NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	216579/S-001
Priority or Standard	Standard
Submit Date(s)	July 7, 2025 and July 11, 2025
Received Date(s)	July 11, 2025
PDUFA Goal Date	May 7, 2026
Division/Office	Division of Pulmonology, Allergy, and Critical Care
Review Completion Date	
Established/Proper Name	Budesonide and formoterol fumarate
(Proposed) Trade Name	SYMBICORT AEROSPHERE
Pharmacologic Class	Inhaled corticosteroid/long-acting beta-agonist
Applicant	AstraZeneca Pharmaceuticals LP
Doseage form	Inhalation Aerosol
Applicant proposed Dosing Regimen	160 µg / 9.6 µg or 320 µg /9.6 µg by oral inhalation twice daily
Applicant Proposed Indication(s)/Population(s)	(b) (4) treatment of asthma in patients aged 12 years and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	195967001 | Asthma (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of asthma in adult and pediatric patients aged 12 years and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Asthma (195967001)
Recommended Dosing Regimen	160 µg / 9.6 µg or 320 µg /9.6 µg by oral inhalation twice daily

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Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DPV-II, Division of Pharmacovigilance II; HF, Human Factors; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology

Signatures

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Glossary

ACQ-(X)	X-item asthma control questionnaire (X=5 or 7)
ADaM	Analysis Data Model
AE	adverse event
AQLQ+12	asthma quality of life questionnaire for 12 years of age and older
AUC	area under the curve
$AUC_{0-(X)}$	AUC from 0 to X hours (X=3 or 12)
BD	budesonide
BFF	budesonide/formoterol fumarate
BGF	BD 160 µg /GP 9 µg /FF 4.8 µg
BID	twice daily
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease of 2019
CV	coefficient of variation
CYP	cytochrome P450
DMF	dimethylformamide
ECG	electrocardiogram
eDiary	electronic diary
FDA	Food and Drug Administration
FDC	fixed-dosed combination
FEV_1	forced expiratory volume in 1 second
FF	formoterol fumarate
GCP	good clinical practice
GFF	GP/FF
GP	glycopyrrolate
HPA	hypothalamic-pituitary-adrenal
ICE	intercurrent event
ICS	inhaled corticosteroid
IND	investigational new drug
IP	investigational product
IPD	important protocol deviation
LABA	long-acting $beta_2$-agonist
LAMA	long-acting muscarinic antagonist
LOE	lack of efficacy
LS	least-squares
LTRA	leukotriene receptor antagonist
NDA	new drug application
PK	pharmacokinetic
PMR	postmarketing requirement
PRO	patient-reported outcome

QC	quality control
SAE	serious adverse event
SAP	statistical analysis plan
SCS	systemic corticosteroids
SEE	substantial evidence of effectiveness
sNDA	supplemental new drug application
TBH	Turbuhaler
USPI	U.S. prescribing information

1 Executive Summary

1.1. Product Introduction

The Applicant, AstraZeneca, submitted a 505(b)(1) supplemental new drug application (sNDA 216579) for SYMBICORT AEROSPHERE, a fixed-dosed combination (FDC) pressurized metered-dose inhaler (MDI) containing budesonide (BD) and formoterol fumarate (FF), for the (b) (4) treatment of asthma in patients aged 12 years of age and older. This combination product containing BD and FF delivered in the aerosphere platform will be referred to as BFF in this review. BD is an inhaled corticosteroid (ICS), and FF is a long-acting beta$_2$-agonist (LABA). BFF, at a dose of BD 320 µg /FF 9.6 µg twice daily (BID), delivered as 2 actuations of BD 160 µg /FF 4.8 µg, was originally approved for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in 2023, under NDA 216579.

There are several other drugs containing BD and/or FF approved with other delivery devices (not using the aerosphere platform). A currently marketed FDC MDI containing BD at two different strengths (80 µg, 160 µg) and FF dihydrate 4.5 µg was originally approved by the FDA in 2006 (NDA 21939) under the tradename Symbicort and is approved for the treatment of asthma in patients aged 6 years and older. The FDC of BD 160 µg /glycopyrrolate (GP) 9 µg /FF 4.8 µg (BGF) is approved in the United States under the tradename Breztri Aerosphere, using the same delivery device for the maintenance treatment of COPD (approved 2020, NDA 212122).

For the proposed indication, the Applicant developed two doses of BFF for marketing, both of which are administered as two inhalations BID. Low dose BFF, BD 160 µg /FF 9.6 µg, will be delivered as two actuations of BD 80 µg /FF 4.8 µg (hereafter referred to as BFF 160/9.6). High dose BFF, BD 320 µg /FF 9.6 µg, will be delivered as two actuations of BD 160 µg /FF 4.8 µg (hereafter referred to as BFF 320/9.6).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on the clinical safety and efficacy data submitted, the recommended regulatory action is Approval for BFF 160/9.6 and BFF 320/9.6 administered BID via inhalation for the (b) (4) treatment of patients with asthma 12 years of age and older.

To support this application, the Applicant provided data from two trials evaluating the safety and efficacy of BFF in subjects with asthma. Trial D5982C00005 (hereafter referred to as Lithos) and D5982C00006 (hereafter referred to as Vathos) were designed as adequate and well-controlled trials to provide the basis for demonstration of substantial evidence of effectiveness (SEE).

- Lithos was a 12-week, randomized, double-blind, active-comparator, parallel group trial in subjects with inadequately controlled asthma comparing BFF 160/9.6 to BD 160 in subjects

≥12 years of age. The primary endpoint was the change from baseline in forced expiratory volume in 1 second (FEV_1) area under the curve (AUC) from 0 to 3 hours (AUC_{0-3}) at Week 12.

- Vathos was a 24-week randomized, double-blind, active-comparator, parallel group trial in subjects with inadequately controlled asthma comparing BFF 320/9.6 to BD 320 in subjects ≥12 years of age. There were two other arms in Vathos: BFF 160/9.6 was included to evaluate BFF dose response, and Symbicort Turbuhaler 320/9 µg (hereafter referred to as Symbicort TBH 320/9) served as a marketed comparator in ex-U.S. regions that required it. The primary endpoint was the change from baseline in FEV_1 AUC_{0-3} at Week 24.

Both trials used lung function-based primary and key secondary endpoints (evaluated at Week 12 for Lithos and Week 24 for Vathos): change from baseline in FEV_1 AUC_{0-3} for the primary endpoint and change from baseline in morning pre-dose trough FEV_1 for the key secondary endpoint. In Lithos, BFF 160/9.6 demonstrated statistically significant greater improvements in the primary endpoint of mean change from baseline in FEV_1 AUC_{0-3} (Table 23) and in the key secondary endpoint of morning pre-dose trough FEV_1 compared to BD 160 at Week 12 (Table 24). In Vathos, BFF 320/9.6 demonstrated statistically significant greater improvements in the primary endpoint of FEV_1 AUC_{0-3} (Table 25) and the key secondary endpoint of morning pre-dose trough FEV_1 compared to BD 320 at Week 24 (Table 26). These data supported the contribution of FF to the overall treatment effect of BFF.

Based on the results of the adequate and well-controlled trials, Lithos and Vathos, SEE has been established for both BFF 160/9.6 and BFF 320/9.6 for the treatment of asthma in individuals ≥12 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Asthma is a serious and heterogeneous lung disease, characterized by chronic airway inflammation, obstruction, and hyperresponsiveness. Recurrent symptoms (e.g., wheeze, shortness of breath, chest tightness, cough) adversely impact health-related quality of life and inadequately controlled asthma leads to significant morbidity and high health care costs. There are many marketed treatment options for asthma, and combination inhaled corticosteroid/long-acting beta$_2$-agonist (ICS/LABA) inhalers are recommended as therapy in the most recent updates to national and international guidelines (Cloutier et al. 2020; Global Initiative for Asthma 2025).

The Applicant submitted a supplemental NDA for BFF 160/9.6 and BFF 320/9.6 (tradename SYMBICORT AEROSPHERE), developed to treat patients ≥12 years of age with inadequately controlled asthma. To support this application, the Applicant provided two primary sources of support: a 12-week trial comparing BFF 160/9.6 to one of the mono-components, BD 160 (Lithos), and a 24-week trial comparing BFF 320/9.6 to BD 320, as well as to BFF 160/9.6 and Symbicort Turbuhaler (TBH) 320/9 (Vathos). The primary efficacy analyses for both trials demonstrated a statistically significant improvement for BFF 160/9.6 (Lithos) and BFF 320/9.6 (Vathos) compared to the mono-component BD on the primary endpoint of mean change from baseline in forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 3 hours ($AUC_{0-3)}$. Both Lithos and Vathos also met the key secondary endpoint of change from baseline in morning pre-dose trough FEV_1.

