplasia were increased in all male drug-treated groups and females in the mid and high dose groups.

Nose/turbinates were examined as independent sections 1-4. Incidences and severity of hyaline degeneration of the olfactory epithelium in Section 2 were increased for all male drug-treated group and females in the mid and high dose groups. In Section 3, incidences and severity were increased for high dose males and mid and high dose females. In Section 4, incidences and severity were increased for high dose males.

Days 366 through the Final Sacrifice (week 82): Treatment-related non-neoplastic findings in rats from study day 366 through the final sacrifice (Week 82) were observed in the larynx, lungs, and nasal turbinates. Incidences and severity of findings were generally greater as compared to study days 0 to 365.

In the larynx, incidences of squamous metaplasia were increased in all male and female glycopyrrolate-treated groups relative to the air-control and vehicle-control groups. These findings were generally thought to be rat specific and not relevant to humans.

In the lungs, alveolar macrophage aggregates were noted at higher incidence in HD males (26 of 59). Incidences were also increased for all female drug-treated groups, although a dose-response was not evident. Alveolar macrophage aggregates with septal changes were noted at higher incidence in HD males (40 of 59). Alveolar macrophage aggregates with or without septal change were observed at increased incidences for all female drug-treated groups, although a dose-response was not evident. Granulomatous inflammation was observed at a higher incidence in HD males (13 of 59 males); this finding was regarded as potentially adverse.

Nose/turbinates were examined as independent sections 1-4 and the findings were shown in the histopathology table below. Nose-only inhalation treatment with glycopyrrolate in all male and female groups caused significant irritation characterized by neutrophilic inflammation and infiltration, squamous metaplasia of the respiratory epithelium, and hyaline degeneration of the olfactory epithelium. The findings in the nose/turbinates were not considered clinically relevant, because rats were obligate nose breathers and humans will be dosed via oral inhalation.

Table 11: Non-Neoplastic Findings in Rat Carcinogenicity Study (Study Day 366 through the Final Sacrifice at Week 82)

Organ/Tissue (Non-Neoplastic findings)	Males (µg/kg/day)					Females (µg/kg/day)				
	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose
	NA	NA	151.7	302.92	620.45	NA	NA	165.93	330.66	684.14
# of animals on Study	60	53	53	57	59	52	53	55	55	56
# of animals completed	60	53	53	57	59	52	53	55	55	56
Larynx										
total examined	59	53	53	57	58	52	53	55	55	56
Metaplasia, Squamous	**5**	**15**	**22**	**34**	**47**	2	10	15	32	43
Lung(s)										
total examined	60	53	53	57	59	52	53	55	55	56
Aggregates, Alveolar Macrophage	21	15	11	21	**26**	19	17	**26**	**28**	**27**
Aggregates, Alveolar Macrophage (with Septal changes)	30	18	22	30	**40**	14	17	**20**	**21**	**21**
Aggregates, Alveolar Macrophage (+ Or - Septal change)	47	30	30	41	**51**	30	31	**38**	**44**	**44**
Inflammation, Granulomatous (microgranuloma)	7	2	5	6	**13**	0	3	4	2	4
Nose/Turbinate 1										
total examined	60	53	53	57	59	52	53	55	55	56
Inflammation, histiocytic and neutrophilic (Focal)	0	0	0	0	**1**	0	0	0	0	0
Infiltration, Neutrophilic	0	0	1	**3**	**5**	0	0	0	0	**1**
Inflammation, Neutrophilic	1	4	8	12	11	0	2	**4**	**6**	**7**
Metaplasia, Squamous; Respiratory epithelium	1	3	10	16	12	0	0	2	7	3
Nose/Turbinate 2										
total examined	60	53	53	57	59	52	53	55	55	56
Degeneration, hyaline; Olfactory Epithelium	2	1	**6**	**7**	**23**	2	3	**6**	**11**	**21**
Inflammation, Neutrophilic	0	3	1	2	2	0	1	0	2	**5**
Metaplasia, Squamous; Respiratory epithelium	0	1	1	0	**2**	0	0	0	1	0
Nose/Turbinate 3										
total examined	60	53	53	57	59	52	53	55	55	56
Degeneration, hyaline; Olfactory Epithelium	12	18	10	18	**41**	9	11	**15**	**18**	**36**
Metaplasia, Squamous; Olfactory epithelium	0	0	0	0	1	0	0	0	0	0
Nose/Turbinate 4										
total examined	59	53	53	57	59	52	53	55	55	56
Degeneration, hyaline; Olfactory Epithelium	29	33	24	29	**45**	15	21	**22**	**25**	**39**

Toxicokinetics

Blood samples were collected into K_3EDTA tubes from all animals at the scheduled necropsy or early termination for glycopyrrolate analyses. Blood was centrifuged, plasma was aliquoted into 5 mL cryogenic vials, and frozen for storage (-70 to -90°C).

Toxicokinetic analysis was not conducted. The Sponsor did not request that the samples be analyzed for toxicokinetics and per the Sponsor's request the samples were discarded due to lack of extended stability.

Safety margins for the proposed clinical dose 18 µg/dose BID of glycopyrrolate are calculated for the low dose, mid dose, and high dose in the 83-week rat carcinogenicity study. Toxicokinetic analysis was not conducted, therefore safety margins were calculated on a µg/kg and mg/m^2 basis using the estimated achieved doses. On a mg/kg basis the safety margins for the clinical dose relative to the nonclinical doses were 277 at the low dose, 551 at the mid dose, and 1140 at the high dose. On a mg/m^2 basis the safety margins for the clinical dose relative to the nonclinical doses were 45 at the low dose, 89.37 at the mid dose, and 184.9 at the high dose.

Table 12: Safety Margin/Exposure Multiple Calculations for Glycopyrrolate Carcinogenicity in Rats

Rat Carcinogenicity Safety Margins Based on Clinical Dose of 18 µg/dose Glycopyrrolate BID (36 µg/day)						
Nonclinical Group	Dose Male (µg/kg)	Safety Margin µg/kg	[1]Safety Margin mg/m^2	Dose Female (µg/kg)	Safety Margin µg/kg	[1]Safety Margin mg/m^2
Low	151.7	253	41	165.93	277	44.85
Mid	302.92	505	81.8	330.66	551	89.37
High	620.45	1034	167.69	684.14	1140	184.9

[1] Clinical dose of 0.02 mg/m^2 was used for mg/m^2 safety margin calculation. Daily doses administered to rat in µg/kg were converted to mg/m^2 by multiplying by a conversion factor of 6.

Study title: Glycopyrrolate pMDI: Up to 104 Week Nose-Only Inhalation Toxicology Study in B6C3F1 Mice

Study no.:	FY14-128
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 16, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # N-1304-001A and N-13005-001A CMC reviewer, Dr. Craig Bertha, estimates the purity is > 99.7% for each lot based on the COAs
CAC concurrence:	No

Key Study Findings

- In a 2-year carcinogenicity study, B6C3F1 mice received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 0.347/0.335 (LD, M/F), 0.705/0.7 (MD, M/F), and 1.46/1.42 (HD, M/F) mg/kg/day.

- Doses are represented as the estimated achieved pulmonary doses with the quaternary ammonium bromide salt form of the drug substance (glycopyrrolate).

- Prior concurrence for doses used in this study was not obtained from the Executive Carcinogenicity Assessment Committee.

- Treatment with glycopyrrolate had no effects on survival in male or female mice up to 104 weeks.

- Dose-related decreases of absolute body weights were observed in males and females beginning around Week 3 and Week 11, respectively, and continuing over the course of study. Decreases of absolute body weights at the end of the study appeared to be potentially excessive (>10%) for MD Females (-15.9%), HD males (-15%), and HD females (-27.7%). The Sponsor did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights.

- Toxicokinetic analysis was not conducted; however, histopathological findings in the nose/turbinates demonstrate exposure to glycopyrrolate in the respiratory tract. Decreased body weights in drug-treated groups were suggestive of systemic drug exposure.

- There were no statistically significant test article-related tumor findings in male mice in the LD and MD groups and female mice in the LD group.

- Final results of this study were presented to the ECAC on April 16, 2019. The Committee concluded that body weight decreases in high dose males and mid and high dose females could confound interpretation. The Committee concurred that no drug-related neoplasms were observed at the low dose in females and the mid and low dose in males.

<u>Adequacy of Carcinogenicity Study</u>

• Prior concurrence for doses used in this study was not obtained from the Executive Carcinogenicity Assessment Committee.

• Doses of glycopyrrolate used in this study may have been excessive as reductions of absolute body weights in MD female and HD male and female groups exceeded 10%

relative to control groups. No dose reductions were implemented during the course of the study to reduce decreases of absolute body weight.

Appropriateness of Test Models

• B6C3F1 mice are a standard model for assessment of carcinogenic potential.

Evaluation of Tumor Findings

• There were no treatment-related neoplastic findings based on the lack of statistical significance for both trend and pair-wise statistical analysis. As noted above, decreases of absolute body weight were excessive for high dose males and mid and high dose females, which confounds interpretation of findings for these groups.

• Glycopyrrolate (glycopyronnium bromide) was not tumorigenic in low and mid dose male or low dose female mice.

Methods

Doses:	(M/F) LD 0.347/0.335, MD 0.705/0.7, and HD 1.46/1.42 mg/kg/day
Frequency of dosing:	Daily Group 1 air control: 120 min Group 2 placebo pMDI: 120 min Group 3 Low Dose pMDI: 30 min Group 4 Mid Dose pMDI: 60 min Group 5 High Dose pMDI: 120 min
Route of administration:	Nose-only Inhalation Drug delivered from pressurized metered dose inhalers (pMDIs)
Formulation/Vehicle:	Calcium Chloride Dihydrate (CaCl2) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC) (Vehicle-control)
Basis of dose selection:	The Sponsor conducted a 14-day nose-only inhalation toxicology study in male and female B6C3F1 mice (FY14-111). The in-life phase was completed on October 30, 2014, although the Study Director did not sign the final report until May 10, 2018. Inhaled doses were 0.33, 0.64, and 1.38 mg/kg/day. Body weight gains were unaffected. Histopathology findings were limited to the nose/turbinate for the HD group (degeneration of the hyaline respiratory epithelium and/or olfactory epithelium). The study duration (14 days) was considered inadequate to support dose selection for a 2-year study.
Species/Strain:	B6C3F1
Number/Sex/Group:	60/sex/group
Age:	9 weeks
Animal housing:	Housed with up to 2 animals per cage
Paradigm for dietary restriction:	Unlimited access to chow diet
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	No

Deviation from study protocol: During the in-life phase of the study, various animals missed exposure on different study dates for partial or the whole exposure duration, due to facility evacuation or medical treatments. The impact on the study results was believed to be minimal considering this was a 2-year study.

Doses of glycopyrrolate used in the study may have been excessive as reductions of absolute body weights in MD female and HD male and female groups exceeded 10%, relative to the air control groups. No dose reductions were implemented during the course of the study to reduce decreases of absolute body weight gains.

Inhalation Exposure

Exposure durations and animal assignment numbers are shown in the table below. Animals were exposed to glycopyrrolate aerosol at Low (30 minutes), Mid (60 minutes), or High dose (120 minutes) levels using a pre-qualified inhalation exposure system. The vehicle-control (120 minutes) and air-control (120 minutes) groups were exposed using separate, but identical systems.

Table 13: Experimental Design

Exposure	Animal IDs	Sex	Exposure Duration (min)	N	104 Week Nx*
Air control	1001-1060	M	120	60	20
Air Control	1061-1120	F	120	60	20
Placebo pMDI	2001-2060	M	120	60	20
Placebo pMDI	2061-2120	F	120	60	20
Low Dose pMDI	3001-3060	M	30	60	20
Low Dose pMDI	3061-3120	F	30	60	20
Mid Dose pMDI	4001-4060	M	60	60	20
Mid Dose pMDI	4061-4120	F	60	60	20
High Dose pMDI	5001-5060	M	120	60	20
High Dose pMDI	5061-5120	F	120	60	20

* The target study group size at the terminal necropsy.

(Excerpted from Study Report)

Exposure System

The exposure system schematic was excerpted from the study report and shown below. The aerosol generation system coupled glycopyrrolate pMDIs to an expansion chamber that allowed the propellant to expand and evaporate prior to transitioning into the exposure plenum. pMDIs were actuated directly into the expansion chamber. In the expansion chamber, 25±3 L/min forced air dilution was mixed into the air inside of the chamber which was fitted with 6 pMDI actuators. The actuation of each pMDI was controlled by a two-way pneumatic valve. Identical aerosol generation systems were used for the vehicle-control and air-control groups. It is noted that only 48 ports (3-tiers) are shown in the schematic; however, the actual system that was utilized on study had 80 ports (5-tiers).

The pMDIs were actuated at a rate of 75 shots/min (15 shots/vial/min). The pMDIs were changed every 15 minutes for 19 mL cans or every 10 minutes for 14 mL cans.

The expansion chamber used 25 ± 3 L/min of forced air dilution to mix the air inside of the chamber. From the expansion chamber, the aerosols transitioned into the 80-port nose-only inhalation chamber. For personnel protection, the test and control article exposure chambers were placed inside a secondary containment box. The total air flow through the exposure system was balanced to achieve individual rodent port flows of 1.5 times the respiratory minute volume of a rat (port flow approximated based on total chamber exhaust flow). The exhaust flow through the system was maintained at 24 ± 3 L/min; when the exhaust flow was within these specified limits, the port flow met the required 1.5 times the respiratory minute volume for a 80-port exposure system. The exposure chamber had a slightly higher exhaust flow rate than forced air dilution flow (inlet air flow).

Animals were placed in nose-only restraint tubes connected to the exposure chamber and exposed. Chamber oxygen content was collected directly from the breathing zone of the chamber using an oxygen monitor. The room temperature and ambient pressure were also obtained during the exposure. Daily exposures to aerosol and the test article were determined from samples collected on (b) (4) membrane filters at a flow rate of 0.5 L/min. Samples from the test article and vehicle-control systems were collected for a target of 30 minutes (±15 minutes). Samples from the air-control were collected for a target of 120 minutes (± 60 minutes). Aerosol concentrations were measured gravimetrically by weighing the samples on the filter. Glycopyrrolate concentrations were measured chemically by extracting samples from filters followed by analysis using a HPLC-UV method.

Figure 5 Schematic of (b) (4) pMDI Aerosol Generator coupled to a rodent exposure system

Figure 1. Schematic Diagram of the test and control article exposure chambers, of note is the schematic here in Figure 1 is shown in one pMDI actuator for graphical clarity instead of the six pMDI actuators that are actually present on the system.

(Excerpted from the Sponsor's submission)

Based upon gravimetric analysis, aerosol concentrations for the vehicle-control group and glycopyrrolate-treated groups were 0.17 ± 0.03 and 0.16/0.15 ± 0.03 mg/L (M/F), respectively.

The average (standard deviation) Glycopyrronium bromide aerosol concentrations for the low, mid, and high groups were 12.36/11.43 µg/L (M/F), 12.36/11.78 µg/L (M/F) and 12.51/11.66 µg/L (M/F), respectively.

Table 14: Total Aerosol and Glycopyrronium Bromide (glycopyrrolate) concentrations

	Male		Female	
Group	Total Aerosol (mg/L)	Glycopyrronium Bromide (µg/L)	Total Aerosol (mg/L)	Glycopyrronium Bromide (µg/L)
Air	0.00 (0.00)	<LOD	0.00 (0.00)	<LOD
Placebo	0.17 (0.03)	<LOD	0.17 (0.03)	<LOD
Gly Low	0.16 (0.03)	12.36 (2.74)	0.15 (0.03)	11.43 (2.91)
Gly Mid	0.16 (0.03)	12.36 (2.55)	0.15 (0.03)	11.78 (2.71)
Gly High	0.16 (0.03)	12.51 (2.54)	0.15 (0.03)	11.66 (2.50)

(Excerpted from Study Report)

Table 15: Doses of Glycopyrronium Bromide (mg/kg/day) based upon Chemical Analysis of Filters

Table 8. Group Average Delivered Gly Doses.

	Glycopyrronium Bromide Dose (mg/kg/day)		
Group	Male	Female	Average
Air	ND	ND	ND
Placebo	ND	ND	ND
Low Dose	0.347	0.335	0.341
Mid Dose	0.705	0.700	0.703
High Dose	1.46	1.42	1.44

ND: not detected.

Table 16: Doses of DSPC and $CaCl_2$ (mg/kg/day)

Table 9. Group Average Placebo Doses.

	DSPC Dose (mg/kg/day)		CaCl2 Dose (mg/kg/day)	
Group	Male	Female	Male	Female
Air	ND	ND	ND	ND
Placebo	17.8	18.6	1.26	1.31
Low Dose	4.19	4.11	0.30	0.29
Mid Dose	8.53	8.33	0.60	0.59
High Dose	17.4	17.0	1.23	1.20

ND: not detected.

Particle size
Particle size was determined for each exposure atmosphere (except air controls) at least once per month throughout the study (25 times) using a (b) (4) Impactor. The vehicle-control (placebo) MMAD ranged from (b) (4) and the GSD ranged from (b) (4). The glycopyrrolate aerosol MMAD ranged from (b) (4) (b) (4) and the GSD ranged from (b) (4). The average MMAD and GSD for vehicle-control (placebo) were (b) (4), respectively. The average MMAD and GSD for the glycopyrrolate aerosol groups were (b) (4), respectively (Table 17).

Table 17: Average MMAD and GSD for Each Aerosol Impactor

Aerosol	MMAD (µm)	GSD
Placebo	(b) (4)	
Gly		

Observations and Results

Mortality

During the study period, mortality checks were performed on all animals at a minimum of twice daily.

There were no test article related effects on male or female survival relative to air-control and vehicle-control groups (Table 18, Figure 6, Figure 7). The numbers of animals per group surviving until terminal necropsy exceeded the Sponsor's expected number (~20 surviving/per group at Week 104).

Figure 6: FDA Statistical Reviewer-Generated Kaplan-Meier Survival Curve for Male Mice

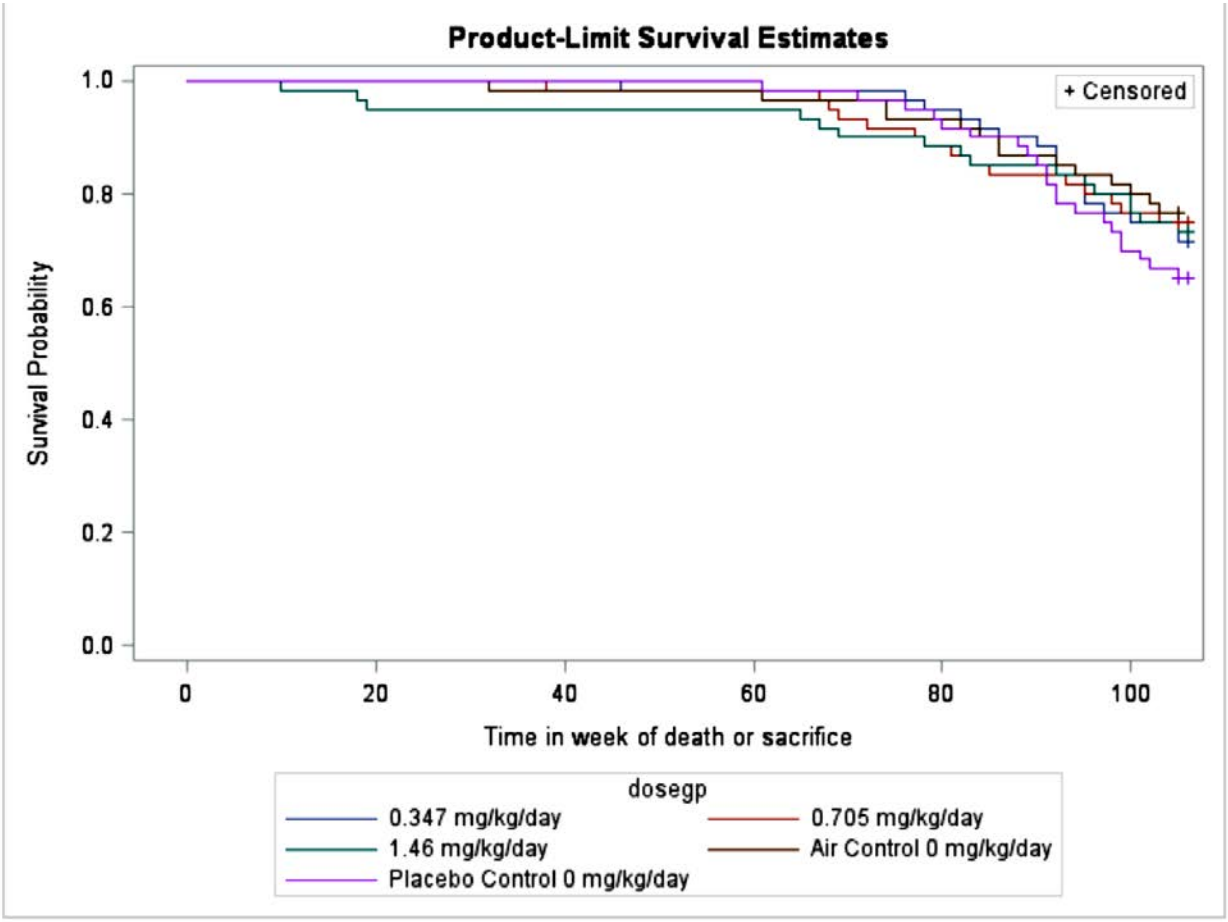


Figure 7: FDA Statistical Reviewer-Generated Kaplan-Meier Survival Curve for Female Mice

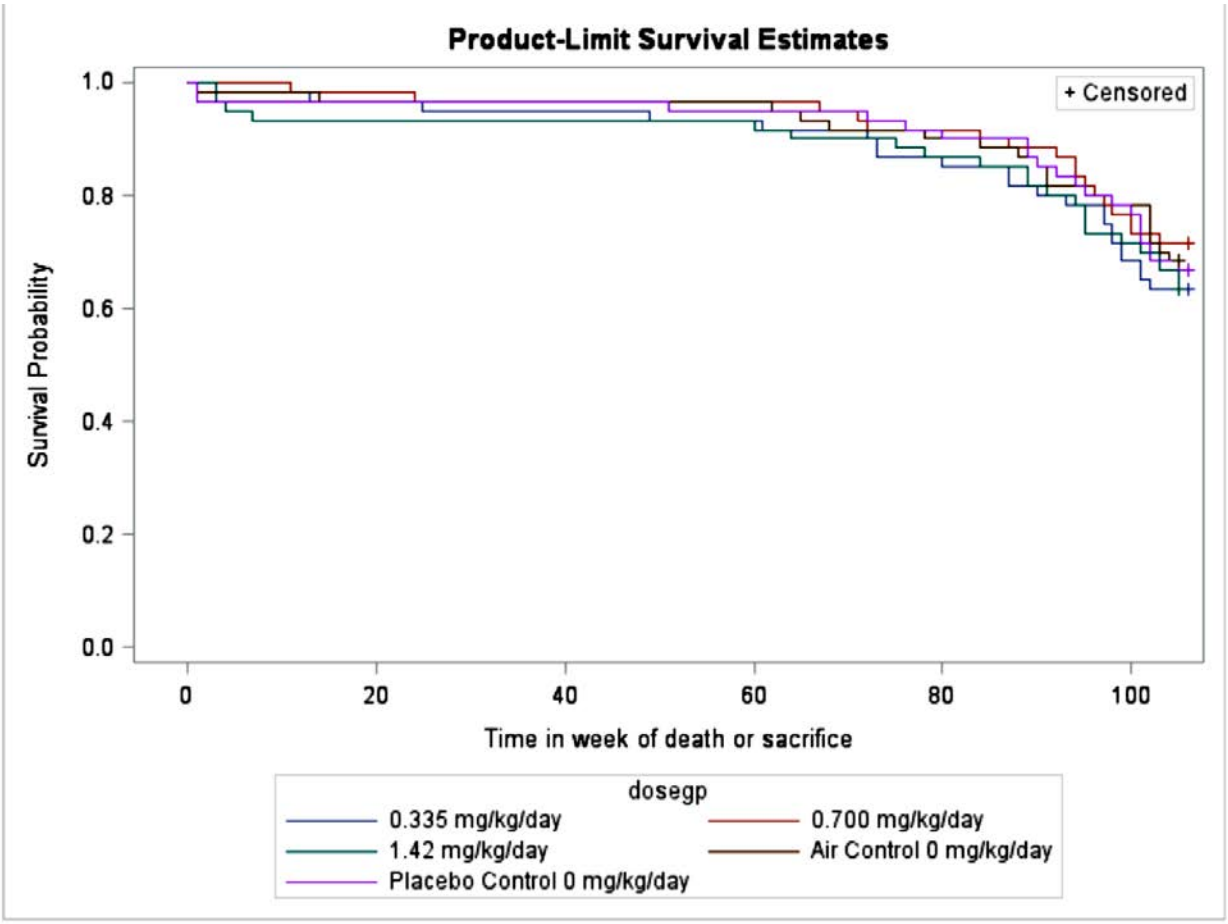


Table 18: Survival Analysis for the 104-Week Carcinogenicity Study in Mice

Mouse Study Glycopyrrolate µg/kg/day	**Males**		**Females**	
Males/Females (interim sacrifice animals excluded)	# of EarlyDeaths	# At terminal necropsy	# of Natural Deaths	# At terminal necropsy
Air Control	14 (23%)	46 (77%)	19 (32%)	41 (68%)
Placebo	21 (35%)	39 (65%)	20 (33%)	40 (67%)
Low Dose	17 (28%)	43 (72%)	22 (37%)	38 (63%)
Mid Dose	15 (25%)	45 (75%)	17 (28%)	43 (72%)
High Dose	16 (27%)	44 (73%)	22 (37%)	38 (63%)

Number of early deaths = unscheduled necropsy + found dead + accidental deaths
Numbers in parentheses represent the percent when compared to the number of main study animals at the start of the study (i.e., 60 animals/sex/group)

Clinical Signs

During the study period, twice daily cage-side or detailed observations and morbidity/mortality checks were performed on all animals. Observations included, but were not limited to, reactivity to general stimuli and description of any abnormal behaviors, lesions, or appearances. Clinical signs associated with the respiratory tract (e.g. apnea, labored breathing, rapid breathing, marked nasal discharge, etc.).

No treatment-related clinical signs were noted during the treatment period.

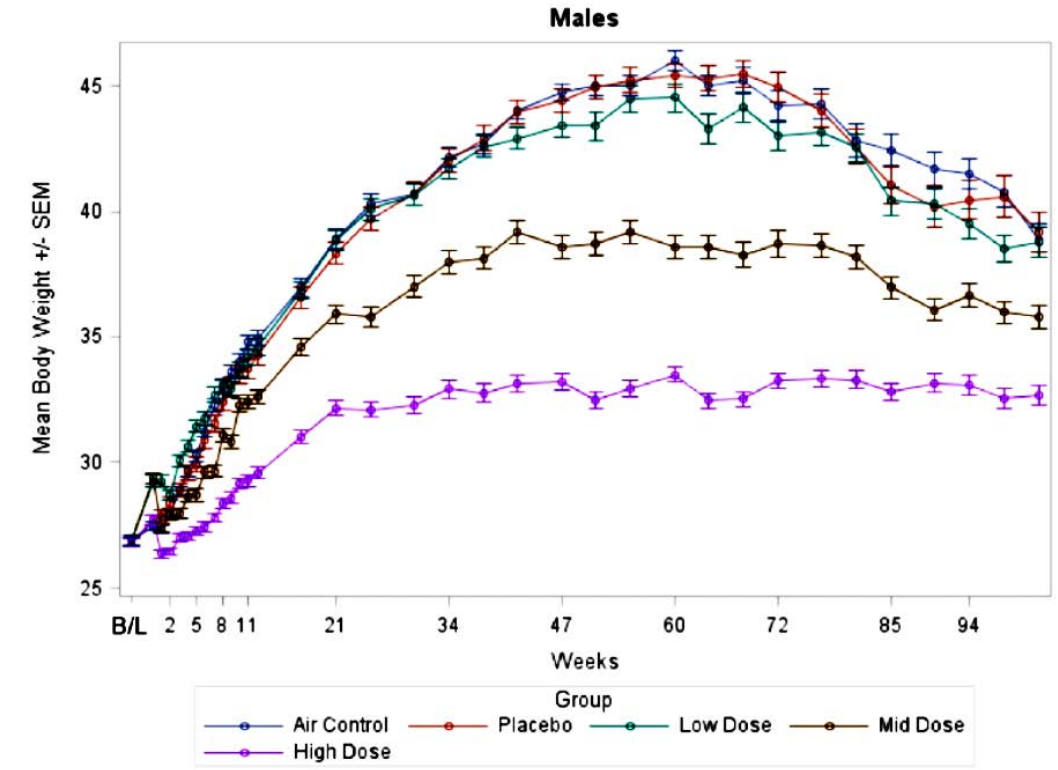
Body Weights

All animals on-study were weighed prior to randomization and then weekly for the first 13 Weeks of the treatment period, then monthly until the time of necropsy. Fasted body weights were measured at necropsy.

In general, there were dose-dependent decreases of absolute body weights for male and female MD and HD glycopyrrolate-treated groups. Examinations of body weight curves indicated that air-control groups separated from drug-treated groups beginning at approximately Week 3 in males and Week 11 in females (Figure 8). Body weight changes at weeks 0, 25, 51, 81, and 102, relative to the air- control groups are shown in Table 34. At the end of the study, decreases of absolute body weight exceeded 10% for the HD male drug-treated group (i.e., 15.9% decrease of absolute body weight, relative to the air control group). Similarly, for females at Week 102, decreases of absolute body weights exceeded 10% for MD and HD female drug-treated groups (i.e., 15% and 27.7% decreases of absolute body weights for females in the MD and HD groups, respectively, relative to the air-control group).

Reductions in BW of greater than 10% relative to air-control groups for the HD male and MD and HD female groups suggested the MTD was exceeded. The body weight curve for the MD male drug-treated group separated from the air-control and vehicle-control group curves, although decreases of absolute body weight were less than 10%. The Sponsor never implemented any dose reductions during the course of the study to minimize decreases of absolute body weights.

Figure 8: Body Weight Changes in Males and Females in the 104-Week Carcinogenicity Study in Mice



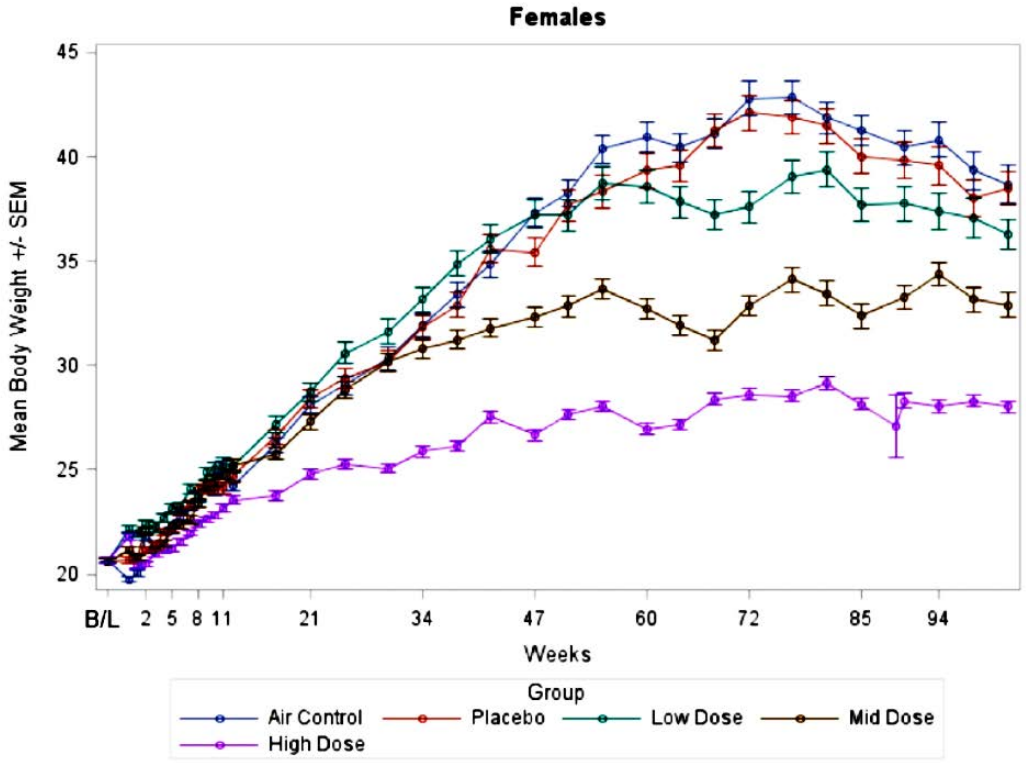


Table 19: Body Weight Changes in 104 Week Inhalation Carcinogenicity Study in Mice

Body Weight	Males					Females				
Mouse (g)	Air Control	Placebo	Low Dose	Mid Dose	High Dose	Air Contro	Placebo	Low Dose	Mid Dose	High Dose
Week 0	27.4	27.6	29.2	27.4	26.8	19.8	20.7	22.2	21.2	20.7
Week 25	40.3	39.7	40.1	35.8	32.1	29.0	29.4	30.6	28.8	25.3
Absolute BW, % Control	0.0	-1.5	-0.5	-11.2	-20.3	0.0	1.4	5.5	-0.7	-12.8
Δ, g	12.9	12.1	10.9	8.4	5.3	9.2	8.7	8.4	7.6	4.6
BW gain, % control	0.0	-6.2	-15.5	-34.9	-58.9	0.0	-5.4	-8.7	-17.4	-50.0
Week 51	45.0	44.9	43.4	38.7	32.5	38.3	37.7	37.2	32.8	27.7
Absolute BW, % Control	0.0	-0.2	-3.6	-14.0	-27.8	0.0	-1.6	-2.9	-14.4	-27.7
Δ, g	17.6	17.3	14.2	11.3	5.7	18.5	17.0	15.0	11.6	7.0
BW gain, % control	0.0	-1.7	-19.3	-35.8	-67.6	0.0	-8.1	-18.9	-37.3	-62.2
Week 81	42.8	42.6	42.5	38.2	33.3	41.9	41.5	39.4	33.5	29.1
Absolute BW, % Control	0.0	-0.5	-0.7	-10.7	-22.2	0.0	-1.0	-6.0	-20.0	-30.5
Δ, g	15.4	15.0	13.3	10.8	6.5	22.1	20.8	17.2	12.3	8.4
BW gain, % control	0.0	-2.6	-13.6	-29.9	-57.8	0.0	-5.9	-22.2	-44.3	-62.0
Week 104	38.9	39.2	38.8	35.8	32.7	38.7	38.5	36.3	32.9	28.0
Absolute BW, % Control	0.0	0.8	-0.3	-8.0	-15.9	0.0	-0.5	-6.2	-15.0	-27.6
Δ, g	11.5	11.6	9.6	8.4	5.9	18.9	17.8	14.1	11.7	7.3
BW gain, % control	0.0	0.9	-16.5	-27.0	-48.7	0.0	-5.8	-25.4	-38.1	-61.4

Feed Consumption

During the study period, animals had unlimited access to chow diet (2016C Teklad Certified Global Rodent Chow)

Feed consumption monitoring was not conducted.