The safety databases were adequate for evaluation, and the overall safety profile for both doses of BFF was consistent with the established safety profiles for ICS/LABA therapies, including marketed Symbicort (hereafter referred to as Symbicort MDI). Overall, there were no notable imbalances between arms in reported serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation that would raise new safety concerns. There were no deaths during the treatment period for either Lithos or Vathos. Thus, the risk profile for BFF 160/9.6 and BFF 320/9.6 does not outweigh the benefit when used as indicated.

Based on the data submitted in support of this supplemental NDA, the Applicant demonstrated substantial evidence of effectiveness as well as sufficient evidence to support the contributions of the components to the effect of the combination product, i.e., address the 'combination rule' (21 CFR 300.50). Following a comprehensive review of the benefit-risk assessment, the review team's assessment is that there is a favorable benefit-risk profile and they recommend approval of BFF 160/9.6 and BFF 320/9.6 for patients ≥12 years of age for the treatment of asthma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is a chronic, heterogeneous, and potentially life-threatening disease, of which airway inflammation is a central component. • The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction, resulting in chronic symptoms despite current standard of care treatment. • Episodic increases in symptoms are referred to as asthma exacerbations. While many exacerbations may be managed as an outpatient with oral corticosteroids, these episodes adversely affect quality of life and increase health-care costs. • Severe exacerbations may require hospitalization and may even lead to death.	Asthma is a heterogeneous, chronic obstructive lung disease that adversely affects patients' quality of life. Exacerbations can be life-threatening and are associated with substantial morbidity and healthcare utilization.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Currently, there are no existing therapies to cure asthma. • There are several classes of medications marketed for the long-term, maintenance treatment of asthma. • The treatment armamentarium primarily consists of locally-acting inhalation drug products that target either airway bronchoconstriction (e.g., SABA, LABA, LAMA) or airway inflammation (ICS). Inhalation therapies are available as single ingredient products and as FDC products. • Oral treatment options include leukotriene modifying agents (montelukast, zafirlukast), as well as corticosteroids and theophylline. However, these therapies are generally considered less effective and/or have an unfavorable safety profile. • Biologic therapies are available for certain asthma subpopulations: severe asthma with an eosinophilic phenotype (mepolizumab, reslizumab, benralizumab, dupilumab), moderate to severe asthma with aeroallergen sensitization (omalizumab), or oral steroid dependent asthma (tezepelumab).	BFF provides an additional option to treat asthma by acting on airway inflammation and bronchoconstriction, key disease components.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant has demonstrated substantial evidence of effectiveness for BFF in patients with asthma based on the submission of two trials. • Both trials demonstrated an improvement in lung-function-based primary and key secondary endpoints when comparing BFF to BD alone. • Both trials supported the contribution of FF to the overall treatment effect of BFF, satisfying the combination rule. • To support efficacy in adolescents, partial extrapolation from marketed Symbicort and from the adult subjects enrolled in Lithos and Vathos is appropriate given the similarity of disease pathophysiology and expected response to treatment across these age groups.	There is sufficient evidence to conclude that BFF is an effective treatment for asthma in adolescents and adults, as each trial met both of the lung function-based primary and key secondary endpoints (mean change from baseline in FEV_1 AUC_{0-3} and mean change from baseline in morning pre-dose trough FEV_1).
Risk and Risk Management	• The asthma clinical program for BFF demonstrated a safety profile consistent with the known risks of ICS/LABA therapies, including marketed Symbicort, using a different inhalation platform. • The clinical development program in asthma is further supported by the existing safety database with BFF in COPD (for adult patients). • The safety database for the adolescent population (12 to <18 years of age) was small but did not reveal any concerning safety trends. The most common AEs in adolescents were similar to those in the adult population.	Safety findings were similar to those seen in drugs in the same pharmacologic classes (ICS/LABA) and the already marketed product for COPD. Labeling and routine pharmacovigilance are recommended for post-market risk mitigation.

Abbreviations: AE, adverse event; AUC_{0-3}, area under the curve from 0 to 3 hours; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta$_2$-agonist

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		
		X	Patient reported outcome (PRO)	7.1.2
		☐	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):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Asthma is a chronic respiratory disorder characterized by airflow obstruction, inflammation, and hyper-responsiveness, which presents as recurring symptoms of chest tightness, dyspnea, wheeze and cough. Variable and reversible airflow obstruction is typical, but progressive airway remodeling may lead to partially or fully irreversible airway obstruction. Uncontrolled asthma can make it difficult for patients to partake in activities of daily life because of frequent respiratory symptoms that can occur with and without exertion. Patients with poorly controlled asthma are also more prone to exacerbations that may require oral steroids, emergency room visits, and hospitalizations.

The diagnosis and management of this common condition are outlined in national and international guidelines (Cloutier et al. 2020; Global Initiative for Asthma 2025). The goal of asthma management focuses on the maintenance of symptom control, reduction of exacerbation risk, and the improvement in quality of life for patients. Pharmacologic management includes rescue treatment for acute asthma symptoms, as well as preventive maintenance treatment. Maintenance treatment decisions are based on a stepwise approach that entails a continuous cycle of assessment of the patient's response to medication and tailoring treatment plans by escalating and de-escalating therapy in accordance with symptoms.

Current therapies for the maintenance treatment of asthma include the following: ICSs, inhaled LABAs, inhaled long-acting muscarinic antagonists (LAMAs), leukotriene modifiers, and biologics. A summary of currently approved asthma medications is included in Table 1.

2.2. Analysis of Current Treatment Options

Table 1. Current Asthma Treatments Available in the United States

Class	Trade Name	Generic Name	Initial U.S. Approval
		Oral Inhalation Medication	
ICS	Qvar RediHaler	Beclomethasone dipropionate	1976
	Pulmicort Respules Pulmicort Flexhaler	Budesonide	2000
	Alvesco	Ciclesonide	2006
	Arnuity Ellipta	Fluticasone furoate	2014
	Flovent Diskus Flovent HFA	Fluticasone propionate	1994
	Asmanex HFA Asmanex Twisthaler	Mometasone furoate	1987
ICS/LABA	Advair Diskus Advair HFA Airduo Respiclick	Fluticasone propionate/salmeterol xinafoate	2000
	Symbicort	Budesonide/formoterol fumarate dihydrate	2006
	Dulera	Mometasone furoate/formoterol fumarate dihydrate	2010
	Breo	Fluticasone furoate/vilanterol trifenatate	2013
ICS/LABA/LAMA	Trelegy Ellipta	Fluticasone furoate/umeclidinium bromide/vilanterol trifenatate	2017
ICS/SABA	Airsupra	Budesonide/albuterol	2023
LAMA	Spiriva Respimat	Tiotropium bromide	2004

Class	Trade Name	Generic Name	Initial U.S. Approval
SABA	Xopenex HFA	Levalbuterol	
	ProAir HFA ProAir Respiclick Proventil HFA Ventolin HFA Vospire ER	Albuterol sulfate	1981
	Xopenex HFA	Levalbuterol	1999
		Oral Medications	
LTRA	Singulair	Montelukast	1998
	Accolate	Zafirlukast	1996
Xanthines	Multiple	Theophylline	1979
		Biologics	
Anti-IgE	Xolair Omlyclo	Omalizumab	2003
Anti-IL-5	Nucala	Mepolizumab	2015
	Cinqair	Reslizumab	2016
	Exdensur	Depemokimab (YTE-modified)	2025
Anti-IL-5Rα	Fasenra	Benralizumab	2017
Anti-IL-4Rα	Dupixent	Dupilumab	2017
Anti-TSLP	Tezpire	Tezepelumab	2021

Source: Clinical reviewer created table using product labeling for currently approved medications for asthma
Abbreviations: ER, extended-release; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-4R, interleukin-4 receptor; IL-5R, interleukin-5 receptor; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta$_2$-agonist; TSLP, thymic stromal lymphopoietin; U.S., United States; YTE, M252Y/S254T/T256E

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

There are two FDC inhalers approved in the United States using the same aerosphere platform. BFF 320/9.6 is approved for COPD and marketed under the tradename SYMBICORT AEROSPHERE. A triple combination product that includes BGF is marketed under the tradename Breztri Aerosphere.

The individual components of BD and FF are approved both alone and in combination using different delivery platforms (Table 1). An FDC of BD and FF is marketed as Symbicort for the treatment of asthma and COPD. In addition, FF is approved for COPD (marketed as Perforomist [nebulizer solution]). BD is approved as an individual product for asthma (marketed as Pulmicort Flexhaler or Pulmicort Respules [nebulizer solution]) as well as part of an FDC with albuterol sulfate (marketed as Airsupra).

3.2. Summary of Presubmission/Submission Regulatory Activity

BFF was studied under IND 122166, opened in 2014. Relevant interactions for the asthma program are noted in Table 2.