Ophthalmology

All animals on study were examined by a board-certified veterinary ophthalmologist prior to start of drug exposure. A second examination was conducted on surviving animals within the last 4 days of exposure before necropsy.

No treatment-related ophthalmology findings were noted.

Gross Pathology

Detailed gross necropsies were performed on all animals (found dead, moribund euthanasia, sentinel/serology, or scheduled necropsy). Complete external and internal examinations of body orifices (ears, nostrils, mouth, anus, etc.) and cranial, thoracic, and abdominal organs and tissues were conducted. Gross findings were recorded in descriptive terms to capture shape, color, consistency, and number. Full tissue collection was performed on moribund and animals were found dead for histopathology examinations.

Tissues listed in Table 35 were harvested and fixed in 10% neutral buffer formalin (NBF) or Bouin's fixative. All wet tissues collected from study necropsy were shipped at ambient temperature to [redacted] (b) (4) for preparation of microscopic slides and hematoxylin and eosin (H&E) staining. Prepared slides were then transferred to Dr. [redacted] (b) (4) for microscopic evaluation. Remaining tissues, blocks, and slides were shipped back to [redacted] (b) (4) for archive.

All tissues were examined including those from the found dead or moribund euthanasia animals. Missing tissues were noted in the study record.

Table 20: Routine Organs Collected for the Mouse Carcinogenicity Study

Table 2. Routine Organ/Tissue Collections.

Tissues	Weigh	Examine	Comments
Abnormal Tissue		X	Representative examples.
Adrenal × 2	X	X	
Aorta (thoracic)		X	
Brain	X	X	Five levels
Epididymis (Male) × 2	X	X	Fixed in Bouin's fluid
Eye × 2 (+ Optic Nerve)		X	Fixed in Bouin's fluid. At least one optic nerve should be present on the slide.
Femur (including bone marrow for smear)		X	
Gastrointestinal tract:			
Stomach		X	
Duodenum		X	
Jejunum		X	
Ileum		X	
Cecum		X	
Colon		X	
Rectum		X	
Harderian Gland × 2		X	
Heart	X	X	Sections including all four chambers
ID (microchip or tatoo)			Retained for identification purposes
Kidney × 2	X	X	
Lacrimal Glands × 2		X	
Liver	X	X	Samples from two lobes
Mammary Gland		X	Histopathology on males only if present in routine skin section
Mesenteric Lymph Nodes		X	
Esophagus		X	
Ovary (Female)× 2	X	X	
Pancreas		X	
Parathyroid × 2		X	At least one parathyroid should be present on the slide
Pituitary		X	
Prostate (Male)		X	
Sciatic Nerve		X	
Skin		X	Caudoventral abdomen
Seminal Vesicles (Male) (+ Coagulating Gland)		X	
Spinal Cord		X	Cervical, midthoracic and lumbar

Table 2. Routine Organ/Tissue Collections.

Tissues	Weigh	Examine	Comments
Spleen	X	X	
Sternum (including Bone Marrow)		X	
Mandibular Lymph Node		X	
Submandibular Salivary Gland × 2		X	
Testis (Male) × 2	X	X	Fixed in Bouin's
Thigh Muscle		X	
Thymus	X	X	
Thyroid × 2		X	Left attached to the trachea for tracheal trimming and gland sampling
Tongue		X	
Urinary Bladder		X	
Uterus (Female)	X	X	Body and horns
Vagina (Female)		X	Cervix
Tracheobronchial Lymph Node		X	
Larynx		X	
Lungs	X	X	Whole lung was harvested, weighed, perfused with 10% NBF via tracheal cannula until pleura was tense
Nasal Cavity (with olfactory bulbs)		X	After dissection from the carcass, the nasal cavity was gently flushed with 10% NBF in order to ensure removal of air pockets from within the nasal cavity. Decalcification was undertaken using formic acid. Four transverse sections of the nasal cavity were produced and evaluated. Sections were taken from approximate areas as follows: (I) caudal surface of upper incisor (II) between the incisive papilla and the first palatal ridge (III) between last palatal ridge and mid-point of first molar (IV) 2nd molar
Trachea		X	Two sections at level of thyroid and carina.

Organ weights

Absolute weights were measured for the organs listed in (Table 20) and relative weights were calculated. Organ weight data was not reviewed as it was not critical to the evaluation of neoplastic findings.

Histopathology

Adequate battery: Yes

Histopathologic examination was initially conducted in a "read down" fashion: i.e. all tissues and gross lesions were examined for Groups 1-Air Control, 2-Placebo (Vehicle-control) pMDI Control, and 5-'High Dose Glycopyrrolate pMDI'. Additionally, all lungs, respiratory tracts, and macroscopic findings in scheduled sacrificed low and mid dose

groups were also processed and examined. After the initial examination, remaining tissues from all dead and moribund animals from all groups and from all low and mid dose sacrificed animals were processed and examined.

Peer Review
A peer review of the microscopic findings was conducted by Dr. (b) (4) of (b) (4). The overall results reported by the study pathologist reflect the mutually agreed on diagnoses and interpretation of all pertinent data.

Neoplastic
In the right lung in females, alveolar-bronchiolar adenoma was noted in 7 of 60 in the LD group, 1 of 60 in the MD, and 6 of 60 in the HD group, indicating a positive trend, despite the lack of a clear dose-response. This finding reached statistical significance in the LD and HD group (p-values, 0.0058 and 0.0126, respectively) compared to the air control and vehicle control group. However, when alveolar-bronchiolar adenomas from the right lungs were combined with the left lungs, the p-value no longer achieved statistical significance.

Table 21: Neoplastic Findings in the 104-Week Inhalation Carcinogenicity Study in Female Mice

Mouse	**Females (mg/kg/day)**				
Organ/Tissue (Neoplastic findings)	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose
	NA	NA	0.335	0.7	1.42
# of animals on Study	60	60	60	60	60
Lung, Left					
total examined	60	60	60	60	60
Alveolar-Bronchiolar Adenoma	3	2	1	0	2
Alveolar-Bronchiolar Carcinoma	1	1	0	0	1
Lung, Right					
total examined	60	60	60	60	60
Alveolar-Bronchiolar Adenoma	0	0	7	1	6
Alveolar-Bronchiolar Carcinoma	2	1	1	2	2
Lung, Right + Left					
total examined	53	53	51	55	51
Alveolar-Bronchiolar Adenoma	3	2	8	1	7
Alveolar-Bronchiolar Carcinoma	2	2	1	2	3
Alveolar-Bronchiolar Adenoma/Carcinoma	4	4	9	3	10

Non-neoplastic

Nose/turbinates were examined as independent sections 1-4 and notable findings were listed in the histopathology table below. In the nasal cavity turbinate L1, acute inflammation increased with the dose in males. However, acute inflammation was not

observed in any female treatment groups. In the nasal cavity turbinate L2, hyaline degeneration of the olfactory epithelium increased with the dose of glycopyrrolate in males and females. Hyaline degeneration of the olfactory epithelium was not noted in any air control animals of either sex. In nasal cavity turbinate L3, hyaline degeneration of the olfactory epithelium and respiratory epithelium was noted at high incidence in the placebo and treatment groups. The findings in the nose/turbinates were not considered clinically relevant, because mice, which were obligate nose breathers, received glycopyrrolate by nose-only inhalation and humans will be dosed via oral inhalation.

Table 22: Non-Neoplastic Findings in Mouse Carcinogenicity Study through terminal sacrifice

Mouse	Males (mg/kg/day)					Females (mg/kg/day)				
Organ/Tissue (Non-Neoplastic findings)	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose	Air Ctrl	Placebo	Low Dose	Mid Dose	High Dose
	NA	NA	0.347	0.705	1.46	NA	NA	0.335	0.7	1.42
No. Examined	60	60	60	60	60	60	60	60	60	60
Nasal Cavity w/ Turbinates L1										
total examined	60	60	60	60	60	60	60	60	60	60
Inflammation, Acute	1	0	2	3	5	1	1	0	0	0
Nasal Cavity w/ Turbinates L2										
total examined	60	60	60	60	60	60	60	60	60	60
Degeneration, Hyaline, Olfactory, Epithelium	0	1	2	10	15	0	2	5	8	31
Nasal Cavity w/ Turbinates L3										
total examined	60	60	60	60	60	60	60	60	60	60
Degeneration, Hyaline, Olfactory, Epithelium	0	38	39	44	52	0	53	17	40	55
Degeneration, Hyaline, Respiratory, Epithelium	0	42	13	35	47	0	14	42	41	56

Toxicokinetics

Toxicokinetic analysis was not conducted.

Safety margins for the proposed clinical dose 18 µg/dose BID of glycopyrrolate are calculated for the low dose, mid dose, and high dose in the 104-week mouse carcinogenicity study. Toxicokinetic analysis was not conducted, therefore safety margins were calculated on a mg/kg and mg/m^2 basis using the estimated achieved doses. On a mg/kg basis the safety margins for the clinical dose relative to the nonclinical doses were 558 at the low dose and 1167 at the mid dose. On a mg/m^2 basis the safety margins for the clinical dose relative to the nonclinical doses were 45 at the low dose and 95 at the mid dose.

Table 23: Safety Margins for Clinical dose of 18 µg Glycopyrrolate BID based on 104 Week Carcinogenicity Study in Mice

Mouse Carcinogenicity Safety Margins Based on Clinical Dose of 18 µg/dose Glycopyrrolate BID						
Nonclinical Group	Dose Male (µg/kg)	Safety Margin µg/kg	Safety Margin mg/m^2	Dose Female (µg/kg)	Safety Margin mg/kg	Safety Margin mg/m^2
Low	347	578	47	335	558	45
Mid	705	1175	95	700	1167	95
High	1460	2433	197	1420	2367	192

Clinical dose of 0.02 mg/m^2 was used for mg/m^2 safety margin calculation. Daily doses administered to mice in µg/kg were converted to mg/m^2 by multiplying by a conversion factor of 3.

11 Integrated Summary and Safety Evaluation

The Sponsor has submitted a marketing application for the inhaled triple combination product composed of glycopyrrolate (G), budesonide (B), and formoterol (F or FF) as a treatment for COPD. The Sponsor currently markets the combination of glycopyrrolate and formoterol under the tradename of Bevespi Aerosphere as a treatment for COPD. The inhaled triple combination product represents the addition of budesonide to the approved combination of glycopyrrolate and formoterol. The Sponsor also markets the combination of formoterol and budesonide under the tradename of Symbicort for the treatment of asthma and COPD. The Sponsor has complete nonclinical programs for formoterol and budesonide. The Sponsor used a 505b2 approach for the development of Bevespi Aerosphere that involved referencing nonclinical studies with glycopyrrolate from another Sponsor's label.

During the IND development phase for the inhaled triple combination product, the Sponsor was requested to conduct only one nonclinical study, a 90-day inhalation toxicology study in dogs with the combination of BGF.

In an attempt to support a 505b1 application for the inhaled combination of glycopyrrolate, budesonide, and formoterol, the Sponsor provided a complete nonclinical program for glycopyrrolate. In the current application, the Sponsor provided reproductive toxicology studies that consisted of a fertility and early embryonic development (FEED) study in rats, embryo-fetal development (EFD) studies in rats and rabbits, and a pre- and postnatal development (PPND) study in rats as well as 2-year inhalation carcinogenicity studies with glycopyrrolate in Sprague-Dawley rats and B6C3F1 mice. In NDA 208294 for the Bevespi Aerosphere, the Sponsor submitted 6-month inhalation toxicology studies with glycopyrrolate in rats and dogs, a 90-day inhalation toxicology study in dogs with the combination of glycopyrrolate and formoterol, and a complete battery of genetic toxicity studies with glycopyrrolate. It is noted that the Sponsor never conducted their own pharmacology studies with glycopyrrolate, but rather relied on the published literature. This review primarily evaluated the reproductive toxicity studies and 2-year carcinogenicity studies in rats and

mouse with glycopyrrolate. As described below, the Sponsor's 505b1 approach was determined to not be viable given that 2-year inhalation carcinogenicity study in rats was considered invalid.

Excipients
This product contains no novel excipients. BGF contains HFA-134a as the propellant (DMF (b) (4)) and porous particles (PP) as an excipient. Both excipients are present in approved and currently marketed products including Bevespi Aerosphere (NDA 208294). Porous particles (PP) are comprised of (b) (4) DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and (b) (4) $CaCl_2$ (calcium chloride).

Pharmacology
The Sponsor did not conduct any pharmacology studies with glycopyrrolate, but rather relied on the published literature. The Sponsor conducted pharmacology studies with formoterol fumarate under NDA 21929 for Symbicort and with budesonide under NDA 20929 for Pulmicort Respules. Established pharmacological classifications for glycopyrrolate, budesonide, and formoterol fumarate are anticholinergic, corticosteroid, and long-acting beta2-adrenergic agonist.

ADME
The Sponsor conducted very limited ADME studies with glycopyrrolate. The Sponsor conducted ADME studies with formoterol fumarate under NDA 21929 for Symbicort and with budesonide under NDA 20929 for Pulmicort Respules.

General Toxicology
During the IND development phase for the inhaled triple combination product, the Sponsor was requested to conduct only one nonclinical study, a 90-day inhalation toxicology study in dogs with the combination of BGF.

In NDA 208294 for the Bevespi Aerosphere, the Sponsor submitted 6-month inhalation toxicology studies with glycopyrrolate in rats and dogs as well as a 90-day inhalation toxicology study in dogs with the combination of glycopyrrolate and formoterol. The Sponsor conducted inhalation toxicology studies with formoterol fumarate and the combination of formoterol and budesonide under NDA 21929 for Symbicort and with budesonide under NDA 20929 for Pulmicort Respules.

90-day inhalation toxicology study in dogs with BGF
In the 90-day BGF-triple combination and BFF-dual combination inhalation study (Study No. FY14-148A), beagle dogs (4/sex/group) were dosed with budesonide (B), glycopyrrolate (G), and formoterol fumarate (F or FF) as a triple combination (BGF) or budesonide and formoterol fumarate (BFF) as a double combination at low, mid, or high doses, via face mask inhalation daily for 90 days to study the potential toxicological interactions between the three drugs. The study used the clinical formulations of budesonide, glycopyrrolate, and formoterol fumarate. There were no deaths during the study period. The most notable histopathology findings were cortical atrophy in the adrenal gland, lymphocyte decrease in the tracheobronchial lymph nodes, and

hepatocellular alteration in the liver. The observed histopathological findings were generally consistent with known corticosteroid class effects of budesonide with the exception of the findings in the liver that could be attributed to formoterol fumarate (known class effect of beta2-adrenergic agonists). It was not possible to discern if there were any toxicokinetic interactions on the basis of how the study was designed. There was no evidence of additive or synergistic toxic effects when adding budesonide to the approved combination of glycopyrrolate and formoterol (i.e., Bevespi Aerosphere).

Carcinogenicity

The Sponsor conducted carcinogenicity studies in mice and rats with formoterol under NDA 21929 for Symbicort and budesonide under NDA 20929 for Pulmicort Respules.

In an attempt to support a 505b1 application for the inhaled triple combination of glycopyrrolate, budesonide, and formoterol, the Sponsor conducted two-year inhalation carcinogenicity studies with glycopyrrolate in Sprague-Dawley rats and B6C3F1 mice. Prior concurrence for doses used in these studies was not obtained from the Executive Carcinogenicity Assessment Committee. Final results of these studies were presented to the ECAC on April 16, 2019.

2-year inhalation carcinogenicity study in rats: In a 2-year carcinogenicity study, Sprague Dawley rats received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 151.7/165.93 (LD, M/F), 302.9/330.66 (MD, M/F), and 620.45/684.14 (HD, M/F) µg/kg/day. The study included an interim sacrifice of 10 rats/sex/group after 52 weeks of treatment. Doses are represented as the estimated achieved pulmonary doses with the quaternary ammonium bromide salt form of the drug substance (glycopyrrolate).

Treatment with glycopyrrolate had no effects on survival of male or female rats. Dose-related decreases of absolute body weights were observed in male and female rats beginning at approximately week 12 and continuing over the course of study. At Week 81, absolute body weights were reduced for drug-treated male groups by 11.8% (LD), 19.9% (MD), and 20% (HD) and for female drug-treated groups by 16% (LD), 11.4% (MD), and 23.4% (HD), relative to air-control groups. Decreases of absolute body weights appeared to be potentially excessive (>10%). The Sponsor did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights.

The Sponsor elected to terminate the entire study early (starting at Week 82) for all male and female groups due to low survival (22 of 60 [37%] females remaining) in the female air-control group at week 82. According to ECAC criteria for study termination, if the number of animals of a sex within the control group declines to 20, then all groups of that sex including drug-treated should be terminated. Based on these criteria, it was inappropriate to terminate female groups at that time. Further, in the male air-control and vehicle-control groups, 37 of 60 (62%) and 27 of 60 (45%) animals, respectively, were alive at week 82. Male groups were inappropriately terminated per ECAC criteria

for study termination. The study duration was potentially inadequate to assess drug-induced tumor development. The ECAC concluded that the carcinogenicity study was inadequate in male and female rats due to early termination of the study (see meeting minutes dated April 16, 2019).

A 505b1 application was no longer considered viable with the judgement that the 2-year carcinogenicity study in rats was inadequate. As a path forward to avoid repeating the 2-year carcinogenicity study with rats, the Sponsor administratively changed the application to the 505(b)(2) pathway in order to rely on the Agency's previous findings of safety for glycopyrrolate with the reference listed drug, ROBINUL Injection (NDA 17558) and published literature on the pharmacology of glycopyrrolate. The label will provide a description of the 2-year carcinogenicity study with glycopyrrolate administered by oral gavage to rats that can be found in the label for the referenced listed drug, CUVPOSA® (pending).