Table 2. Summary of Presubmission Regulatory Activity

Date	Interaction	Highlights
February 19, 2016	Pre-IND Written Responses	• BFF to placebo comparison was not recommended by the Agency, as both BD and FF demonstrated activity against placebo in respective dose-ranging studies • Applicant must demonstrate higher dose has benefit over lower for approval of both doses, descriptive comparison acceptable
October 1, 2021	Phase 3 Protocol Feedback	• Agency recommended including severe asthma exacerbations in the key secondary endpoints
February 2, 2023	Phase 3 Protocol Feedback	• Agency recommended pre-specified pooling of exacerbation data
October 9, 2024	Statistical Analysis Plan Feedback	• Agency recommended that each intercurrent event is listed with the specific strategy for both the primary and supportive analyses
November 4, 2024	Type B Written Responses	• Agency agreed that the safety database appeared adequate to support filing the sNDA

Date	Interaction	Highlights
April 11, 2025	iPSP Agreement	• Applicant to defer enrollment of subjects 4 to <12 years of age • Waiver of studies for the age group <4 years

Source: Clinical Reviewer
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FF, formoterol fumarate; IND, investigational new drug; iPSP, initial pediatric study plan; sNDA, supplemental new drug application

4 Nonclinical Pharmacology/Toxicology

4.1. Executive Summary

No new nonclinical data was submitted nor required for this supplemental application. The relevant information was previously reviewed.

5 Clinical Pharmacology

5.1. Executive Summary

BFF is a fixed-dose dual combination of BD, an ICS, and FF, a LABA that is currently marketed as SYMBICORT AEROSPHERE under the same NDA (i.e., NDA 216579) for the maintenance treatment of COPD (BFF 320/9.6 µg BID). In this sNDA (S-001), the Applicant seeks approval of SYMBICORT AEROSPHERE (BFF 320/9.6 µg and 160/9.6 µg BID) for the indication of (b) (4) treatment of asthma in patients 12 years of age and older. Individual components BD and FF were characterized as active comparators in the earlier development programs of Bevespi Aeroshere (NDA 208294), and/or Breztri Aerosphere for COPD and Symbicort MDI for asthma (NDA 021929).

The sNDA 216579 S-001 consists of one supportive dose-finding study for BD (Study PT008001) in subjects with asthma, two phase 3 studies (Lithos and Vathos) as well as two supportive studies (Kalos and Logos) in subjects with asthma. The full dose-ranging and phase 3 program for FF MDI was submitted under NDA 208294 for COPD indication (GP/FF [GFF] MDI, Bevespi Aerosphere). Refer to Study PT009001 in subjects with COPD submitted under the original NDA 216579; there is no clinically relevant drug-drug interaction between BD and FF in the context of BFF product.

Recommendation: The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology recommends approval of this application from a clinical pharmacology perspecitive.

5.2. Summary of Clinical Pharmacology Assessment

In this review, the Clinical Pharmacology review team mainly focuses on the dose-ranging study for BD in asthma and pharmacokinetic (PK) characterization of BD and FF in Kalos. Conclusions from FF dose-ranging studies, PK interaction studies between BD and FF that were reviewed in the COPD program will be briefly described.

Table 3. Key Clinical Pharmacology Studies Submitted in This Supplement (S-001)

Study	Type	Study Design	Treatment	Comparator	Primary Endpoints	Population
Kalos N=2149	Supportive	Randomized, double-blind, parallel	BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg	BFF 320/9.6 µg or Symbicort MDI 320/9 µg	Change from baseline in FEV_1 AUC_{0-3} at Week 24	Adult and adolescent subjects with inadequately controlled asthma
PT008001 N=120	Dose-ranging	Randomized doubleblind, crossover	BD MDI 40, 80, 160, 320 µg	Placebo MDI	Change from baseline in morning pre-dose trough FEV_1 at Week 4	Adult subjects with mild to moderate persistent asthma

Source: Clinical pharmacology reviewer
Abbreviations: AUC_{0-3}, area under the concentration-time curve from 0 to 3 hours postdose; BD, budesonide; BFF, budesonide/formoterol fumarate; BGF, BD 160 µg /GP 9 µg /FF 4.8 µg; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; GP, glycopyrrolate; MDI, metered-dose inhaler

5.2.1. Pharmacology and Clinical Pharmacokinetics

The general clinical pharmacology information of BD and FF is based on the approved drug label of BFF and is summarized below.

Absorption

- **BD**: Following inhaled administration of BFF in subjects with COPD, maximum observed plasma concentration (C_{max}) occurred within 20 to 60 minutes. Steady state is estimated to be achieved after approximately 1 day of repeated dosing of BFF via population PK analysis and the AUC from 0 to 12 hours (AUC_{0-12}) is approximately 1.3 times higher than after the first dose.
- **FF**: Following inhaled administration of BFF in subjects with COPD, C_{max} occurred within 40 to 60 minutes. Steady state is estimated to be achieved after approximately 2 days of repeated dosing of BFF via population PK analysis and the AUC_{0-12} is approximately 1.4 times higher than after the first dose.

Distribution

- **BD**: The estimated BD apparent volume of distribution at steady-state in subjects with COPD is approximately 1200 L, via population PK analysis. Over the concentration range of 1 to 100 nmol/L, mean plasma protein binding of BD ranged from 86% to 87%.
- **FF**: The estimated FF apparent volume of distribution at steady-state in subjects with COPD is approximately 2400 L, via population PK analysis. Over the concentration range of 10 to 500 nmol/L, plasma protein binding of FF ranged from 46% to 58%.

Elimination

- **BD:** BD was excreted in urine and feces in the form of metabolites. Only negligible amounts of unchanged BD have been detected in the urine. The effective half-life of BD in subjects with COPD derived via population PK analysis was approximately 5 hours.
- **FF:** The excretion of FF was studied in six healthy subjects following simultaneous administration of radiolabeled FF via the oral and intravenous routes. In that study, 62% of the drug related radioactivity of FF was excreted in the urine while 24% was eliminated in the feces. The effective half-life of FF in subjects with COPD derived via population PK analysis was approximately 10 hours.

Metabolism

- **BD**: BD undergoes cytochrome P450 (CYP) 3A4-catalyzed biotransformation. Two major metabolites have been identified: 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.
- **FF**: FF undergoes direct glucuronidation and 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.

Specific Populations

Population PK analysis showed no evidence of a clinically significant effect of age, sex, race/ethnicity, or body weight on the pharmacokinetics of BD or FF.

Patients With Hepatic and Renal Impairment

Dedicated studies of BFF evaluating effect of hepatic impairment and renal impairment on the pharmacokinetics of BD and FF were not conducted. As BD and FF are primarily eliminated via hepatic metabolism, an increased systemic exposure can be expected in patients with severe hepatic impairment.

The effect of renal impairment on the systemic exposure to BD and FF for up to 24 weeks was evaluated in a population PK analysis. Renal function was found not to significantly affect exposure to BD or FF after drug clearance adjusted by age or body weight in a population PK analysis.

Drug Interaction Studies

No PK interaction has been observed between BD and FF when co-administered via Aerosphere inhalation device, as evaluated in subjects with COPD following repeat dosing with BFF (320/9.6 µg), BD MDI (320 µg) or FF MDI (9.6 µg) in Study PT009001. For a detailed review of drug interaction study, see the clinical pharmacology review by Dr. Liping Pan in the Unireview for NDA 216579 (dated April 27, 2023). PK-related drug-drug interaction between BD and FF in the combination product, BFF 320/9.6 µg, was not observed.

Other Drug-Drug interactions

The main route of metabolism of BD is via CYP3A4. Concomitant administration of a CYP3A4 inhibitor may inhibit the metabolism of, and increase the systemic exposure to, BD. Therefore, in line with the approved NDA 021929 (Symbicort MDI), BFF should be used with caution when co-administered with strong CYP3A4 inhibitors.

FF is a beta-adrenergic receptor agonist. In line with the approved NDA 208294 Bevespi Aerosphere (GFF MDI), Breztri 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 electrocardiogram (ECG) changes.
- Monoamine oxidase inhibitors and tricyclic antidepressants which may potentiate effect of FF on cardiovascular system.
- Beta-blockers which may block bronchodilator effects of beta-agonists (BAs) and produce severe bronchospasm.

Ketoconazole and Itraconazole: Ketoconazole and itraconazole, strong inhibitors of CYP3A4, the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested BD and orally inhaled BD, respectively.

Cimetidine: At recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes, had a slight but clinically insignificant effect on the pharmacokinetics of oral BD.

Evaluation of Effect of BFF on HPA Axis

In the original NDA 212122 submission, a dedicated relative bioavailability Study PT010001 was conducted in healthy subjects which demonstrated that the systemic exposure of BD following BGF is generally comparable to that following Symbicort MDI (NDA 021929) at both dosing levels (i.e., 160 and 320 µg). In the same submission, a dedicated relative bioavailability Study PT010002 was conducted in healthy subjects, which demonstrated that systemic exposure of BD is comparable between BGF MDI and BFF following single dose of 320 µg BD. For details, refer to clinical pharmacology review by Dr. Yunzhao Ren in the Unireview for NDA 212122 (dated July 23, 2020). Therefore, the effect of BFF on the hypothalamic-pituitary-adrenal (HPA) axis function is expected to be similar between BFF, BGF MDI, and Symbicort MDI.