2-year inhalation carcinogenicity study in mice: In a 2-year carcinogenicity study, B6C3F1 mice received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control), 0.347/0.335 (LD, M/F), 0.705/0.7 (MD, M/F), and 1.46/1.42 (HD, M/F) mg/kg/day. Doses are represented as the estimated achieved pulmonary doses with the quaternary ammonium bromide salt form of the drug substance (glycopyrrolate).

Treatment with glycopyrrolate had no effects on survival of male or female mice up to 104 weeks. Dose-related decreases of absolute body weights were observed in males and females beginning around Week 3 and Week 11, respectively, and continuing over the course of study. Decreases of absolute body weights at the end of the study appeared to be potentially excessive (>10%) for MD Females (-15.9%), HD males (-15%), and HD females (-27.7%). The Sponsor did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights.

There were no statistically significant test article-related tumor findings in male mice from the low and mid dose groups and female mice in the low dose group.

The ECAC concluded that body weight decreases in high dose males and mid and high dose females could confound interpretation. The ECAC concurred that no drug-related neoplasms were observed at the low dose in females and the mid and low dose in males.

Toxicokinetic analysis was not conducted; however, histopathological findings in the nose/turbinates demonstrate exposure to glycopyrrolate in the respiratory tract. Decreased body weights in drug-treated groups were suggestive of systemic drug exposure.

Reproductive Toxicity Studies
The Sponsor conducted reproductive toxicity studies with formoterol under NDA 21929 for Symbicort and budesonide under NDA 20929 for Pulmicort Respules. In an attempt

to support a 505b1 application for the inhaled triple combination of glycopyrrolate, budesonide, and formoterol, the Sponsor conducted reproductive toxicity studies with glycopyrrolate that consisted of a FEED study in rats, EFD studies in rats and rabbits, and a PPND study in rats.

Fertility and Early Embryonic Development (FEED) study in rats
In a fertility and early embryonic development study, male rats and female rats received glycopyrrolate (salt) by subcutaneous (SC) administration at doses of 0 (vehicle, sterile saline), 0.1, 1.0, or 10 mg/kg/day. Males were treated during a 4-week premating period, up to 2 weeks during the mating period, and continuing up to necropsy (minimum of 52 days). Females were treated during a 2-week pre-mating period, up to 2 weeks during the mating period, and from gestation day (GD) 0 to GD 6 (minimum of 28 days). Male rats were mated with female rats within the same control or drug-treated group. Dams underwent cesarean sections on GD 13. There were no deaths in the test article-treated groups. Decreased body weight gains, exceeding 10% relative to controls, were seen at all doses in males over the entire treatment period (Day 52 at minimum). Decreased body weight gains, exceeding 10% relative to control, were seen at all doses in females during the pre-mating period; however, body weight gains were unaffected from GDs 0 to 6. Glycopyrrolate at doses up to 10 mg/kg/day did not affect fertility or reproductive performance (mating and fertility indices) in male or female rats. The NOAEL for male and female mating and fertility was the high-dose (10 mg/kg/day) which was associated with AUC_{0-24} of 6443 ng*hr/mL in males and 3371 ng*hr/mL in females. NOAELs for paternal and maternal toxicity were not identified based on decreased body weight gains exceeding 10% at all doses.

Embryo-Fetal Development (EFD) Studies in Rabbits and Rats
In an embryofetal development (EFD) study, time-mated female rabbits were treated by subcutaneous injection with 0 (control), 0.1 (low-dose), 1.0 (mid-dose), or 10 (high-dose) mg/kg/day glycopyrrolate during the period of organogenesis from GD 6 to 18 (day of confirmed mating was GD 0). Maternal toxicity was noted in mid- and high-dose pregnant females based upon decreased body weight gains, exceeding 10% relative to control, at the MD and body weight losses at the HD. Decreased body weight gain at the MD and body weight loss at the HD correlated with reduced food consumption. Body weight gain for the low dose group was comparable to the concurrent control group. Using body weights and body weight gains corrected for gravid uterus weights confirmed maternal toxicity was present at the MD and HD. Decreased male fetal body weights observed at the high dose were attributed to maternal toxicity. There were no dose dependent changes in cesarean section parameters, or test article related malformations or variations up to the high dose of 10 mg/kg, which was associated with an AUC of 5693 ng*hr/mL in gravid females on GD 18. The NOAEL for maternal toxicity was 1 mg/kg based on reduced BWG at the MD and body weight loss at the HD. The NOAEL for developmental toxicity was the MD, 1 mg/kg, based on reduced body weights for male fetuses in the 10 mg/kg treated group; however, this could be attributed to excessive maternal toxicity at the HD.

In an EFD study, time-mated female rats were treated by subcutaneous injection with 0 (control), 0.1 (low-dose), 1.0 (mid-dose), or 10 (high-dose) mg/kg/day glycopyrrolate during the period of organogenesis from GD 6 to 17 (day of confirmed mating was GD 0). Maternal toxicity was noted in mid- and high-dose pregnant females based upon decreased body weight gains, exceeding 10%, which correlated with reduced food consumption. Treatment with glycopyrrolate caused reduced fetal body weights in fetuses in the high-dose group that appeared to be the result of maternal toxicity. Glycopyrrolate did not cause any structural abnormalities (no external, visceral, or skeletal variations or malformations) and did not affect fetal survival at maternal subcutaneous doses up to 10 mg/kg/day. The NOAEL for maternal toxicity was the low-dose (0.1 mg/kg/day). The NOAEL for EFD toxicity was the mid-dose (1 mg/kg/day); decreased fetal body weights observed at the high dose were attributed to maternal toxicity.

Prenatal and Postnatal Development (PPND) Study in Rats
In a rat PPND study, mated female rats (F0 generation) were treated by subcutaneous injection with 0 (control), 0.1 (low-dose), 1.0 (mid-dose), and 10 (high-dose) mg/kg/day glycopyrrolate from GD 6 to Postnatal Day/Lactation Day (PND/LD) 21-23. In the F0 generation, the mid- and high-dose groups had dose-dependent reductions of body weight gain (MD -15%, HD -29%) relative to the control group by GD 20 (correlated with decreased food consumption). Body weight gains for F0 drug-treated female group were unaffected from LDs 1 to 20. Toxicokinetic studies indicated that resulting plasma glycopyrrolate concentrations in F0 dams were dose-proportional based on C_{max}. The plasma C_{max} values for glycopyrrolate detected in F1 generation pups were from 4 to 16 times lower than in corresponding F0 dams. Absolute body weights of F1 pups in the high dose group from birth throughout the lactation period were approximately 10% lower relative to the control group. However, body weight gains of F1 generation pups from PND 0 to 21 and PND 28 to 70(M)/63(F) were comparable between control and drug-treated groups. There were no effects on physical or neurological development in F1 generation pups. Drug-treatment of F0 dams had no effects on fertility of F1 offspring. Drug-treatment of the F0 dams had no effects on numbers of corpora lutea, implantations, pre-and post-implantation losses, and live fetuses for pregnant F1 females. Development of F2 pups from PND 0 to 21 was unaffected by drug treatment of F0 dams. The NOAEL for maternal toxicity was the low-dose (0.1 mcg/kg/day) based on decreases of body weight gain at the mid- and high-doses. The NOAEL for the F1 pup development was the high-dose (10 mg/kg/day). Exposure margin calculations relative to the clinical dose were performed by extrapolation using exposure data from the EFD study with rats.

Table 24: Comparison of Daily Clinical doses of Budesonide, Glycopyrrolate, and Formoterol Fumarate in Symbicort, Bevespi, and Breztri BGF for COPD

Drug Substance	Symbicort	Bevespi	Breztri (BGF)
Budesonide	640 µg	--	640 µg
Glycopyrrolate	--	36 µg	36 µg
Formoterol Fumarate	19.2 µg	19.2 µg	19.2 µg

Table 25: Systemic Safety/Exposure Margins for Breztri (BGF) on AUC basis using the 90-Day Inhalation Toxicology Study with BGF in Dogs

90-Day Dog inhalation study with BGF	Estimated inhaled dose at the HD µg/kg/day		Dog AUC_{last} Day 90 (ng*hr/mL)		*Clinical AUC_{24hr} Day 8 (ng*hr/mL)	Animal to Human Exposure Margin
	Male	Females	Male	Female		Avg (M/F)
Budesonide	58.39	61.37	13.8	13.1	6	2.2
Glycopyrrolate	3.39	3.56	0.634	0.688	0.148	4.5
Formoterol Fumarate	1.94	2.03	0.370	0.324	0.094	3.7

*From clinical Study PT010018 after 7 days of twice daily dosing of BGF to patients with moderate to severe COPD. Mean AUC_{0-12} value for B, G, and F were multiplied by 2 to estimate AUC_{24hr} values.

Table 26: Animal to Human Local Exposure Margins for BGF Based on Lung Weight for the Proposed Daily Clinical Doses

90-Day Dog inhalation study with BGF	**[1]Estimated inhaled dose at the HD µg/kg/day**		**[2]Pulmonary Deposited Dose (µg/kg)**		**[3]Dose by Lung weight (µg/g)**		**[4]Local Lung Safety Margin**	
	Male	Females	Male	Females	Males	Females	Males	Females
Budesonide	58.39	61.37	14.60	15.34	2.18	1.92	3.4	3
Glycopyrrolate	3.39	3.56	0.85	0.89	0.13	0.11	3.6	3
Formoterol Fumarate	1.94	2.03	0.49	0.51	0.07	0.06	3.6	3.1

[1]Estimated inhaled dose was calculated with the following formula: $RMV = 0.499BW^{0.809}$

[2]Pulmonary deposited dose is 25% of the estimated inhaled dose for dogs

[3]Dose by lung weight was calculated by multiplying the pulmonary deposited dose by the body weight then dividing by the lung weight.

-Lung weights were calculated by adding the weights for the 6 sections weighed. Male- 77 g, Females 68 g.

-Average BGF HD body weights at Day 91 were used. Males- 11.5 kg, Females 8.5 kg

[4]Local lung safety margins were calculated by dividing the nonclinical lung weight dose by the clinical lung weight dose (Budesonide = 0.64 µg/g; Glycopyrrolate = 0.036 µg/g, Formoterol fumarate= 0.0192 µg/g)

Table 27: Exposure and Safety Margins for Glycopyrrolate, Formoterol Fumarate and Budesonide

Toxicity Studies with <u>Glycopyrrolate</u>			**AUC_{0-24} (ng*hr/mL)**		**Animal to Human Exposure Margin**
Study	**NOAEL (mg/kg/day)**	**TK Analysis**	**Male**	**Female**	**Human AUC_{24hr} 0.148 (ng*hr/mL)**
Reproductive and Developmental Toxicity (subcutaneous)					
FEED rat (No. 14-746)	HD = 10 (NOAEL fertility)	M= Day 28 F= Day 14	6443	3371	43533/22777
EFD rat (No. 14-762)	MD = 1 (NOAEL developmental)	GD 17	n/a	214	1446
	HD = 10 (LOAEL)		n/a	3575	24155
EFD rabbit (No. 14-763)	MD = 1 (NOAEL developmental)	GD 18	n/a	452*	3054
	HD = 10 (LOAEL)			5693	38466
PPND rat	HD = 10 (NOAEL)	GD 17	n/a	3575**	24155

(No. 14-765)	(F1 and F2 males and females)				
*AUC0-4 was used because AUC0-24 could not be calculated for this TK group **AUC at 10 mg/kg from EFD rat study (No. 14-762) was used for PPND study exposure at 10 mg/kg					
Carcinogenicity Studies with Glycopyrrolate (inhalation)		**ROA**	**Nonclinical Dose (µg/m²)**		**Animal to Human Safety Margin (Clinical Daily dose = 22.2 µg/m²)**
Mouse	MD = 705 µg/kg (males)	inhalation	2115		95
	LD = 335 µg/kg (females)	inhalation	1005		45
Rat	(b) (4)				(b) (4)

Reproductive and Developmental Toxicity Studies with Formoterol Fumarate			**Nonclinical Dose µg/m²**		**Animal to Human Safety Margin (Clinical Daily dose = 11.84 µg/m²)**	
Study	**NOAEL/LOAEL µg/kg/day**	**ROA**	**Male**	**Female**	**Male**	**Female**
Reproductive and Developmental Toxicity						
FEED rat (No. T3015)	Male= 3000 Female = 15000 (NOAEL fertility)	oral	18,000	90,000	1520	7,601
EFD rat (No. T2628)	690 (NOAEL)	inhalation	n/a	4140	n/a	350
	3000 (LOAEL)	oral	n/a	18,000	n/a	1520
EFD rabbit (No. 93025)	3500 (NOAEL)	oral	n/a	42,000	n/a	3,547
	60,000 (LOAEL)		n/a	720,000	n/a	60810
PPND rat (No. T2905)	210 (LOAEL)	oral	n/a	1,260	n/a	106
Carcinogenicity Studies with Formoterol Fumarate						
Mouse	100 (LOAEL)	oral	300		25.3	
Rat	22 (NOAEL)	inhalation	132		11	
	130 (LOAEL)		780		66	

Reproductive and Developmental Toxicity Studies with Budesonide			**Nonclinical Dose ($\mu g/m^2$)**		**Animal to Human Safety Margin (Clinical Daily dose = 396 $\mu g/m^2$)**	
Study	**NOAEL/LOAEL (µg/kg/day)**	**ROA**	**Male**	**Female**	**Male**	**Female**
FEED rat	80 (NOAEL fertility)	S.C.	480		1.2	
	20 (LOAEL prenatal viability)		120		0.3	
EFD rat	250 (NOAEL)	S.C.	1500		3.8	
	500 (LOAEL)		3000		7.6	
EFD rabbit	25 (LOAEL)	S.C.	n/a	300	n/a	0.75
PPND rat	25 (LOAEL)	S.C.	n/a	150	n/a	0.38
Carcinogenicity Studies with Budesonide						
Rat	Male = 25 Female = 50 (NOAEL)	oral	150	300	0.4	0.8
	Male = 50 (LOAEL)		300	n/a	0.8	n/a
Mouse	M/F = 200 (NOAEL)	oral	600		1.51	

Conclusions
The Sponsor owns complete nonclinical programs for formoterol fumarate (NDA 21929 for Symbicort) and budesonide (NDA 20929 for Budesonide).

The nonclinical program for glycopyrrolate consists of chronic inhalation toxicology in rats and dogs, a standard battery of genetic toxicity tests, a 2-year inhalation carcinogenicity study in mice, and reproductive toxicity studies. A 90-day inhalation toxicology study with BGF in dogs was also provided. The 2-year inhalation carcinogenicity study in rats was judged to be inadequate. Further, the Sponsor did not conduct any pharmacology studies with glycopyrrolate, but rather relied on the published literature.

IR Regarding Rat Carcinogenicity Study and Regulatory Impact:
On June 5, 2019 an IR was sent to the Sponsor stating that the duration of the rat carcinogenicity study at 82-83 weeks was judged inadequate by the ECAC. We advised that as a path forward to avoid repeating the 2-year carcinogenicity study with

glycopyrrolate in rats, the Sponsor could administratively change the application to the 505(b)(2) path and cite reliance on another glycopyrrolate product for nonclinical information. Additionally, we noted that AstraZeneca did not submit their own pharmacology studies, and do not own the literature that they reference to support the pharmacology of glycopyrrolate. Therefore, citing reliance on this literature may also make the pending NDA, a 505(b)(2) application (unless AZ owns or has right of reference to the data needed for approval).

The Sponsor, responded to the IR on June 13, 2019, acknowledging the comments provided in our IR and indicated that AstraZeneca will utilize the 505(b)(2) pathway in order to rely on the Agency's previous finding of safety for glycopyrrolate using the reference listed drug ROBINUL Injection (NDA 017558) and published literature on the pharmacology of glycopyrrolate. It should be noted that carcinogenicity studies were never conducted to support the approval of ROBINUL Injection (NDA 017558).

The nonclinical program with the 3 individual agents as well as the combination were considered adequate to support approval of the triple combination from the nonclinical perspective. It should be noted that during the IND development phase for the inhaled triple combination product, the Sponsor was requested to conduct only one nonclinical study, a 90-day inhalation toxicology study in dogs with the combination of BGF.

Recommendations
The application is recommended for approval from the nonclinical perspective. There are no outstanding nonclinical issues.

12 Appendix/Attachments

1. ECAC Meeting Minutes dated April 16, 2019.

Executive CAC Final Study Minutes
Date of Meeting: April 16, 2019

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Ron Wange, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Terry Miller, PhD, DAIP, Alternate Member
Timothy Robison, PhD, DPARP, Pharm/Tox Team Leader
Ijeoma Uzoma, PhD, DPARP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 212122
Drug Name: Glycopyrronium Bromide (Glycopyrrolate)
Sponsor: AstraZeneca

Background
Glycopyrrolate is an anticholinergic proposed for clinical use in combination with budesonide and formoterol in a metered dose inhaler, for twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

Glycopyrrolate was negative in the Ames test for bacterial gene reverse mutation. Further, glycopyrrolate was negative in the in vitro micronucleus assay in TK6 cells, and negative in the in vivo micronucleus assay in rats.

The Applicant conducted 2-year rat and mouse studies with Glycopyrrolate using the nose-only inhalation route of exposure.

Mouse Carcinogenicity Study
In a 2-year carcinogenicity study, B6C3F1 mice received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control; $CaCl_2$ and Distearoyl-sn-Glycero-3-phosphocholine [DSPC]), 0.347/0.335 (LD, M/F), 0.705/0.7 (MD, M/F), and 1.46/1.42 (HD, M/F) mg/kg/day.

Prior concurrence for doses used in this study was not obtained from the Executive Carcinogenicity Assessment Committee.

Treatment with glycopyrrolate had no effects on survival in male or female mice up to 104 weeks.

Dose-related decreases of absolute body weights were observed in males and females beginning around Week 3 and Week 11, respectively, and continuing over the course of study. Decreases of absolute body weights at the end of the study appeared to be potentially excessive (>10%) for MD Females (-15.9%), HD males (-15%), and HD

females (-27.7%). The Sponsor did not implement any dose reductions during the course of the study to minimize decreases of absolute body weights.

There were no statistically significant test article-related tumor findings in male or female mice.

Rat Carcinogenicity Study

The rat carcinogenicity study was a 104-week inhalation (nose-only) study in Sprague-Dawley rats (60/sex/group). Male and female rats received glycopyrronium bromide (glycopyrrolate) by inhalation (nose-only) at estimated achieved doses of 0 (air-control), 0 (vehicle-control; $CaCl_2$ + DSPC), 151.7/165.93 (LD, M/F), 302.9/330.66 (MD, M/F), and 620.45/684.14 (HD, M/F) µg/kg/day.

Prior concurrence for doses used in this study was not obtained from the Executive Carcinogenicity Assessment Committee.

Treatment with glycopyrrolate had no effects on survival of male or female rats. The Sponsor elected to terminate the entire study early (starting at Week 82) for all male and female groups due to low survival (22 of 60 [37%] females remaining) in the female air-control group at week 82. According to ECAC criteria for study termination, if the number of animals of a sex within the control group declines to 20, then all groups of that sex including drug-treated should be terminated. Based on these criteria, it was inappropriate to terminate female groups at that time. Further, in the male air-control and vehicle-control groups, 37 of 60 (62%) and 27 of 60 (45%) animals, respectively, were alive at week 82. Male groups were inappropriately terminated per ECAC criteria for study termination. The study duration was potentially inadequate to assess drug-induced tumor development.

Dose-related decreases of absolute body weights were observed in male and female rats beginning at approximately week 12 and continuing over the course of study. At Week 81, absolute body weights were reduced for drug-treated male groups by 11.8% (LD), 19.9% (MD), and 20% (HD) and for female drug-treated groups by 16% (LD), 11.4% (MD), and 23.4% (HD), relative to air-control groups. Decreases of absolute body weights appeared to be potentially excessive (>10%).

There were no statistically significant test article-related tumor findings in male or female rats.

Executive CAC Recommendations and Conclusions

Mouse study:

- The Committee concluded that body weight decreases in high dose males and mid and high dose females could confound interpretation. The Committee concurred that no drug-related neoplasms were observed at the low dose in females and the mid and low dose in males.

Rat study:

- The Committee concluded that the carcinogenicity study was inadequate in male and female rats due to early termination of the study.

Karen Davis Bruno, PhD
Chair, Executive CAC

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/s/

ROBEENA M AZIZ
04/18/2019 03:02:32 PM

KAREN L DAVIS BRUNO
04/18/2019 03:44:40 PM

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/s/

IJEOMA K UZOMA
08/19/2019 03:20:24 PM

TIMOTHY W ROBISON
08/19/2019 04:09:25 PM
I concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 212122
Drug Name:	budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol
Indication(s):	(b) (4)(b) (4), maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD (b) (4)
Studies	Two Year Nose-Only Inhalation Carcinogenicity Study in Rats and Mice.
Applicant:	Sponsor: ASTRAZENECA AB c/o AstraZeneca Pharmaceuticals 1800 Concord Pike Wilmington, DE 19803 Test facility: (b) (4)
Documents Reviewed:	Electronic submission, dated: December 14, 2018 via SN0003 Electronic data submitted on February 07, 2019 via SN0005.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewing Pharmacologist:	Ijeoma K. Uzoma, PhD
Project Manager:	Linda Ebonine
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in regular mice. These studies were intended to evaluate the potential carcinogenicity of a pressurized metered dose inhalation (pMDI) formulation of glycopyrrolate (glycopyrrolate pMDI), when administered via nose-only inhalation at appropriate drug levels for about 104 weeks in rats and in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Uzoma.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, one air control group and one placebo group. Three hundred fifty Sprague-Dawley rats of each sex were assigned to three treated groups, one air control group and one placebo control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 70 animals (60 animals designated for the final sacrifice, APPEARS THIS WAY ON ORIGINAL and 10 animals designated for a 52-week interim sacrifice), as indicated in Table 1. The pulmonary doses delivered levels for treated groups were 151.70, 302.92, and 620.45 µg/kg/day for male rats and 165.93, 330.66, and 684.14 µg/kg/day for female rats. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The active drug was not detected in the Air or Placebo aerosols. The placebo group received [Calcium Chloride Dihydrate (CaCl2) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC)], administered via nose inhalation for about 104 weeks in the same manner as the treated groups. The Air Control group for male and female rats was terminated at week 81. All the other groups stayed in the study for one more week and were sacrificed at week 82.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (µg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Air Control	1	ND	ND	70	70
Placebo control	2	ND	ND	70	70
Low	3	151.70	165.93	70	70
Medium	4	302.92	330.66	70	70
High	5	620.45	684.14	70	70

ND: The active drug was not detected in the Air or Placebo aerosols.
60 animals designated for the final sacrifice, and 10 animals designated for a 52-week interim sacrifice
Survival in Placebo control males and Air control females led to study termination at 81-82 weeks

During the administration period, all animals were checked for morbidity, mortality, injury, a minimum of twice daily (a.m. and p.m.). Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations included but were not limited to the following: reactivity to general stimuli and description of any abnormal behaviors, lesions, or appearances, if applicable. Special attention was paid to observe for clinical signs associated with the respiratory tract (such as apnea, labored breathing, rapid breathing, marked nasal discharge, etc.). Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights and food consumption for all animals were measured and recorded at receipt, prior to randomization and once weekly for the first 13 weeks of the study and once monthly thereafter.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The probability of survival was determined by the product-limit procedure of Kaplan and Meier (1958). Animals found dead of other natural causes were censored (i.e., interim sacrifices); animals dying from natural causes were not censored. Statistical analyses for possible exposure-related effects on survival performed using Cox's (1972) method for testing two groups equality.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 37, 27, 35, 32, and 37 in the air control, placebo control group, low, medium, and high dose groups, in male rats, respectively, and 22, 25, 29, 22, and 29 in air control, placebo control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report concluded that, there was no statistically significant increase or decrease in mortality across the placebo control or the air control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups, and the placebo control or the air control group in either sex of rats.

2.1.2. Tumor data analysis

Tumor incidence data were analyzed within each sex, using both the poly-3 statistical analysis as first described by Bailer and Portier (1988) and modified by Bieler and Williams (1993), and the Peto's mortality-prevalence method (Peto, 1980) without continuity correction, incorporating the context (incidental or fatal) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: weeks 0-52 (including interim sacrifices), 53-end of study (up to but excluding terminal sacrifice in week 83), and terminal sacrifice. Tumors classified as mortality-independent, such as, but not limited to, those of the mammary gland and skin, were analyzed with Peto's mortality independent method incorporating the day of detection.

For all organs, the incidence of each tumor type was analyzed with a 1-sided trend test using ordinal coefficients. In addition, pairwise comparisons with the control was conducted for each active treatment group. The trend tests and pairwise comparisons were conducted separately for the Air and Placebo control. In addition, a 2-sided comparison of the Placebo control group versus the Air control group was conducted. An exact permutation test was conducted for analyses with low tumor incidence.

All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the scheduled terminal sacrifice interval for the incidental finding analyses. All tumors in the scheduled terminal sacrifice interval were considered incidental for statistical analysis.

Adjustment for the multiplicity:

For multiplicity adjustment, the sponsor used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons. Site-specific background historical control database was used to determine whether the tumors should be designated as rare or common.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased glycopyrrolate (glycopyrrolate pMDI) dose. the pairwise comparisons showed statistically significant increases in the low dose group for the incidences of adenoma, mammary gland, in the mammary gland, when compared to the air control group in female rats with (p-value =0.0004 using Peto, p=0.0005 using asymptotic poly-3, and p=0.0008 using the conditional exact poly-3 tests), since this tumor type was considered as common tumor. Also, in female rats the pairwise comparisons showed statistically significant increases in the medium dose group for the incidences of adenoma, c-cell, in the thyroid gland, when compared to the placebo control group in female rats by the asymptotic poly-3 (p=0.0061).

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on February 07, 2019 via SN0005.

Animals designed for the interim sacrifice i.e. all the animal designated for the 52-week interim sacrifice (10/sex/group) were excluded for this study.

All male and female rats were sacrificed during the week 83, which is too short to enable animals to develop tumors during their later life.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 37, 27, 35, 32 and 37 in the air control, placebo control group, low, medium, and high dose groups, in male rats, respectively, and 22, 25, 29, 22, and 29 in the air control, placebo control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the placebo control group and the three treated groups in either sex of rats. The pairwise comparison showed a statistically significant decreased mortality in high dose group when compared to the placebo control group in male rats with p-value = 0.0449.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across placebo control group and the treated groups, as well as the pairwise comparisons of placebo control group with

each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (151.70, 302.92, and 620.45 for males and 165.93, 330.66, and 684.14 for females) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the placebo control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of placebo control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Placebo Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Air Cont (N=60)	0 mg Placebo Cont (N=60) P - Trend	165.93 µg Low (N=60) P - C vs. L	330.66 µg Med (N=60) P - C vs. M	684.14 µg High (N=60) P - C vs. H
Female	mammary gland(s)	adenoma, mammary gland	0/59 (19) NC	2/60 (23) 0.9835	10/60 (29) 0.0287[@]	1/60 (22) 0.8752	0/60 (22) 1.0000
	thyroid gland(s)	adenoma, c-cell	5/60 (23) NC	0/60 (21) 0.0574	2/60 (24) 0.2788	5/60 (25) 0.0388[*]	4/60 (25) 0.0775

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.05 for rare tumors in pairwise comparisons.
[@]: not statistically significant at 0.01 level for common tumor in pairwise comparisons.

Following the multiple testing adjustment method described above, this reviewer's analysis showed no statistically significant increasing dose response relationships across the placebo control and the treated groups in either male or female rats. the pairwise comparisons showed a statistically significant increase in the meduim dose group for the incidences of adenoma c-cell, in the thyroid gland, when compared to the placebo control group in female rats, (p= 0.0388), since this tumor type was considered as rare tumor.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. Three hundred B6C3F1 mice of each sex were assigned randomly to one of the five groups which included three treated groups one air control group and one placebo control group in equal size of 60 animals, as indicated in Table 3. The dose levels for treated groups were 0.347, 0.705, and 1.46 mg/kg/day for male mice and 0.335, 0.700, and 1.42 mg/kg/day for female mice. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The placebo group received (Calcium Chloride Dihydrate (CaCl2) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC)), administered via nose inhalation for about 104 in the same manner as the treated groups.

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Air Control	1	ND	ND	60	60
Placebo control	2	ND	ND	60	60
Low	3	0.347	0.335	60	60
Medium	4	0.705	0.700	60	60
High	5	1.46	1.42	60	60

ND: The active drug was not detected in the Air or Placebo aerosols

During the administration period, all animals were checked for morbidity, mortality, injury, a minimum of twice daily (a.m. and p.m.). Observations included but were not limited to the following: reactivity to general stimuli and description of any abnormal behaviors, lesions, or appearances, if applicable. Special attention was paid to observe for clinical signs associated with the respiratory tract (such as apnea, labored breathing, rapid breathing, marked nasal discharge, etc.). Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body

weights and food consumption for all animals were measured and recorded at receipt, prior to randomization and once weekly for the first 13 weeks of the study and once monthly thereafter. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized.

3.1. Sponsor's analyses

3.1.1 Survival analysis

Kaplan-Meier curves were presented graphically for male and female mice separately, and were used to estimate the survival function for each dose group following Test article exposure. Log-rank test was used to compare the survival distributions of groups. Dunnett-Hsu's procedure (Hsu, 1992) was used to identify statistically significant differences between each of two control groups and each test article-dosed group at the 0.05 level of significance.

Any animal with accidental injury that causes its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 46, 39, 43, 45, and 44, in air control, placebo, low, medium, and high dose groups in male mice, respectively, and 41, 40, 38, 43, and 38, in female mice, respectively. The sponsor's report concluded that there were no significant dose response and pairwise increases in treated groups when compared with either air control or placebo control group in either sex of mice.

3.1.2 Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as those used to analyze the rat tumor data.

The analysis of tumors was based on the following fixed time intervals: weeks 0-50, 51-80, 81-end of study (up to but excluding terminal sacrifice), and terminal sacrifice for both male and female mice. The actual dose levels were used as the scores.

Multiple testing adjustment:

trend tests were conducted at the 0.005 and 0.025 significance levels for common and rare tumors, respectively. Pairwise comparisons with the control groups were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1%.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis showed in male mice a statistically significant dose response relationships with the air control and active treatment groups in malignant adenocarcinoma in harderian gland (p=0.0033 using Peto, and p=0.0035 using asymptotic poly-3 test), and in female mice, the active treatment groups were statistically significant with

the air control and with the placebo control in malignant adenocarcinoma in mammary gland (p=0.0148, and p=0.0149, respectively using the asymptotic poly-3 test).

The pairwise comparisons showed statistically significant increases in the medium dose group for the incidences of histiocytic sarcoma in the systemic neoplasms, when compared to the placebo control group in male mice (p=0.0397, by the asymptotic poly-3 test). Also, in male mice the pairwise comparison in incidence between the air control and the placebo control was statistically significant (p=0.0155 by Peto test).

In female mice, the pairwise comparisons showed statistically significant increases in the low dose group for the incidences of adenoma in the intest-sm, duodenum, alveolar-bronchiolar adenoma in the right lung, and fibrosacoma in the skin when compared to the air control group (p=0.0362 by Peto, p<0.01 by the Peto, asymptotic poly-3, and conditional exact poly-3 tests, and p=0.0456 by asymptotic poly-3 test, respectively), and when compared to the placebo control group (p=0.0357 by the asymptotic poly-3 test, p<0.01 by the Peto, asymptotic poly-3, and conditional exact poly-3 tests, and p=0.0446 by the asymptotic poly-3 test, respectively). Also, the pairwise comparisons showed a statistically significant increase in the high dose group for the incidences of alveolar-bronchiolar adenoma in the right lung, when compared with both the air control and placebo control group in female mice (p<0.01 by the Peto and asymptotic poly-3 tests). the pairwise comparison between the air control and the placebo control showed a statistically significant increase incidence in adenoma, follicular cell in the thyroid glands in female mice (p=0.0031 by Peto test).

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer’s findings:

This reviewer’s analysis showed the numbers of mice surviving to their terminal necropsy were 46, 39, 43, 45, and 44, in air control, placebo control, low, medium, and high dose groups in male mice, respectively, and 41, 40, 38, 43, and 38, in female mice, respectively. This reviewer’s analysis showed no statistically significant increase in mortality across the placebo control group and the three treated groups in either sex of mice. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the placebo control group in either sex of mice.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise

comparisons of placebo control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

For mouse study, this reviewer used similar test levels of significance as those used for rat study to adjust for multiple testing. This reviewer used the number of animals bearing tumors in the placebo control group to determine the common or rare tumor status.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of placebo control and treated groups are reported in Table 4.

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Placebo Control Group in Mice

Sex	Organ Name	Tumor Name	0 mg/Kg Air Cont. (N=60)	0 mg/Kg Placebo Cont. (N=60) P - Trend	0.335mg/kg Low (N=60) P - PC vs. L	0.7 mg/kg Med (N=60) P - PC vs. M	1.42 mg/kg High (N=60) P - PC vs. H
Male	Systemic Neoplasms	Lymphoma	1/60 (54) NC	1/60 (53) 0.6462	7/60 (55) 0.0340@	3/60 (54) 0.3160	2/60 (52) 0.4928
Female	Lung, Right	Alveolar-Bronchiolar Adenoma	0/60 (52) NC	0/60 (52) 0.0680	7/60 (51) 0.0058*	1/60 (54) 0.5094	6/60 (51) 0.0126*
	Lung, Left + Right	Alveolar-Bronchiolar Adenoma	3/60 (52) NC	2/60 (52) 0.1534	8/60 (51) 0.0430@	1/60 (54) 0.8854	7/60 (51) 0.0756

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.05 for rare tumors, in pairwise comparisons.
@: not statistically significant at 0.05 level in rare tumor nor at 0.01 level in common tumor for pairwise comparison.

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased glycopyrrolate (glycopyrrolate pMDI) dose in either sex of mice. The pairwise comparisons showed statistically significant increases in the low and high dose groups for the incidences of alveolar-bronchiolar adenoma in the right lung, when compared to the placebo control group in female mice (p-values =0.0058, and 0.0126, respectively), since this tumor type was considered as rare tumors.

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in B6C3F1 mice. These studies were intended to assess the carcinogenic potential of glycopyrrolate (glycopyrrolate pMDI) (P005672-HC1) in rats and mice when administered via nose-only inhalation at appropriate drug levels for about 104 weeks in rats and in mice.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of

these two experiments there were three treated groups, one air control group and one placebo group. Three hundred fifty Sprague-Dawley rats of each sex were assigned to three treated groups, one air control group and one placebo group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals designated for the final sacrifice, the 10 animals/sex/group, designated for a 52-week interim sacrifice were excluded for this study. The pulmonary doses delivered levels for treated groups were 151.70, 302.92, and 620.45 μg/kg/day for male rats and 165.93, 330.66, and 684.14 μg/kg/day for female rats. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The active drug was not detected in the Air or Placebo aerosols. The placebo group received [Calcium Chloride Dihydrate (CaCl2) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC)], administered via nose inhalation for about 104 weeks in the same manner as the treated groups. The Air Control group for male and female rats was terminated at week 81. All the other groups stayed in the study for one more week and were sacrificed at week 82.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 37, 27, 35, 32 and 37 in the air control, placebo control group, low, medium, and high dose groups, in male rats, respectively, and 22, 25, 29, 22, and 29 in the air control, placebo control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the placebo control group and the three treated groups in either sex of rats. The pairwise comparison showed a statistically significant decreased mortality in high dose group when compared to the placebo control group in male rats with p-value = 0.0449.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analysis showed no statistically significant increasing dose response relationships across the placebo control and the treated groups in either male or female rats. the pairwise comparisons showed a statistically significant increase in the medium dose group for the incidences of adenoma c-cell, in the thyroid gland, when compared to the placebo control group in female rats, (p= 0.0388), since this tumor type was considered as rare tumor.