5.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen for the indication of asthma is two inhalations of BFF 320/9.6 µg or 160/9.6 µg BID. Dosing regimens of BD 320 µg and 160 µg BID via inhalation were selected for pivotal phase 3 studies based on the observed dose response relationship for BD from Study PT008001. The dose of FF was chosen based on dose-ranging study of FF MDI in subjects with COPD (Study PT0050801; GFF Bevespi Aerosphere, NDA 28294). The dose-ranging results in the Phase 2 studies and the efficacy results in Phase 3 studies overall support the recommendation of the dosing regimen as proposed by the Applicant.

Therapeutic Individualization

No therapeutic individualization is needed based on the submitted clinical pharmacology data.

Outstanding Issues

None

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology information of the individual components, BD and FF, has been fully characterized in healthy subjects and subjects with COPD and described in the original NDA 216579 (SYMBICORT AEROSPHERE) and NDA 212122 (BGF MDI; Breztri Aerosphere).

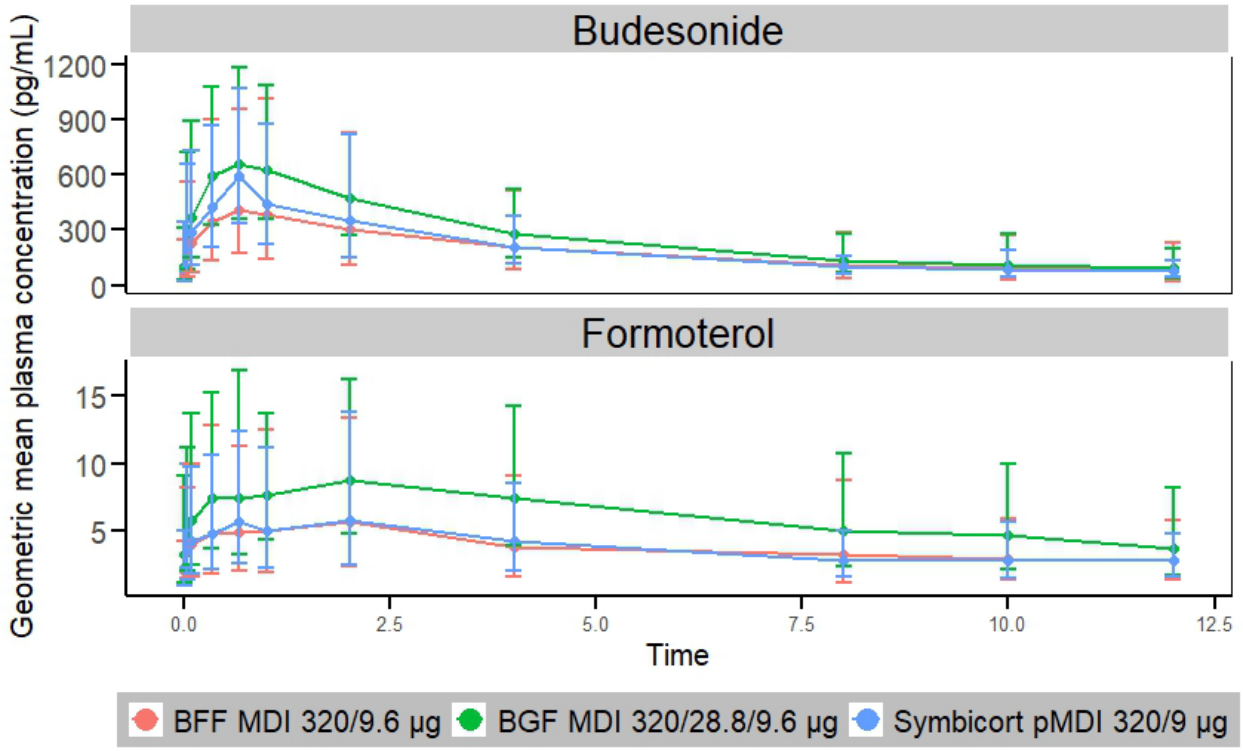
All labeling pertaining to extrinsic factors will be the same as the currently approved label for BFF. Information related to HPA axis suppression in the asthma population is being borrowed from the COPD program of BFF as well as in asthma population from the approved label of Symbicort MDI (320/9 µg; NDA 021929).

In this supplement, the Applicant has provided 2 pivotal phase 3 study reports: Lithos and Vathos. However, the pharmacokinetics of BD or FF was not evaluated in these two studies. Hence, these two studies will not be reviewed by the clinical pharmacology review team. Refer to the clinical review and statistical review for more details regarding efficacy assessment for these two studies.

Pharmacokinetics of BD and FF in Asthma

In support of the clinical pharmacology program of BFF (320/9.6 µg) for asthma, the Applicant has evaluated the pharmacokinetics of BD and FF in BFF in a PK sub-study of Kalos. A total of 164 consented to be entered in the PK sub-study, but 20 subjects who consented were excluded from the final PK Set due to either not having at least one post-dose PK measurement (or measurements affected by protocol deviations/AEs) or not correctly self-administering the last 3 doses of study treatment (6 inhalations) needed to achieve steady-state by Visit 8 (Week 12). Therefore, a total of 144 (6.7%) subjects out of 2144 from the main study were included in the PK Analysis Set. Among them, 50 subjects were in the BFF group. PK samples were collected at Week 12 (steady state) at pre-dose and 2, 5, 20, 40 minutes, and 1, 2, 4, 8, 10, 12 hours post-dose. Samples were collected from treatment groups: BGF MDI 320/18/9.6 µg, BGF MDI 320/36/9.6 µg, BFF 320/9.6 µg (high BD dose only), Symbicort MDI 320/9 µg (BD/FF) and placebo. Plasma concentration time profiles from Kalos in the BFF, BGF MDI and Symbicort MDI subgroups are shown in Figure 1. The PK profiles of BD and FF are generally similar between BFF and Symbicort.

Figure 1. Geometric Mean (±SD) Steady-State Plasma Concentration (pg/mL) of BD, FF, and GP Over Time by Treatment, PK Set, Kalos



Source: Reviewer's analysis based on Kalos ADPC
LLOQ BD: 3 pg/mL, FF: 1 pg/mL, GP: 1 pg/mL
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; BGF, BD 160 µg /GP 9 µg /FF 4.8 µg; FF, formoterol fumarate; GP, glycopyrrolate; LLOQ, lower limit of quantification; MDI, metered-dose inhaler; PK, pharmacokinetic; pMDI, pressurized metered-dose inhaler; SD, standard deviation

C_{max} and AUC were calculated using noncompartmental analysis of the PK data. Results are summarized in Table 4. A total of seven subjects were excluded from BD statistical analysis due to CYP3A inhibitor use. In addition, some subjects with PK samples having insufficient blood volume (19 for FF) were also excluded from the analysis.

Table 4. Geometric Mean (%CV) PK Parameters of BD and FF by Treatment Group at Week 12, Kalos

Parameter	BFF 320/9.6 µg	Symbicort 320/9 µg
BD		
N	36	28
AUC_{0-12} (pg·hr/mL)	2153 (115)	2516 (52)
C_{max} (pg/mL)	496 (95)	597 (77)
FF		
N	35	26
AUC_{0-12} (pg·hr/mL)	47 (95)	46 (72)
C_{max} (pg/mL)	8 (99)	7 (96)

Source: Reviewer's analysis based on Kalos ADPC with PK exclusions
Abbreviations: AUC_{0-12}, area under the curve from 0 to 12 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; FF, formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects with evaluable time points for calculating C_{max} and AUC; PK, pharmacokinetic

At Week 12, the steady state systemic exposures of BD and FF following BFF (320/9.6 µg) were generally comparable to Symbicort MDI (320/9 µg) in subjects with asthma from Kalos. Comparison between the exposures from BFF and Symbicort with respect to geometric mean ratio and 90% confidence intervals (CI) of AUC_{0-12} and C_{max} is shown in Table 5.

Table 5. GMR and 90% CIs for Comparison of PK Parameters Between Different Treatment Groups, Kalos

Parameter	BFF 320/9.6 µg	Symbicort MDI 320/9 µg	GMR (BFF *vs.* Symbicort)	90% CI
BD				
N	36	28		
AUC_{0-12} (pg·hr/mL)	2153	2516	85.6	62.1, 117.9
C_{max} (pg/mL)	496	597	83.0	62.0, 111.0
FF				
N	35	26		
AUC_{0-12} (pg·hr/mL)	47	46	102.0	74.0, 1.41
C_{max} (pg/mL)	8	7	113.5	82.4, 156.5

Source: Reviewer calculated GMR and 90% CIs based on Kalos ADPC
Abbreviations: AUC_{0-12}, area under the curve from 0 to 12 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; C_{max}, maximum observed plasma concentration; FF, formoterol fumarate; GMR, geometric mean ratio; MDI, metered-dose inhaler; N, number of subjects for whom PK parameters were able to be calculated; PK, pharmacokinetic

A cross-study comparison demonstrated similar mean steady state systemic exposure FF following BFF 320/9.6 µg BID treatment between subjects with asthma (Kalos) and subjects with COPD (phase 3 Study PT010006) (Table 6). However, the BD mean systemic exposure following BFF at steady state in subjects with asthma is slightly lower than in subjects with COPD (AUC_{0-12} and C_{max} are 17% and 24% lower, respectively). It is unclear whether this

difference is impacted by small sample size of the PK subset from Kalos, as PK samples were only collected from 6.7% of the enrolled subjects.