No other significant dose response relationship or pairwise comparisons were noted in either sex.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. Three hundred B6C3F1 mice of each sex were assigned randomly to one of the five groups which included three treated groups one air control group and one placebo control group in equal size of 60 animals, as indicated in Table 3. The dose levels for treated groups were 0.347, 0.705, and 1.46 mg/kg/day for male mice and 0.335, 0.700, and 1.42 mg/kg/day for female mice. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The placebo group received (Calcium Chloride Dihydrate (CaCl2) and 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC)), administered via nose inhalation for about 104 in the same manner as the treated groups.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 46, 39, 43, 45, and 44, in air control, placebo control, low, medium, and high dose groups in male mice, respectively, and 41, 40, 38, 43, and 38, in female mice, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the placebo control group and the three treated groups in either sex of mice. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the placebo control group in either sex of mice.

For tumor data, Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with

increased glycopyrrolate (glycopyrrolate pMDI) dose in either sex of mice. The pairwise comparisons showed statistically significant increases in the low and high dose groups for the incidences of alveolar-bronchiolar adenoma in the right lung, when compared to the placebo control group in female mice (p-values =0.0058, and 0.0126, respectively), since this tumor type was considered as rare tumors.

No other significant dose response relationship or pairwise comparisons were noted in either sex of mice

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
Hepei Chen, secondary reviewer

cc:
Archival NDA 212122- GLYCOPYRROLATE (GLYCOPYRROLATE PMDI)

Dr. Tsong Ms. Patrician
Dr. Lin Linda Ebonine
Dr. Uzoma

5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

	0 µg|kg|day Air Control		0 µg|kg|day Placebo Control		151.70 µg|kg|day Low		302.92 µg|kg|day Med		620.45 µg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	.	.	7	11.67	7	11.67	3	5.00	1	1.67
53 - 78	20	33.33	25	53.33	12	31.67	17	33.33	19	33.33
79 - 83	3	38.33	1	55.00	6	41.67	8	46.67	3	38.33
Ter. Sac.	37	61.67	27	45.00	35	58.33	32	53.33	37	61.67
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

The Air Control group was terminated at week 81. All the other groups stayed in the study for one more week and were sacrificed at week 82. Animals designed for the interim sacrifice (10/sex/group) were excluded for this study.

Table1B: Intercurrent Mortality Rate
Female Rats

	0 µg|kg|day Air Control		0 µg |kg|day Placebo Control		165.93 µg|kg|day Low		330.66 µg|kg|day Med		684.14 µg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	8	13.33	7	11.67	5	8.33	5	8.33	4	6.67
53 - 78	27	58.33	23	50.00	23	46.67	24	48.33	26	50.00
79 - 83	3	63.33	5	58.33	3	51.67	9	63.33	1	51.67
Ter. Sac.	22	36.67	25	41.67	29	48.33	22	36.67	29	48.33
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

The Air Control group was terminated at week 81. All the other groups stayed in the study for one more week and were sacrificed at week 82. Animals designed for the interim sacrifice (10/sex/group) were excluded for this study.

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Placebo Cont. Low, Med, High	P-value for Placebo Cont. vs Low	P-value for Placebo Cont. vs Med	P-value for Placebo Cont. vs High
Dose-Response (Likelihood Ratio)	0.0731	0.1228	0.1893	0.0449*
Homogeneity (Log-Rank)	0.1726	0.1196	0.1841	0.0427*

* = statistically significant at the 0.05 significance level.

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Placebo Cont. Low, Med, high	P-value for Placebo Cont. vs Low	P-value for Placebo Cont. vs Med	P-value for Placebo Cont. vs High
Dose-Response (Likelihood Ratio)	0.6309	0.4153	0.8163	0.4441
Homogeneity (Log-Rank)	0.6134	0.4097	0.8139	0.4391

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo (N=60) P - Trend	151.70 mg Low (N=60) P - PC vs. L	302.92 mg Med (N=60) P -PC vs. M	620.45 mg High (N=60) P - PC vs. H
Adrenal Gland(S)	Carcinoma, Cortex	0/60 (25) NC	0/60 (22) 0.7708	1/60 (24) 0.5217	0/60 (25) NC	0/60 (25) NC
	Pheochromocytoma	8/60 (29) NC	9/60 (27) 0.5937	5/60 (26) 0.9309	7/60 (29) 0.8547	8/60 (30) 0.7993
Brain	Astrocytoma	0/60 (25) NC	0/60 (22) 0.2680	0/60 (24) NC	0/60 (25) NC	1/60 (26) 0.5417
	Glioma	0/60 (25) NC	2/60 (23) 0.3885	0/60 (24) 1.0000	1/60 (25) 0.8976	2/60 (26) 0.7409
Intestine, Duodenum	Adenoma	0/60 (25) NC	1/60 (22) 1.0000	0/60 (24) 1.0000	0/60 (25) 1.0000	0/60 (25) 1.0000
Multicentric	Histiocytic Sarcoma	0/60 (25) NC	1/60 (22) 0.6404	2/60 (25) 0.5489	0/60 (25) 1.0000	1/60 (26) 0.7952
	Lymphoma	0/60 (25) NC	0/60 (22) 0.3291	1/60 (25) 0.5319	1/60 (25) 0.5319	1/60 (26) 0.5417
Pancreas	Adenoma, Islet Cell	2/60 (26) NC	0/60 (22) 0.5208	0/59 (24) NC	1/60 (25) 0.5319	0/60 (25) NC
	Carcinoma, Islet Cell	0/60 (25) NC	0/60 (22) 0.0727	0/59 (24) NC	1/60 (25) 0.5319	2/60 (26) 0.2881
	Adenoma/Carcinoma Islet Cell	2/60 (26) NC	0/60 (22) 0.0852	0/60 (24) NC	2/60 (26) 0.2881	2/60 (26) 0.2881
	Schwannoma	0/60 (25) NC	1/60 (22) 1.0000	0/59 (24) 1.0000	0/60 (25) 1.0000	0/60 (25) 1.0000
Pituitary Gland	Adenoma	28/59 (41) NC	28/60 (38) 0.9682	21/57 (35) 0.9324	20/60 (36) 0.9701	19/60 (37) 0.9878
Prostate Gland	Carcinosarcoma	0/60 (25) NC	1/60 (22) 1.0000	0/60 (24) 1.0000	0/60 (25) 1.0000	0/60 (25) 1.0000
Salivary Gland(S), Mandibular	Schwannoma	0/60 (25) NC	0/60 (22) 0.2680	0/60 (24) NC	0/60 (25) NC	1/60 (26) 0.5417
Skeletal Muscle	Rhabdomyosarcoma	0/60 (25) NC	1/59 (22) 1.0000	0/60 (24) 1.0000	0/60 (25) 1.0000	0/60 (25) 1.0000
Skin	Carcinoma, Squamous Cell	0/60 (25) NC	0/60 (22) 0.2680	0/60 (24) NC	0/60 (25) NC	1/60 (26) 0.5417
	Fibroma	1/60 (26) NC	1/60 (22) 0.8675	1/60 (24) 0.7768	1/60 (25) 0.7863	0/60 (25) 1.0000
	Keratoacanthoma	0/60 (25) NC	0/60 (22) 0.2680	0/60 (24) NC	0/60 (25) NC	1/60 (26) 0.5417

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo (N=60) P - Trend	151.70 mg Low (N=60) P - PC vs. L	302.92 mg Med (N=60) P -PC vs. M	620.45 mg High (N=60) P - PC vs. H
	Lipoma	0/60 (25) NC	0/60 (22) 0.6524	1/60 (24) 0.5217	1/60 (25) 0.5319	0/60 (25) NC
Spleen	Hemangiosarcoma	0/60 (25) NC	1/60 (22) 1.0000	0/60 (24) 1.0000	0/60 (25) 1.0000	0/60 (25) 1.0000
Testis(Es)	Adenoma, Interstitial Cell	2/60 (26) NC	3/60 (24) 1.0000	0/60 (24) 1.0000	0/60 (25) 1.0000	0/60 (25) 1.0000
	Adenoma, Interstitial Cell (2nd)	0/60 (25) NC	1/60 (22) 1.0000	0/60 (24) 1.0000	0/60 (25) 1.0000	0/60 (25) 1.0000
Thyroid Gland(S)	Adenoma, C-Cell	1/60 (26) NC	3/60 (24) 0.9270	1/60 (24) 0.9454	4/60 (27) 0.5683	0/60 (25) 1.0000
	Adenoma, Follicular Cell	1/60 (26) NC	1/60 (22) 0.9493	1/60 (24) 0.7768	0/60 (25) 1.0000	0/60 (25) 1.0000
	Carcinoma, C-Cell	1/60 (26) NC	0/60 (22) 0.2680	0/60 (24) NC	0/60 (25) NC	1/60 (26) 0.5417
	Adenoma/Carcinoma, C-Cell	2/60 (26) NC	3/60 (24) 0.8019	1/60 (24) 0.9454	4/60 (27) 0.5683	1/60 (26) 0.9539
Urinary Bladder	Papilloma, Transitional Cell	0/59 (25) NC	0/60 (22) 0.7708	1/60 (24) 0.5217	0/60 (25) NC	0/60 (25) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont (N=60)	0 mg Placebo (N=60) P - Trend	165.93 mg Low (N=60) P - PC vs. L	330.66 mg Med (N=60) P - PC vs. M	684.14 mg High (N=60) P - PC vs. H
Adrenal Gland(S)	Adenoma	0/60 (20) NC	0/60 (21) 0.7546	3/60 (24) 0.1426	0/60 (22) NC	0/60 (22) NC
	Carcinoma, Cortex	0/60 (20) NC	1/60 (22) 1.0000	0/60 (23) 1.0000	0/60 (22) 1.0000	0/60 (22) 1.0000
	Pheochromocytoma	1/60 (20) NC	0/60 (21) 0.3119	1/60 (23) 0.5227	1/60 (22) 0.5116	1/60 (23) 0.5227
Bone, Femur W/ Marrow	Lymphoma	0/60 (20) NC	0/60 (21) 0.7640	1/60 (24) 0.5333	0/60 (22) NC	0/60 (22) NC
Bone, Sternum W/ Marrow	Lymphoma	0/60 (20) NC	0/60 (21) 0.7640	1/60 (24) 0.5333	0/60 (22) NC	0/59 (22) NC
Liver	Cholangioma	1/60 (20) NC	0/60 (21) NC	0/60 (23) NC	0/60 (22) NC	0/60 (22) NC
Lung(S)	Chordoma	1/60 (20) NC	0/60 (21) NC	0/60 (23) NC	0/60 (22) NC	0/60 (22) NC
Mammary Gland(S)	Adenocarcinoma, Mammary Gland	10/59 (26) NC	13/60 (31) 0.8921	9/60 (29) 0.8737	7/60 (27) 0.9411	7/60 (27) 0.9411
	Adenoma, Mammary Gland	0/59 (19) NC	2/60 (23) 0.9835	10/60 (29) 0.0287	1/60 (22) 0.8752	0/60 (22) 1.0000
	Fibroadenoma	11/59 (28) NC	14/60 (30) 0.7920	19/60 (34) 0.3138	17/60 (33) 0.4475	12/60 (30) 0.7826
	Adenocarcinoma / Adenoma	10/60 (26) NC	14/60 (31) 0.9737	17/60 (33) 0.3983	8/60 (28) 0.9442	7/60 (27) 0.9645
Multicentric	Lymphoma	2/60 (21) NC	1/60 (22) 0.9423	1/60 (24) 0.7768	0/60 (22) 1.0000	0/60 (22) 1.0000
Nose/Turbinate 4	Osteochondroma	0/60 (20) NC	0/60 (21) 0.2584	0/60 (23) NC	0/60 (22) NC	1/60 (23) 0.5227
	Osteosarcoma	0/60 (20) NC	0/60 (21) 0.7614	1/60 (23) 0.5227	0/60 (22) NC	0/60 (22) NC
Pancreas	Adenoma, Islet Cell	1/60 (20) NC	2/60 (22) 0.8835	0/60 (23) 1.0000	2/60 (23) 0.7132	0/60 (22) 1.0000
Pituitary Gland	Adenoma Pars Distallis	39/60 (44) NC	38/59 (44) 0.6795	35/60 (44) 0.8718	30/60 (40) 0.9460	35/59 (43) 0.8216
	Adenoma, Pars Intermedia	2/60 (21) NC	0/59 (21) 0.2584	0/60 (23) NC	0/60 (22) NC	1/59 (23) 0.5227
	Adenoma Pars Distallis / Pars intermedia	41/60 (45) NC	38/60 (44) 0.6582	35/60 (44) 0.8718	30/60 (40) 0.9460	36/60 (44) 0.8087

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont (N=60)	0 mg Placebo (N=60) P - Trend	165.93 mg Low (N=60) P - PC vs. L	330.66 mg Med (N=60) P - PC vs. M	684.14 mg High (N=60) P - PC vs. H
Skin	Fibroma	0/60 (20) NC	1/60 (22) 1.0000	0/60 (23) 1.0000	0/59 (21) 1.0000	0/60 (22) 1.0000
	Papilloma	0/60 (20) NC	1/60 (22) 1.0000	0/60 (23) 1.0000	0/59 (21) 1.0000	0/60 (22) 1.0000
Thymus	Lymphoma	2/59 (21) NC	0/58 (21) NC	0/57 (21) NC	0/56 (20) NC	0/58 (22) NC
Thyroid Gland(S)	Adenoma, C-Cell	5/60 (23) NC	0/60 (21) 0.0574	2/60 (24) 0.2788	5/60 (25) 0.0388*	4/60 (25) 0.0775
	Adenoma, Follicular Cell	0/60 (23) NC	1/60 (22) 0.9410	1/60 (23) 0.7667	0/60 (22) 1.0000	0/60 (22) 1.0000
	Carcinoma, C-Cell	0/60 (20) NC	2/60 (22) 1.0000	0/60 (23) 1.0000	0/60 (22) 1.0000	0/60 (22) 1.0000
	Adenoma / Carcinoma C-Cell	5/60 (23) NC	2/60 (22) 0.2106	2/60 (24) 0.7287	5/60 (25) 0.2647	4/60 (25) 0.3975
Urinary Bladder	Papilloma, Transitional Cell	1/58 (19) NC	0/60 (21) NC	0/60 (23) NC	0/60 (22) NC	0/60 (22) NC
Uterus	Adenocarcinoma, Endometrial	0/60 (20) NC	1/60 (22) 1.0000	0/60 (23) 1.0000	0/60 (22) 1.0000	0/60 (22) 1.0000
	Endometrial Stromal Sarcoma	1/58 (19) NC	0/60 (21) 0.5000	0/60 (23) NC	1/60 (22) 0.5116	0/60 (22) NC
	Endometrial Stromal Sarcoma/Polyp	1/60 (21) NC	3/60 (23) 0.7938	0/60 (23) 1.0000	1/60 (22) 0.9406	1/60 (23) 0.9457
	Polyp, Endometrial-Stromal	0/60 (20) NC	3/60 (23) 0.8067	0/60 (23) 1.0000	0/60 (22) 1.0000	1/60 (23) 0.9457
	Polyp, Glandular	1/60 (20) NC	3/60 (23) 0.2127	1/60 (23) 0.9457	0/60 (22) 1.0000	4/60 (24) 0.5249

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.05 for rare tumors, in pairwise comparisons.

Figure 1A: Kaplan-Meier Survival Curves for
Male Rats

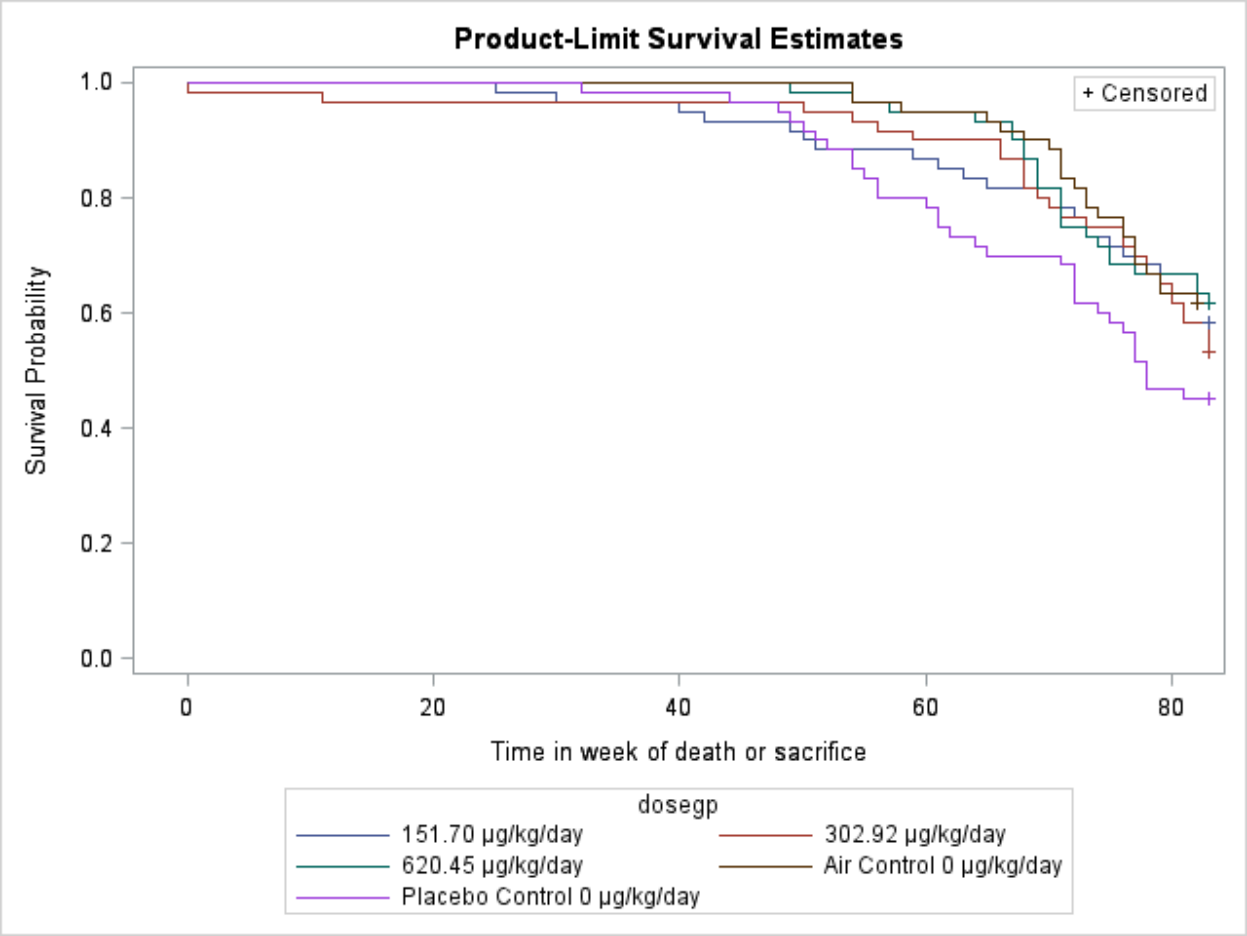


Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

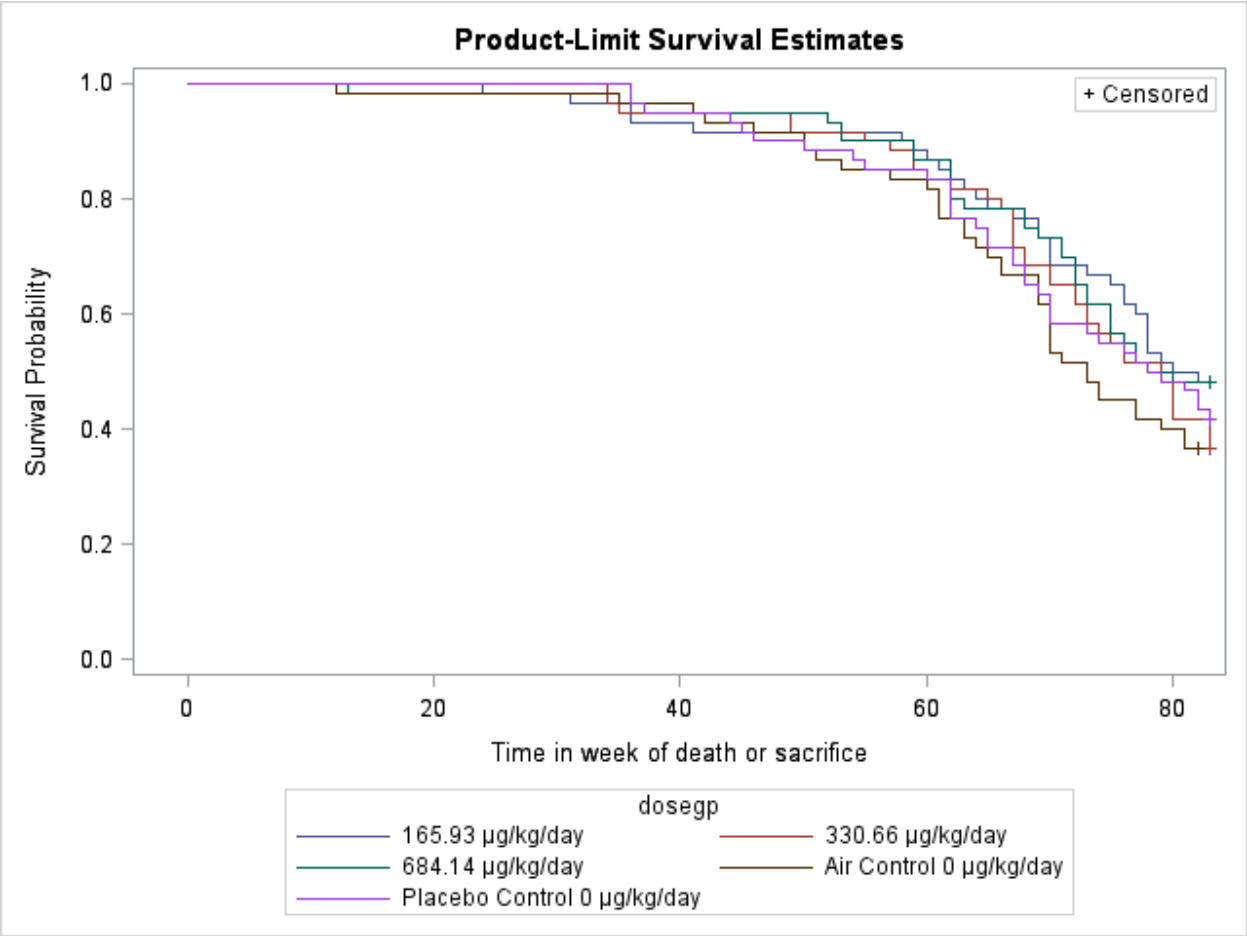


Table4A: Intercurrent Mortality Rate
Male Mice

	0 mg|kg|day Air Control		0 mg|kg|day Placebo Control		0.347mg|kg|day Low		0.705mg|kg|day Med		1.46mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	1	1.67	.	.	1	1.67	1	1.67	3	5.00
53 - 78	3	6.67	3	5.00	2	5.00	6	11.67	4	11.67
79 - 92	5	15.00	10	21.67	7	16.67	3	16.67	3	16.67
93 - 106	5	23.33	8	35.00	7	28.33	5	25.00	6	26.67
Ter. Sac.	46	76.67	39	65.00	43	71.67	45	75.00	44	73.33
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Table4B: Intercurrent Mortality Rate
Female Mice

	0mg|kg|day Air Control		0mg|kg|day Placebo Control		0.335mg|kg|day Low		0.700mg|kg|day Med		1.42mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	2	3.33	3	5.00	4	6.67	2	3.33	4	6.67
53 - 78	4	10.00	2	8.33	4	13.33	3	8.33	4	13.33
79 - 92	5	18.33	5	16.67	4	20.00	3	13.33	4	20.00
93 - 105	8	31.67	10	33.33	10	36.67	9	28.33	10	36.67
Ter. Sac.	41	68.33	40	66.67	38	63.33	43	71.67	38	63.33
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	**P-value for Placebo Cont. Low, Med, high**	**P-value for Placebo Cont. vs Low**	**P-value for Placebo Cont. vs Med**	**P-value for Placebo Cont. vs High**
Dose-Response (Likelihood Ratio)	0.4340	0.4304	0.3083	0.3862
Homogeneity (Log-Rank)	0.7201	0.4282	0.3084	0.3856

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	**P-value for Placebo Cont. Low, Med, high**	**P-value for Placebo Cont. vs Low**	**P-value for Placebo Cont. vs Med**	**P-value for Placebo Cont. vs High**
Dose-Response (Likelihood Ratio)	0.7990	0.6154	0.6104	0.6692
Homogeneity (Log-Rank)	0.7323	0.6129	0.6090	0.6672

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo Cont. (N=60) P - Trend	0.347 mg Low (N=60) P - PC vs. L	0.705 mg Med(N=60) P - PC vs. M	1.46 mg High (N=60) P - PC vs. H
Adrenal Glands	Adenoma, Subcapsular Cell	1/60 (54) NC	1/60 (53) 0.9384	1/60 (54) 0.7570	0/60 (53) 1.0000	0/60 (52) 1.0000
	Adenoma, Subcapsular Cell, Unilateral	0/60 (54) NC	1/60 (53) 1.0000	0/60 (54) 1.0000	0/60 (53) 1.0000	0/60 (52) 1.0000
	Adenoma Subcapsular Cell + Cell Unilateral	1/60 (54) NC	2/60 (53) 0.9850	1/60 (54) 0.8820	0/60 (53) 1.0000	0/60 (52) 1.0000
	Carcinoma, Cortex	1/60 (54) NC	0/60 (53) NC	0/60 (54) NC	0/60 (53) NC	0/60 (52) NC
	Pheochromocytoma, Medulla, Unilateral	0/60 (54) NC	1/60 (53) 1.0000	0/60 (54) 1.0000	0/60 (53) 1.0000	0/60 (52) 1.0000
Bone Marrow, Femur	Mast Cell Tumor	0/60 (54) NC	0/60 (53) 0.2453	0/60 (54) NC	0/60 (53) NC	1/60 (52) 0.4952
Harderian Glands	Adenocarcinoma	0/60 (54) NC	0/60 (53) 0.2488	0/60 (54) NC	0/60 (53) NC	1/60 (53) 0.5000
	Adenocarcinoma, Unilateral	0/60 (54) NC	3/60 (53) 0.2027	1/60 (54) 0.9433	2/60 (54) 0.8243	4/60 (53) 0.5000
	Adenoma, Unilateral	9/60 (55) NC	4/60 (53) 0.9404	4/60 (54) 0.6526	2/60 (53) 0.8974	1/60 (52) 0.9703
	Adenocarcinoma+ Adenoma, Unilateral Adenocarcinoma, Unilateral	9/60 (55) NC	7/60 (54) 0.5630	5/60 (55) 0.8291	4/60 (54) 0.8991	6/60 (54) 0.7221
Intest-Lg, Cecum	Leiomyosarcoma	0/60 (54) NC	0/60 (53) 0.4953	0/60 (54) NC	1/60 (53) 0.5000	0/60 (52) NC
Intest-Sm, Duodenum	Adenoma	1/60 (54) NC	0/60 (53) 0.0590	0/60 (54) NC	1/60 (53) 0.5000	2/60 (52) 0.2429
Intest-Sm, Jejunum	Adenocarcinoma	0/60 (54) NC	0/60 (53) 0.7500	1/60 (54) 0.5047	0/60 (53) NC	0/60 (52) NC
	Adenoma	0/60 (54) NC	0/60 (53) 0.2453	0/60 (54) NC	0/60 (53) NC	1/60 (52) 0.4952
	Adenocarcinoma/Adenoma	0/60 (54) NC	0/60 (53) 0.3081	1/60 (54) 0.5047	0/60 (53) NC	1/60 (52) 0.4952
Liver	Hepatocellular Adenoma	20/60 (56) NC	17/60 (54) 0.6967	11/60 (54) 0.9383	14/60 (53) 0.7853	13/60 (54) 0.8587
	Hepatocellular Carcinoma	19/60 (57) NC	18/60 (55) 0.9599	11/60 (56) 0.9633	3/60 (53) 1.0000	10/60 (53) 0.9694
	Hepatocellular Adenoma/Carcinoma	34/60 (58) NC	32/60 (56) 0.9494	21/60 (56) 0.9886	17/60 (54) 0.9982	21/60 (54) 0.9827

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo Cont. (N=60) P - Trend	0.347 mg Low (N=60) P - PC vs. L	0.705 mg Med(N=60) P - PC vs. M	1.46 mg High (N=60) P - PC vs. H
	Hepatocholangiocarcinoma	0/60 (54) NC	1/60 (53) 1.0000	0/60 (54) 1.0000	0/60 (53) 1.0000	0/60 (52) 1.0000
Lung, Left	Alveolar-Bronchiolar Adenoma	2/60 (54) NC	3/60 (53) 0.7546	0/60 (54) 1.0000	1/60 (53) 0.9411	1/60 (52) 0.9387
	Alveolar-Bronchiolar Carcinoma	2/60 (54) NC	2/60 (53) 0.7225	2/60 (54) 0.6981	2/60 (53) 0.6911	1/60 (52) 0.8750
Lung, Right	Alveolar-Bronchiolar Adenoma	6/60 (55) NC	6/60 (53) 0.9903	9/60 (54) 0.3031	4/60 (53) 0.8403	1/60 (52) 0.9932
	Alveolar-Bronchiolar Carcinoma	2/60 (54) NC	7/60 (53) 0.8825	7/60 (54) 0.6268	2/60 (53) 0.9843	4/60 (52) 0.8934
Lung Left + Right	Alveolar-Bronchiolar Adenoma	7/60 (55) NC	9/60 (54) 0.9931	9/60 (54) 0.6015	5/60 (53) 0.9196	2/60 (52) 0.9952
	Alveolar-Bronchiolar Carcinoma	4/60 (54) NC	8/60 (54) 0.8514	8/60 (54) 0.6063	4/60 (53) 0.9343	5/60 (52) 0.8671
	Alveolar Bronchiolar Adenoma/Carcinoma	10/60 (55) NC	17/60 (55) 0.9946	17/60 (55) 0.5816	9/60 (54) 0.9762	7/60 (52) 0.9924
Pancreas	Adenoma, Islet Cell	0/60 (54) NC	1/60 (53) 0.4313	0/60 (54) 1.0000	0/60 (53) 1.0000	1/60 (52) 0.7476
Pituitary Gland	Adenoma, Pars Distalis	0/60 (54) NC	1/60 (53) 0.4313	0/60 (54) 1.0000	0/60 (53) 1.0000	1/60 (52) 0.7476
Skin	Fibrosarcoma	1/60 (55) NC	0/60 (53) NC	0/60 (54) NC	0/60 (53) NC	0/60 (52) NC
	Sarcoma Nos	0/60 (54) NC	0/60 (53) 0.4953	0/60 (54) NC	1/60 (53) 0.5000	0/60 (52) NC
Stomach	Adenoma, Glandular	0/60 (54) NC	0/60 (53) 0.6209	1/60 (54) 0.5047	1/60 (53) 0.5000	0/60 (52) NC
Systemic Neoplasms	Hemangiosarcoma	5/60 (55) NC	1/60 (53) 0.4916	4/60 (54) 0.1874	2/60 (53) 0.5000	2/60 (52) 0.4928
	Histiocytic Sarcoma	2/60 (54) NC	0/60 (53) 0.6236	2/60 (55) 0.2570	3/60 (53) 0.1214	0/60 (52) NC
	Lymphoma	1/60 (54) NC	1/60 (53) 0.6432	7/60 (55) 0.0340	3/60 (54) 0.3160	2/60 (52) 0.4928
Testes	Adenoma, Interstitial Cell	0/60 (54) NC	2/60 (53) 0.6346	0/60 (54) 1.0000	0/60 (53) 1.0000	1/60 (52) 0.8750
	Adenoma, Interstitial Cell, Unilateral	1/60 (54) NC	0/60 (53) 0.7500	1/60 (54) 0.5047	0/60 (53) NC	0/60 (52) NC
	Adenoma Interstitial Cell + Interstitial Cell, Unilateral	1/60 (54) NC	2/60 (53) 0.7220	1/60 (54) 0.8820	0/60 (53) 1.0000	1/60 (52) 0.8750

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo Cont. (N=60) P - Trend	0.347 mg Low (N=60) P - PC vs. L	0.705 mg Med(N=60) P - PC vs. M	1.46 mg High (N=60) P - PC vs. H
Thyroid Glands	Adenoma, Follicular Cell	4/60 (54) NC	6/60 (53) 0.9886	4/60 (54) 0.8477	1/60 (53) 0.9937	1/60 (52) 0.9932
	Adenoma, Follicular Cell, Unilateral	4/60 (54) NC	13/60 (53) 0.7645	7/60 (54) 0.9634	13/60 (53) 0.5891	8/60 (52) 0.9221
	Adenoma Follicular Cell + Follicular Cell, Unilateral	8/60 (54) NC	19/60 (53) 0.9657	11/60 (54) 0.9776	14/60 (53) 0.8961	9/60 (52) 0.9916
Urinary Bladder	Sarcoma Nos	0/60 (54) NC	1/60 (53) 1.0000	0/60 (54) 1.0000	0/60 (53) 1.0000	0/60 (52) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo Cont (N=60) P - Trend	335 mg Low (N=60) P - PC vs. L	700 mg Med(N=60) P - PC vs. M	1420 mg High (N=60) P - PC vs. H
Adrenal Glands	Adenoma, Cortex, Unilateral	0/60 (52) NC	1/60 (53) 0.8260	1/60 (50) 0.7377	1/60 (53) 0.7524	0/60 (50) 1.0000
	Adenoma, Subcapsular Cell, Unilateral	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
	Pheochromocytoma, Medulla, Unilateral	0/60 (52) NC	1/60 (52) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
Bone Marrow, Femur	Hemangiosarcoma	0/60 (52) NC	0/60 (52) 0.2439	0/60 (50) NC	0/60 (53) NC	1/60 (50) 0.4902
Cervix	Leiomyoma	0/60 (52) NC	0/60 (52) 0.5024	0/60 (50) NC	1/60 (53) 0.5048	0/60 (50) NC
	Leiomyosarcoma	0/60 (52) NC	0/60 (52) 0.2439	0/60 (50) NC	0/60 (53) NC	1/60 (50) 0.4902
Harderian Glands	Adenocarcinoma	0/60 (52) NC	0/60 (52) 0.7463	1/60 (50) 0.4902	0/60 (53) NC	0/60 (50) NC
	Adenocarcinoma, Unilateral	1/60 (53) NC	1/60 (53) 0.1467	0/60 (50) 1.0000	0/60 (53) 1.0000	2/60 (50) 0.4779
	Adenoma	0/60 (52) NC	0/60 (52) 0.7463	1/60 (50) 0.4902	0/60 (53) NC	0/60 (50) NC
	Adenoma, Unilateral	1/60 (52) NC	5/60 (53) 0.8617	2/60 (50) 0.9343	1/60 (53) 0.9865	2/60 (50) 0.9343
	Adenocarcinoma/ Adenoma Unilateral	2/60 (53) NC	6/60 (53) 0.7374	4/60 (51) 0.8243	1/60 (53) 0.9937	4/60 (50) 0.8157
Intest-Sm, Duodenum	Adenoma	0/60 (52) NC	0/60 (52) 0.8428	3/60 (50) 0.1142	0/60 (53) NC	0/60 (50) NC
	Carcinoma	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
Kidneys	Adenoma, Tubule, Unilateral	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
Lacrimal Glands	Mast Cell Tumor, Unilateral	0/60 (52) NC	1/60 (53) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
Liver	Hepatocellular Adenoma	4/60 (52) NC	8/60 (52) 0.9999	0/60 (50) 1.0000	1/60 (53) 0.9988	0/60 (50) 1.0000
	Hepatocellular Carcinoma	1/60 (52) NC	2/60 (52) 0.6879	1/60 (50) 0.8713	1/60 (53) 0.8821	1/60 (50) 0.8713
	Hepatocellular Adenoma/Carcinoma	5/60 (52) NC	10/60 (52) 0.9987	1/60 (50) 0.9997	2/60 (53) 0.9983	1/60 (50) 0.9997