Table 6. Cross-Study Comparison of Mean Systemic Exposure of BD and FF at Steady State Following BFF Treatment (320/9.6 µg BID) in Subjects With Asthma (Kalos) and Subjects With COPD (Study PT010006)

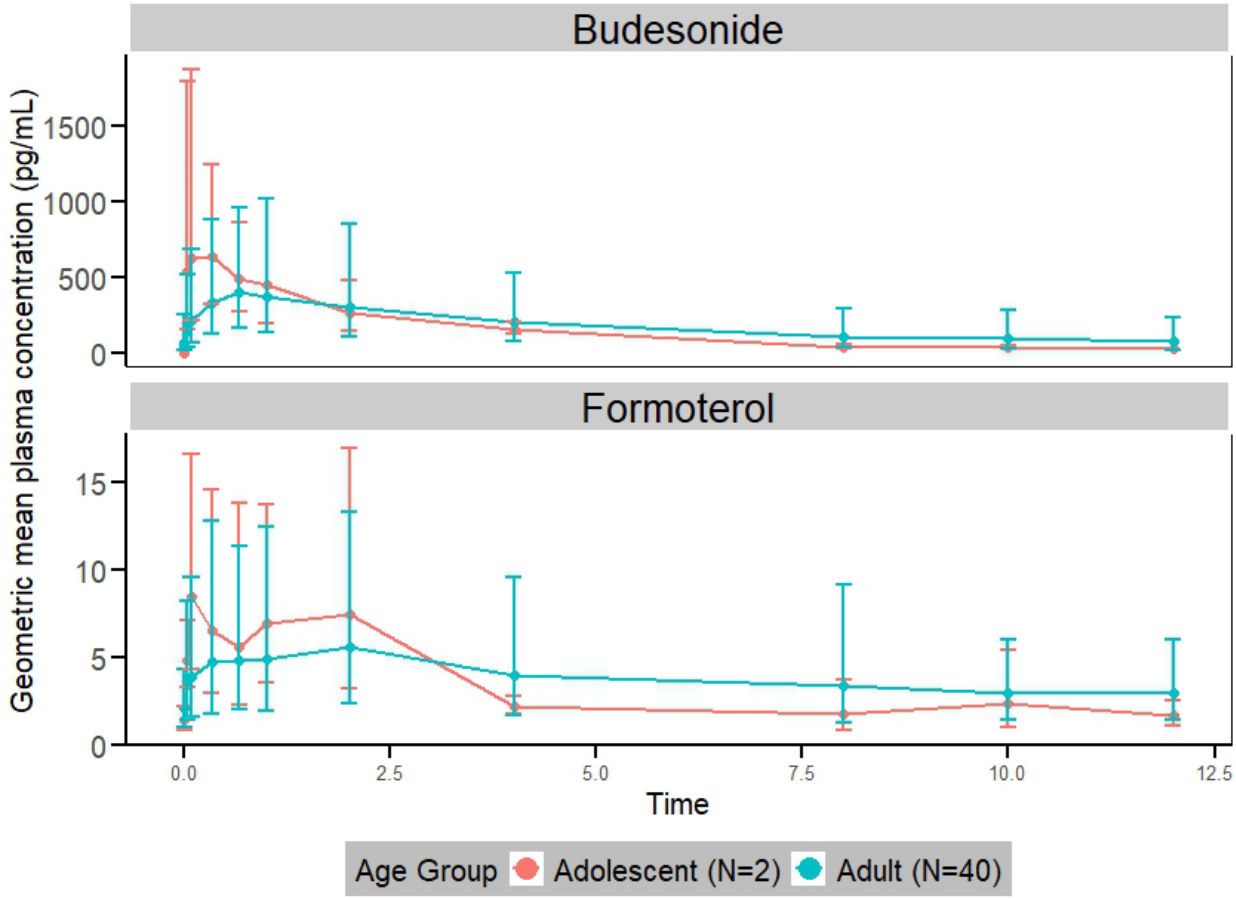
Parameter	Kalos[1]	PT010006[2]
BD		
N	36	39
AUC_{0-12} (pg·hr/mL)	2153 (115)	2583 (56)
C_{max} (pg/mL)	496 (95)	654 (59)
FF		
N	35	39
AUC_{0-12} (pg·hr/mL)	47 (95)	47 (44)
C_{max} (pg/mL)	8 (99)	7.5 (57)

Source:
[1] Week 12 results from Table 5
[2] Week 24 results from Table 64 and Table 66 CSR PT010006.
Abbreviations: AUC_{0-12}, area under the curve from 0 to 12 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; BID, twice daily; C_{max}, maximum observed plasma concentration; COPD, chronic obstructive pulmonary disease; CSR, clinical study report; FF, formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects in analysis

Comparison of Adolescent and Adult Exposure

Kalos enrolled a total of 70 adolescents out of which 66 completed the study. Among them, 21 adolescents were randomized to the BFF group and only 4 were enrolled in the PK sub-group. Using the Applicants's exclusion criteria for PK analysis described above, only 2 adolescents with evaluable PK profiles were included in the final analysis. Comparison of geometric mean concentration time profiles between adults and adolescents in the BFF group is provided in Figure 2. Overall, exposures of BD and FF at steady state were comparable between adults and adolescents based on the the small sample size of adolescents. For the analysis of safety and efficacy in adolescents in the phase 3 studies for BFF, refer to section 8 for clinical review and statistical review.

Figure 2. Geometric Mean (±SD) Steady-State Plasma Concentration (pg/mL) of BD and FF Over Time by Age Group (Adults and Adolescents) and by Treatment, PK Set With Exclusions, Kalos



Source: Reviewer's analysis based on Kalos ADPC
LLOQ BD: 3 pg/mL, FF: 1 pg/mL
Abbreviations: BD, budesonide; FF, formoterol fumarate; LLOQ, lower limit of quantification; N, number of subjects in age group; PK, pharmacokinetic; SD, standard deviation

5.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The overall data from Phase 2 and Phase 3 trials provide evidence that BFF (320/9.6 µg) is effective for the treatment of adult and adolescents with asthma. For details, refer to Section 7 (Statistical and Clinical Evaluation) of this multi-disciplinary review. The clinical pharmacology information provides supportive evidence of effectiveness of BFF from dose-ranging studies described below.

Dosing regimens of BD 320 µg and 160 µg BID via inhalation from BFF were selected for pivotal phase 3 studies based on the observed dose response relationship for BD from Study PT008001 in subjects with asthma.

Study PT008001: Dose-Ranging Study for BD MDI

Study PT008001 was a randomized, double-blind, 4-week, cross-over study to evaluate the four different doses of BD inhalation aerosol (BD MDI) compared to a placebo MDI in adult subjects with mild to moderate persistent asthma. The study assessed four BID dosing levels of BD MDI: 320 µg, 160 µg, 80 µg, and 40 µg. The 4-week treatment duration was selected to allow subjects to reach a steady state in lung function improvement with BD.

Table 7 shows the primary endpoint for the study, the change from baseline in morning pre-dose trough FEV_1 at the end of the treatment period. All four doses of BD MDI demonstrated statistically significant improvements when compared to the placebo MDI. The least-squares (LS) mean differences from placebo were 0.114 L, 0.115 L, 0.083 L, and 0.085 L for the 320 µg, 160 µg, 80 µg, and 40 µg doses, respectively. Among them, only 320 µg and 160 µg doses demonstrated ≥100 mL improvement of trough FEV_1 at the end of Week 4. While a numerical trend of dose-response was observed, the differences between the various BD MDI doses were not statistically significant.

Table 7. Change From Baseline in Morning Pre-Dose Trough FEV_1 at the End of the Treatment Period, ITT Population

Parameter	BD MDI 320 µg	BD MDI 160 µg	BD MDI 80 µg	BD MDI 40 µg	Placebo MDI
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 vs. placebo MDI (L)					
LS mean (SE)	0.114 (0.0229)	0.115 (0.0229)	0.083 (0.0285)	0.085 (0.0284)	-
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	-

Source: Adapted from in the CSR PT008001-clinical-study-report.pdf, page 84, Table 7-1
Baseline was defined as the mean among treatment periods of the mean of evaluable 60- and 30-minute pre-dose values on Day 1. End of the Treatment Period was Day 29, or Day 15 if the Day 29 value was missing or unevaluable. LS means are for the linear mixed model, which included the following covariates: treatment, baseline, and period.
Abbreviations: BD, budesonide; CI, confidence interval; CSR, clinical study report; FEV_1, forced expiratory volume in 1 second; ITT, intent-to-treat; LS, least-squares; MDI, metered-dose inhaler; SE, standard error

For the secondary endpoint of change from baseline in morning pre-dose peak expiratory flow rate, all four BD MDI doses showed statistically significant improvements over placebo. The LS mean differences from placebo ranged from 19.9 L/min to 24.3 L/min.

Based on these results, doses of 160 and 320 µg BD were selected for the subsequent BFF asthma phase 3 trials.

PT0050801: Dose-Ranging Study for FF MDI

The dose of FF was chosen based on dose-ranging study of FF MDI in subjects with COPD (Study PT0050801; GFF Bevespi Aerosphere, NDA 28294). For details, refer to clinical pharmacology review by Dr. Sheetal Agrawal (dated March 14, 2016).

Briefly, Study PT0050801 was a randomized, double-blind, placebo and active-controlled, single-dose, cross-over, five-period study to evaluate the bronchodilator efficacy and safety of a single administration of three different doses of FF MDI in subjects with moderate-to-severe COPD. The study compared three ex-actuator doses of FF MDI (2.4 µg, 4.8 µg, and 9.6 µg) to a placebo MDI and an open-label active control, Foradil Aerolizer (12 µg). A total of 34 subjects were enrolled in the study. The primary objective was to evaluate the bronchodilator efficacy in terms of FEV_1 AUC_{0-12} compared with placebo. For the primary endpoint, each of the three FF MDI doses demonstrated statistically significant superiority compared to placebo ($p<0.001$), with a clear dose-response relationship. The improvement with the FF MDI 9.6 µg dose was similar to that of the active control, Foradil Aerolizer.

Table 8. Mean Change in FEV_1 AUC_{0-12} Compared to Placebo, ITT Population

Parameter	FF MDI 2.4 µg	FF MDI 4.8 µg	FF MDI 9.6 µg	Placebo MDI
Difference vs. placebo MDI (L)				
LS mean (SE)	0.081 (0.0185)	0.103 (0.0189)	0.176 (0.0195)	-
95% CI	(0.045, 0.117)	(0.066, 0.140)	(0.138, 0.214)	-
p-value	<0.001	<0.001	<0.001	-

Source: Adapted from Study-report-body-pt0050801, Page 44, Table 7-3
P-values for comparisons with placebo from repeated measures ANOVA, in which treatment was a fixed effect, within-subject errors were correlated, and between-subject errors were independent. Covariates included in the model were age, sex, height, and test day baseline.
Abbreviations: ANOVA, analysis of variance; AUC_{0-12}, area under the curve from 0 to 12 hours; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; ITT, intent-to-treat; LS, least-squares; MDI, metered-dose inhaler; SE, standard error

Based on this results, doses of 9.6 µg FF was selected for the subsequent BFF asthma phase 3 trials.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. BFF is currently approved for COPD in adult patients only. The current application supports use as (b) (4) treatment of asthma in patients aged 12 years and older. Two different doses of BFF are proposed in asthma: BFF 80/4.8 µg BID or 160/4.8 µg BID. The recommended starting dosage are based upon patients' asthma severity or level of control of asthma symptoms, and risk of exacerbations on current ICSs. The proposed dosing regimen were based on efficacy finding in the phase 3 studies Lithos and Vathos in adults and adolescents. For discussion of efficacy and safety results from Phase 3 studies and efficacy comparison between single and dual-combination products, refer to Section 8 statistical and clinical evaluation.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alternative dosing regimen or management strategy is required based on intrinsic factors (e.g., age, race, [redacted] hepatic impairment, and renal impairment). This is consistent with treatment management strategy in adults as outlined in the approved label of BFF for COPD.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Specific drug-drug interaction studies of BFF with other co-administered drugs have not been performed. The proposed management strategy for subjects 12 years of age and above regarding drug-drug interactions is consistent with the approved recommendations for adults, which is reasonable. Refer to the approved drug label of NDA 216579 for details.

What are the bioanalytical methods?

Determinations of FF and BD concentrations in human plasma in Kalos were performed using the same liquid chromatography with tandem mass spectrometry methods developed in the COPD program for Breztri Aerosphere. The addendums to the bioanalytical assays submitted under this NDA supplement are acceptable. Refer to Section 12.1 for details.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

The Applicant submitted two studies, Lithos and Vathos, as the primary support for safety and efficacy to support the proposed indication. Key design elements for these studies are outlined in Table 9.

Table 9. Listing of Clinical Trials Relevant to This sNDA

Trial Identity/ NCT No.	Trial Duration and Design	Regimen/Route	Primary and Key Secondary Endpoints	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Controlled Studies To Support Efficacy and Safety						
Lithos D5982C00005 NCT05755906	12 weeks Phase 3 R, DB, AC, PG, MC	• BFF 160/9.6 µg BID • BD 160 µg BID	Primary: Change from baseline in FEV_1 AUC_{0-3} at Week 12 Key secondary: Change from baseline in morning pre-dose tough FEV_1 at Week 12	353 randomized BFF 160/9.6: 179 BD 160: 174	Subjects ≥12 yrs of age with inadequately controlled asthma despite low dose ICS or ICS/LABA	106 sites in 7 countries
Vathos D5982C00006 NCT05202262	24 weeks Phase 3 R, DB, AC, PG, MC	• BFF 320/9.6 µg BID • BFF 160/9.6 µg BID • BD 320 µg BID • Symbicort TBH 320/9 µg BID (open label)	Primary: Change from baseline in FEV_1 AUC_{0-3} at Week 24 Key secondary: Change from baseline in morning pre-dose tough FEV_1 at Week 24	581 randomized BFF 320/9.6: 163 BFF 160/9.6: 88 BD 320: 168 Symbicort TBH: 162	Subjects ≥12 yrs of age with inadequately controlled asthma despite medium dose ICS or ICS/LABA	147 sites in 7 countries

Source: Clinical reviewer created based on information in the clinical study reports (CSR) of Lithos and Vathos
Abbreviations: AC, active comparator; AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; BID, twice daily; DB, double-blind; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; MC, multicenter; NCT, National Clinical Trial; No., number; PG, parallel-group; R, randomized; sNDA, supplemental new drug application; TBH, Turbuhaler; yrs, years

6.2. Review Strategy

Support for the efficacy and safety of BFF for asthma is based on two pivotal trials, Lithos and Vathos. The clinical protocols are described in Section 7.1.2 with efficacy and safety results in Sections 7.1.3 and 7.2.3, respectively.

Data from Lithos provides the primary evidence for evaluating the safety and efficacy of the addition of FF to the FDC of BFF 160 by comparing BFF 160/9.6 to BD 160. The primary analyses in Vathos compares BFF 320/9.6 to BD 320, and BFF 160/9.6 was included as a comparator to BFF 320/9.6 to evaluate dose response. Open-label Symbicort TBH 320/9 was added only in countries that required a marketed comparator arm; however, it is not a marketed product in the United States. Data from this arm was taken into consideration to inform the safety evaluation but not efficacy.

Efficacy data from Lithos and Vathos were only pooled to support the secondary objective evaluating the effect of BFF 320/9.6 and BFF 160/9.6 relative to BD on asthma exacerbations. Safety data from Lithos and Vathos were not pooled because of the trials' disparate populations, comparator arms, and durations.

Efficacy analyses were performed by FDA biostatisticians to confirm the Applicant's efficacy analyses as well as to generated tables and figures for this review. Safety analyses and safety tables were conducted by the clinical reviewer with support from FDA Clinical Data Scientists using Analysis Studio.

7 Statistical and Clinical and Evaluation

7.1. Protocol Review of Pivotal Trials Lithos and Vathos

The pivotal trials Lithos and Vathos were similar in study design. The following unified protocol review will summarize the common trial design features and highlight notable differences between the two protocols.