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo Cont (N=60) P - Trend	335 mg Low (N=60) P - PC vs. L	700 mg Med(N=60) P - PC vs. M	1420 mg High (N=60) P - PC vs. H
Lung, Left	Alveolar-Bronchiolar Adenoma	3/60 (52) NC	2/60 (52) 0.4218	1/60 (50) 0.8713	0/60 (53) 1.0000	2/60 (50) 0.6763
	Alveolar-Bronchiolar Carcinoma	1/60 (53) NC	1/60 (52) 0.4292	0/60 (50) 1.0000	0/60 (53) 1.0000	1/60 (50) 0.7426
	Osteosarcoma, Metastatic	0/60 (52) NC	1/60 (53) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
Lung, Right	Alveolar-Bronchiolar Adenoma	0/60 (52) NC	0/60 (52) 0.0680	7/60 (51) 0.0058*	1/60 (54) 0.5094	6/60 (51) 0.0126*
	Alveolar-Bronchiolar Carcinoma	2/60 (53) NC	1/60 (52) 0.2556	1/60 (50) 0.7426	2/60 (54) 0.5143	2/60 (50) 0.4851
	Osteosarcoma, Metastatic	1/60 (52) NC	1/60 (53) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
Lung, Left + Right	Alveolar-Bronchiolar Adenoma	3/60 (52) NC	2/60 (52) 0.1534	8/60 (51) 0.0430	1/60 (54) 0.8854	7/60 (51) 0.0756
	Alveolar-Bronchiolar Carcinoma	2/60 (53) NC	2/60 (52) 0.2208	1/60 (50) 0.8713	2/60 (54) 0.7053	3/60 (50) 0.4812
	Alveolar Bronchiolar Adenoma/Carcinoma	4/60 (53) NC	4/60 (52) 0.0952	9/60 (51) 0.1100	3/60 (55) 0.8039	10/60 (51) 0.0690
	Osteosarcoma, Metastatic	1/60 (52) NC	1/60 (53) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
Mammary Gland	Adenocarcinoma	0/60 (52) NC	0/60 (52) 0.0604	0/60 (50) NC	0/60 (53) NC	2/60 (51) 0.2427
	Adenoma	0/60 (52) NC	0/60 (52) 0.5024	0/60 (50) NC	1/60 (53) 0.5048	0/60 (50) NC
	Carcinoma, Adenosquamous	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
	Adenoma/Adenocarcinoma	0/60 (52) NC	0/60 (52) 0.0616	0/60 (50) NC	1/60 (53) 0.5048	2/60 (51) 0.2427
Ovaries	Cystadenoma	0/60 (52) NC	1/60 (53) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
	Cystadenoma, Unilateral	1/60 (52) NC	0/60 (52) 0.1853	0/60 (50) NC	1/60 (53) 0.5048	1/60 (50) 0.4902
	Granulosa Cell Tumor, Unilateral	0/60 (52) NC	0/60 (52) 0.3049	1/60 (50) 0.4902	0/60 (53) NC	1/60 (50) 0.4902
	Interstitial Cell Adenoma, Unilateral	0/60 (52) NC	0/60 (52) 0.5024	0/60 (50) NC	1/60 (53) 0.5048	0/60 (50) NC
	Luteoma, Unilateral	0/60 (52) NC	0/60 (52) 0.6219	1/60 (50) 0.4902	1/60 (53) 0.5048	0/60 (50) NC

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo Cont (N=60) P - Trend	335 mg Low (N=60) P - PC vs. L	700 mg Med(N=60) P - PC vs. M	1420 mg High (N=60) P - PC vs. H
	Tubulostromal Adenoma, Unilateral	1/60 (52) NC	1/60 (52) 0.9366	1/60 (50) 0.7426	0/60 (53) 1.0000	0/60 (50) 1.0000
Ovaries	Cystadenoma/Unilateral	1/60 (52) NC	1/60 (53) 0.3848	0/60 (50) 1.0000	1/60 (53) 0.7524	1/60 (50) 0.7377
Pancreas	Adenoma, Islet Cell	1/60 (52) NC	3/60 (53) 0.4569	2/60 (50) 0.8000	0/60 (53) 1.0000	3/60 (51) 0.6424
	Carcinoma, Islet Cell	1/60 (52) NC	0/60 (52) 0.7463	1/60 (50) 0.4902	0/60 (53) NC	0/60 (50) NC
	Adenoma/Carcinoma Islet Cell	2/60 (52) NC	3/60 (53) 0.5422	3/60 (50) 0.6327	0/60 (53) 1.0000	3/60 (51) 0.6424
Pituitary Gland	Adenoma, Pars Distalis	6/60 (52) NC	4/60 (52) 0.9887	4/60 (50) 0.6201	2/60 (53) 0.9018	0/60 (50) 1.0000
	Adenoma, Pars Intermedia	0/60 (52) NC	0/60 (52) 0.6219	1/60 (50) 0.4902	1/60 (53) 0.5048	0/60 (50) NC
	Carcinoma, Pars Distalis	0/60 (52) NC	0/60 (52) 0.2439	0/60 (50) NC	0/60 (53) NC	1/60 (50) 0.4902
	Adenoma/Carcinoma Pars distalis /Pars intermedia	6/60 (52) NC	4/60 (52) 0.9420	5/60 (50) 0.4749	3/60 (53) 0.7894	1/60 (50) 0.9688
Skin	Fibrosarcoma	1/60 (53) NC	1/60 (53) 0.7477	5/60 (52) 0.0982	2/60 (53) 0.5000	1/60 (50) 0.7377
	Hemangiosarcoma	0/60 (52) NC	0/60 (52) 0.2439	0/60 (50) NC	0/60 (53) NC	1/60 (50) 0.4902
	Sarcoma Nos	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
Spleen	Hemangioma	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
	Hemangiosarcoma	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
Submandibular Sal Gl	Hemangioma, Unilateral	0/60 (52) NC	0/60 (52) 0.2439	0/60 (50) NC	0/60 (53) NC	1/60 (50) 0.4902
Systemic Neoplasms	Hemangiosarcoma	1/60 (53) NC	2/60 (53) 0.5509	0/60 (50) 1.0000	2/60 (53) 0.6911	1/60 (51) 0.8714
	Histiocytic Sarcoma	3/60 (52) NC	1/60 (52) 0.7268	3/60 (50) 0.2940	0/60 (53) 1.0000	1/60 (50) 0.7426
	Lymphoma	19/60 (54) NC	17/60 (55) 0.9941	10/60 (51) 0.9410	17/60 (55) 0.5816	4/60 (50) 0.9995
	Plasma Cell Tumor	0/60 (52) NC	0/60 (52) 0.7463	1/60 (50) 0.4902	0/60 (53) NC	0/60 (50) NC

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Air Cont. (N=60)	0 mg Placebo Cont (N=60) P - Trend	335 mg Low (N=60) P - PC vs. L	700 mg Med(N=60) P - PC vs. M	1420 mg High (N=60) P - PC vs. H
	Schwannoma	0/60 (52) NC	0/60 (52) 0.5024	0/60 (50) NC	1/60 (53) 0.5048	0/60 (50) NC
Thyroid Glands	Adenoma, Follicular Cell	1/60 (52) NC	3/60 (52) 0.6028	1/60 (50) 0.9363	0/60 (53) 1.0000	2/60 (50) 0.8063
	Adenoma, Follicular Cell, Unilateral	11/60 (52) NC	24/60 (54) 0.9966	16/60 (51) 0.9432	14/60 (53) 0.9846	10/60 (51) 0.9985
	Adenoma Follicular Cell / Follicular Cell, Unilateral	12/60 (52) NC	27/60 (54) 0.9971	17/60 (51) 0.9734	14/60 (53) 0.9968	12/60 (51) 0.9988
Urinary Bladder	Hemangioma	0/60 (52) NC	1/60 (52) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
Uterus	Endometrial Stromal Sarcoma	1/60 (52) NC	0/60 (52) NC	0/60 (50) NC	0/60 (53) NC	0/60 (50) NC
	Fibrosarcoma	0/60 (52) NC	1/60 (53) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
	Hemangioma	0/60 (52) NC	1/60 (52) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000	0/60 (50) 1.0000
	Leiomyoma	0/60 (52) NC	1/60 (52) 0.4292	0/60 (50) 1.0000	0/60 (53) 1.0000	1/60 (50) 0.7426
	Stromal Polyp	0/60 (52) NC	4/60 (53) 0.6984	1/60 (50) 0.9672	2/60 (53) 0.8974	2/60 (51) 0.8884
Vagina	Squamous Cell Carcinoma	0/60 (52) NC	0/60 (52) 0.7463	1/60 (50) 0.4902	0/60 (53) NC	0/60 (50) NC
Cervix	Leiomyoma/Leiomyosarcoma	0/60 (52) NC	0/60 (52) 0.1853	0/60 (50) NC	1/60 (53) 0.5048	1/60 (50) 0.4902

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant 0.05 for rare tumors, in pairwise comparisons.

Figure 2A: Kaplan-Meier Survival Curves for
Male Mice

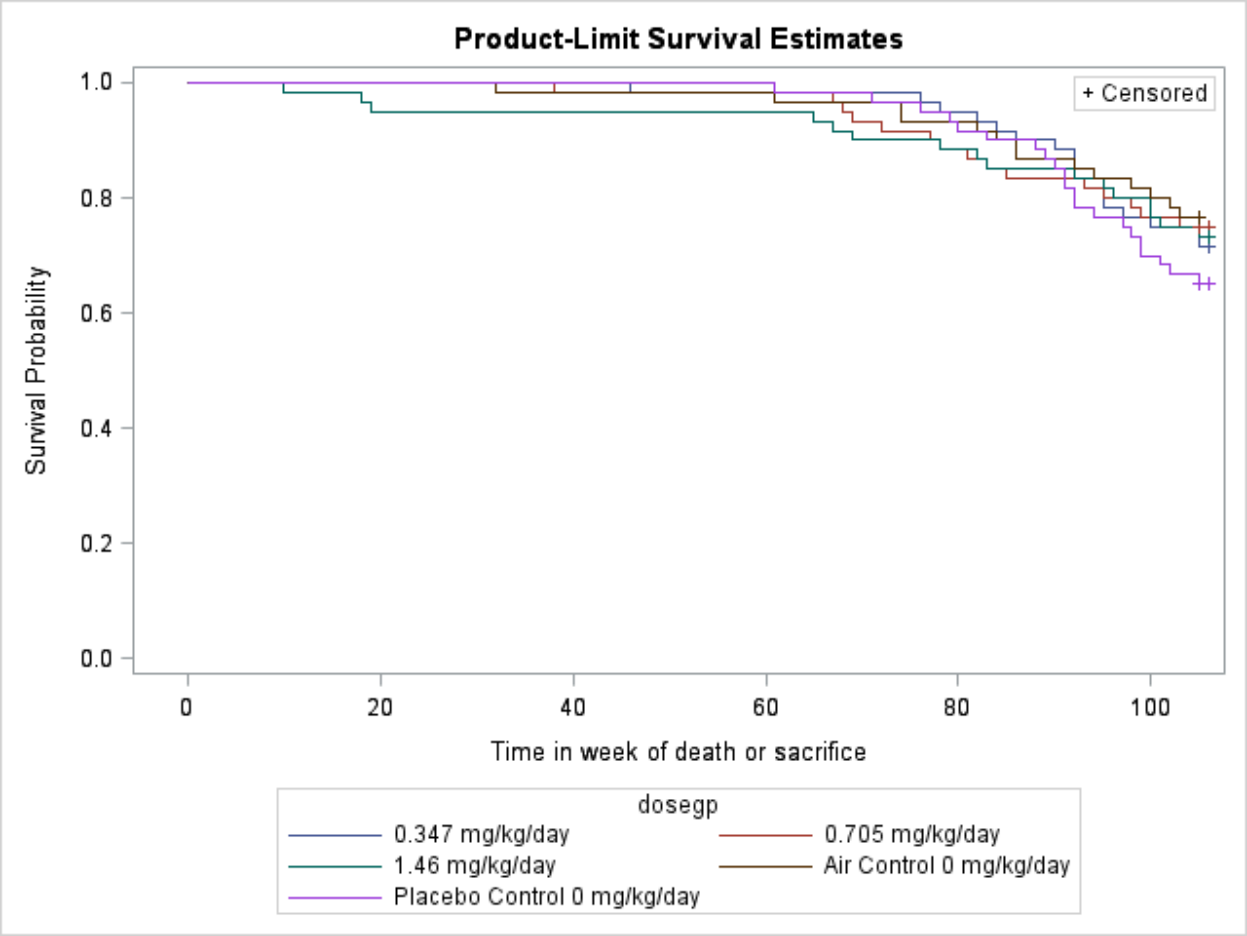
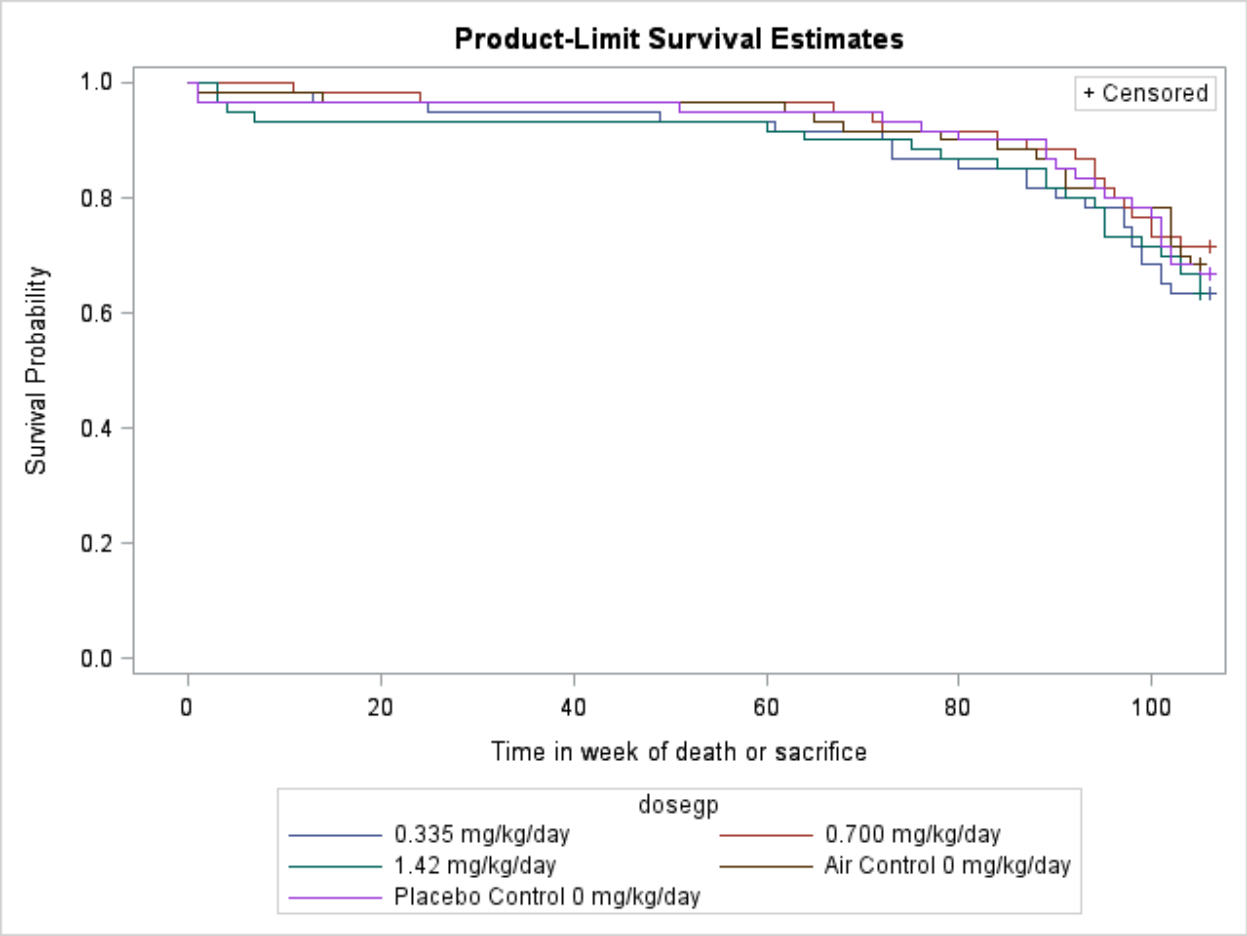


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



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