7.1.1. Trial Administrative Information

Table 10. Administrative Information for Lithos and Vathos

Item	Lithos	Vathos
Title	A Randomized, Double-Blind, Parallel Group, Multicenter 12 Week Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler Relative to Budesonide Metered Dose Inhaler in Participants with Inadequately Controlled Asthma (Lithos)	A Randomized, Double-Blind, Parallel Group, Multicenter 24 Week Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler Relative to Budesonide Metered Dose Inhaler and Open-Label Symbicort Turbuhaler in Participants with Inadequately Controlled Asthma (Vathos)
Trial dates	February 27, 2023 - November 19, 2024	January 12, 2022 - February 26, 2025
Countries	106 sites in 7 countries	147 sites in 7 countries

Source: Clinical reviewer

7.1.2. Trial Design

Both Lithos and Vathos were multicenter, randomized, double-blind, active-comparator, parallel-group trials to assess the efficacy and safety of BFF in adolescents and adults with inadequately controlled asthma despite treatment with low-dose (Lithos) or medium-dose (Vathos) ICS or ICS/LABA. After screening, subjects ≥12 years of age entered a 3-week run-in on BD before being randomized to the following study treatments for 12 (Lithos) or 24 (Vathos) weeks:

Lithos (Randomized 1:1)

- BFF 160/9.6 µg BID (2 actuations of 80/4.8 µg BID)
- BD 160 µg BID (2 actuations of 80 µg BID)

Vathos (Randomized 1:2:2:2)

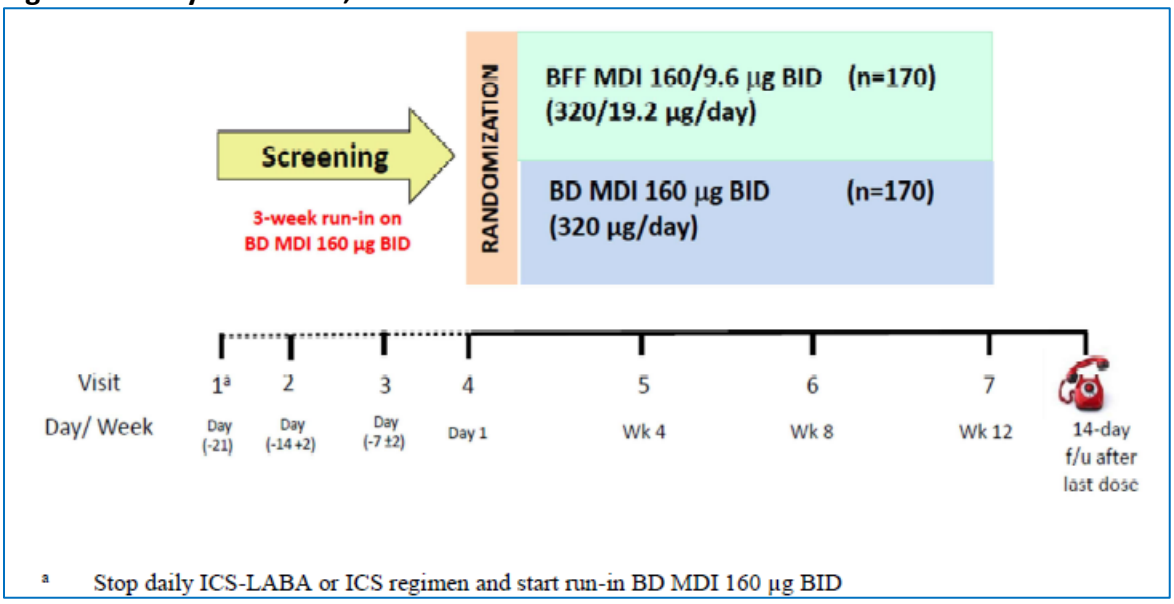
- BFF 160/9.6 µg BID (2 actuations of 80/4.8 µg BID)
- BFF 320/9.6 µg BID (2 actuations of 160/4.8 µg BID)
- BD 320 µg BID (2 actuations of 160 µg BID)
- Open-label Symbicort TBH 320/9 µg BID (2 actuations of 160/4 µg BID)

The Schedule of Assessments and key aspects of the study visits can be found in the Appendices (Table 50 through Table 53) and are summarized here:

- The screening period included Visit 1 through Visit 3 and lasted for approximately 3 weeks. Eligible subjects discontinued baseline asthma medications at Visit 1 and started run-in BD until the evening prior to Visit 4.
- Randomization occurred at Visit 4, and study drug was initiated. Randomization was stratified by age (12 to 18, ≥18 years) and baseline asthma treatment (ICS, ICS/LABA).
- After randomization, there were 3 additional study visits for Lithos between weeks 4-12 and 6 additional study visits for Vathos between weeks 4-24 during the treatment periods.
- Safety follow-up via telephone occurred approximately 2 weeks after completion of the treatment period.

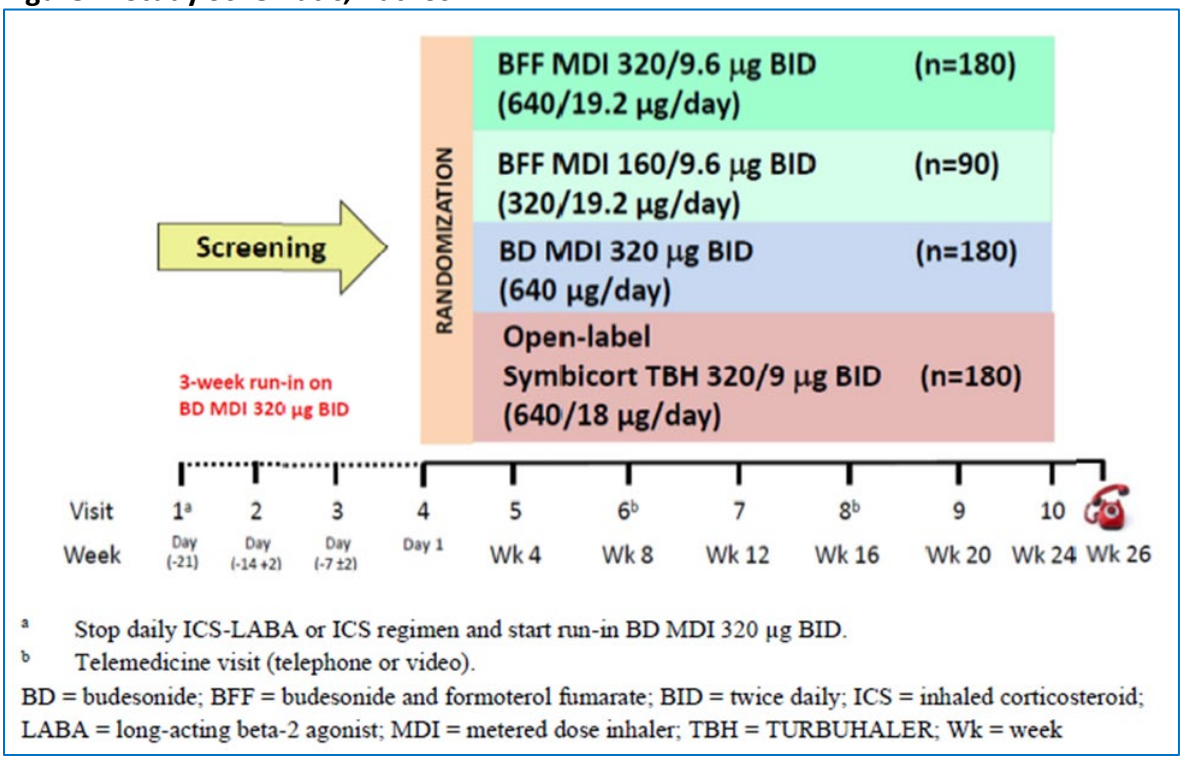
The Lithos study schematic is shown in Figure 3 and the Vathos schematic is shown in Figure 4. Overall, the design of Lithos is similar to Vathos except for a shorter treatment period (12 vs 24 weeks), a smaller sample size (357 vs 585 randomized) and fewer treatment arms (2 vs 4 treatment arms), respectively.

Figure 3. Study Schematic, Lithos



Source: Lithos Clinical Study Report, Figure 1, page 32
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; BID, twice daily; f/u, follow up; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; MDI, metered-dose inhaler; Wk, week

Figure 4. Study Schematic, Vathos



Source: Vathos Clinical Study Report

Study Population

The study population consisted of adolescent and adult subjects with inadequately controlled asthma despite treatment with ICS or ICS/LABA treatment.

Key inclusion Criteria (Lithos and Vathos)

- 12 to 80 years of age (inclusive)
- Physician-diagnosed asthma ≥6 months prior to Visit 1
- 7-item asthma control questionnaire (ACQ-7) total score ≥1.5 at Visits 1 and 4
- Pre-bronchodilator/pre-dose FEV_1<90% predicted normal value at visits 1, 2 and 3, and a pre-dose FEV_1 of 50-90% at Visit 4 (pre-randomization)
- Reversibility to albuterol (defined as post-albuterol increase in FEV_1 of ≥12% and ≥200 mL for subjects ≥18 years of age *or* post-albuterol increase in FEV_1 of ≥12% for subjects 12 to <18 years of age) documented in either the 12 months prior to Visit 1 or at Visit 2 or Visit 3

Key Inclusion Criteria (Lithos)

- Regular use of a stable, low-dose daily ICS or ICS/LABA treatment regimen for at least 8 weeks

Key Inclusion Criteria (Vathos)

- Regular use of a stable, medium-dose daily ICS or ICS/LABA treatment regimen for at least 8 weeks

Key Exclusion Criteria

- Life-threatening asthma
- Hospitalization for asthma within 8 weeks of Visit 1
- Completed treatment for any respiratory infection or asthma exacerbation treated with systemic corticosteroids and/or additional ICS treatment in the 8 weeks prior to Visit 1 and throughout the screening period
- Current smokers, former smokers with >10 pack-years history, or former smokers who stopped smoking <6 months prior to Visit 1 (includes all forms of tobacco, e-cigarettes or other vaping devices and marijuana)

Study Endpoints

The following discusses U.S. endpoints, and this review will not discuss endpoints chosen for European or Japanese sites. They are ordered according to the Applicant's prespecified multiplicity hierarchy (Figure 5), which were similar for both studies.

Primary Endpoints

- Change from baseline in FEV_1 AUC_{0-3} at Week 12 (Lithos) or Week 24 (Vathos)

Key Secondary Endpoints

- Change from baseline in morning pre-dose trough FEV_1 at Week 12 (Lithos) or Week 24 (Vathos)

Secondary Endpoints

- Absolute change in FEV_1 at 5 minutes post-dose on Day 1 (onset of action)
- Percentage of responders in ACQ-5 (≥0.5 decrease) at Week 12/24
- Percentage of responders in ACQ-7 (≥0.5 decrease) at Week 12/24
- Percentage of responders in asthma quality of life questionnaire(s) for 12 years of age and older (AQLQ(s)+12) (≥0.5 decrease) at Week 12/24
- Change from baseline in rescue medication use (mean number of puffs/day) over 12/24 weeks

- Rate of severe exacerbations defined as worsening of asthma that requires a medical intervention such as systemic corticosteroids, emergency department/urgent care visit, hospitalization or death (exacerbation data pooled across Lithos and Vathos)

Lung Function Parameters

Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society guidelines. The schedule of spirometry measurements is outlined in the schedule of assessments (Appendices Table 51 and Table 53). The morning dose on the day of the clinic visit was withheld until after all pre-dose assessments were completed, and albuterol was withheld for at least 6 hours prior to the start time of the visit. Spirometry measurements were conducted at various timepoints during the study visit, depending on the visit number (refer to Appendices, Table 51 and Table 53 for timing of spirometry). Baseline spirometry values were defined as the mean of the pre-dose measurements at Visit 4 (Day 1). Spirometry-based endpoints were defined as the following:

- FEV_1 AUC_{0-3} is the area under the curve for FEV_1 between 0 to 3 hours post-dose. Change from baseline in FEV_1 AUC_{0-3} reflects the bronchodilation in the first 3 hours post-dose.
- Trough FEV_1 is the morning pre-dose FEV_1. Change from baseline in morning pre-dose trough FEV_1 represents the impact of the treatment effect at the end of the dosing interval.
- The onset of action was defined in the protocol as the absolute change from baseline in FEV_1 at 5 minutes post-dose.

Patient-Reported Outcomes

The ACQ-5 and -7 and the AQLQ+12 are patient-reported outcomes (PROs) that were captured electronically throughout the trial.

The ACQ-5 is a 5-item questionnaire that measures the frequency and impact of respiratory symptoms (i.e., wheezing, shortness of breath) on daily activities in the previous week. ACQ-7 is a 7-item questionnaire that incorporates the 5 symptom questions from the ACQ-5, an additional question about the frequency of rescue bronchodilator use (i.e., albuterol) and an additional question about pre-bronchodilator percent predicted FEV_1. The responses are scored on a scale from 0 to 6, where 0 represents 'no symptoms' and 6 represents 'uncontrolled symptoms.' The mean ACQ score is the mean of the 5 or 7 responses, and responders were defined as subjects with a decrease in total score of at least 0.5 points from baseline.

The AQLQ+12 is a 32-item questionnaire designed to assess the impact of asthma symptoms on the health-related quality of life in the previous 2 weeks. The AQLQ+12 is composed of four domains (symptoms, activity limitation, emotional function, and environmental stimuli). The responses to the questions are scored on a scale of 1 to 7, where 1 represents 'severe impairment' and 7 represents 'no impairment.' Responders were defined as subjects with an increase in total score of at least 0.5 points from baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

For Lithos and Vathos, the administration of on-site investigational product (IP) was recorded in the electronic case report form and at-home IP was evaluated during site visits by reviewing the daily electronic diary (eDiary) recordings as well as the remaining doses of the dose counter.

Permitted and Prohibited Concomitant Medications

In both Lithos and Vathos, current ongoing medications (including herbal supplements, over the counter medications and vaccinations) were allowed as long as they were not specifically prohibited. Pertinent prohibited medications for both trials included oral corticosteroids, LAMAs, leukotriene receptor antagonists (LTRAs), and biologic therapies (see Appendix, Table 54 through Table 56).

The only rescue asthma medication that was allowed for both studies was albuterol sulfate.

Lithos Statistical Analysis Plan

Lithos Analysis Populations

- **Screened Set**: Defined as all subjects who sign the informed consent form.
- **Randomized Set**: Defined as all subjects who are randomized to study intervention.
- **Efficacy Set**: Defined as all subjects who are randomized to study intervention and receive any amount of study intervention. Subjects were analyzed according to the study intervention assigned at randomization, regardless of the actual study intervention received.
- **Safety Set**: Defined as all subjects who were randomized to study intervention and received any amount of study intervention. Subjects were analyzed according to the actual study intervention received rather than randomized treatment. The actual treatment is defined as the study treatment that the subject received the most.
- **Pulmonary Function Test Sub-Study Set**: Defined as all subjects who were randomized and had at least one post-baseline spirometry assessment in the sub-study (after the first dose of study treatment).

Lithos Primary Estimand

The Applicant described a primary estimand for this study:

- **Population***:* Subjects age 12 to 80 years of age with inadequately controlled asthma (symptomatic on low dose ICS or ICS/LABA)
- **Treatment***:* Randomized treatment, BID administration of BFF 160/9.6 µg or BD MDI 160 µg BID
- **Endpoint***:* Change from baseline in FEV_1 AUC_{0-3}
- **Intercurrent events (ICEs; strategy used)**:
  - Initiation of any new asthma therapy or administration of prohibited medications thought to impact efficacy (biological therapy/monoclonal antibodies, LABA, LAMA, LTRA, maintenance ICS, or ICS/BA as needed (to capture anti-inflammatory reliever) in conjunction with premature discontinuation of study intervention.[1] (composite strategy - Imputed the worst FEV_1 value of: 12% decrease from subject's baseline value or subject's worst observed value postbaseline during the study)
  - Premature discontinuation from study intervention, with the exception of ICE 1 (treatment policy - all observed data is used)
  - Prolonged exposure to systemic corticosteroids, increased ICS dose for more than 14 days, or depot corticosteroid injection (treatment policy - all observed data is used)
  - Initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy: biological therapy/monoclonal antibodies, LABA, LAMA, LTRA, maintenance ICS, or ICS/BA as needed (to capture anti-inflammatory reliever) following first dose of randomised IP prior to IP discontinuation (treatment policy - all observed data is used)
  - For lung function endpoints only performed within 7 days following exposure to systemic corticosteroids (SCS) or increased ICS (date of last dose of SCS or increased ICS +7 days): Use of SCS or increased ICS dose for $\leq$14 days consecutive (treatment policy - all observed data is used)
- **Population summary measure***:* Difference in mean change from baseline at Week 12

[1] Defined as medication start date occurring either 2 weeks prior to or within 4 weeks following premature discontinuation of randomized study intervention

Lithos Analysis of Primary Endpoint

Change from baseline in FEV_1 AUC_{0-3} was analyzed using a repeated measures analysis of covariance model on the Efficacy Population. The model included treatment, visit, prior maintenance medication (ICS versus ICS/LABA), and treatment-by-visit interaction as categorical covariates, and baseline trough FEV_1 and percent albuterol reversibility as continuous covariates. This analysis is a maximum likelihood-based approach with a missing at random assumption.

Contrasts were used to obtain estimates of the treatment differences at Week 12. Two-sided p-values and point estimates with 95% CIs were produced for each treatment difference. Model-based statistics for other visits were also reported.

Lithos Missing Data Handling and Sensitivity Analysis of Primary Endpoint

Intermittent or monotone missing data was not imputed and was handled through the analysis model.

Tipping-point analyses was conducted to examine the impact of missing data assumption by varying the treatment mean for data following study discontinuation for the Treatment Policy estimand approach. Multiple imputation was used to impute the missing data for these subjects by varying the mean. The effect of BFF 160/9.6 µg was gradually worsened, and the effect of the control group was gradually improved, to the point where the comparison became not statistically significant.

Lithos Subgroup Analysis of Primary Endpoint

To explore the consistency of the overall treatment effect, subgroup analyses based on the primary analysis will be performed for the following factors:

- Region (North America (United States and Canada) vs rest of the world)
- Age with the following categories:
  - ≥12 and <18
  - ≥18 and <65
  - ≥65
- Baseline asthma treatment (ICS, ICS/LABA)
- Baseline pre-bronchodilator percent predicted FEV_1 (≤60%, >60%)
- Reversibility (≥20%, <20%)
- Sex (female, male)

- Race with the following categories:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Other
- Baseline severe asthma exacerbation history (0, ≥1)

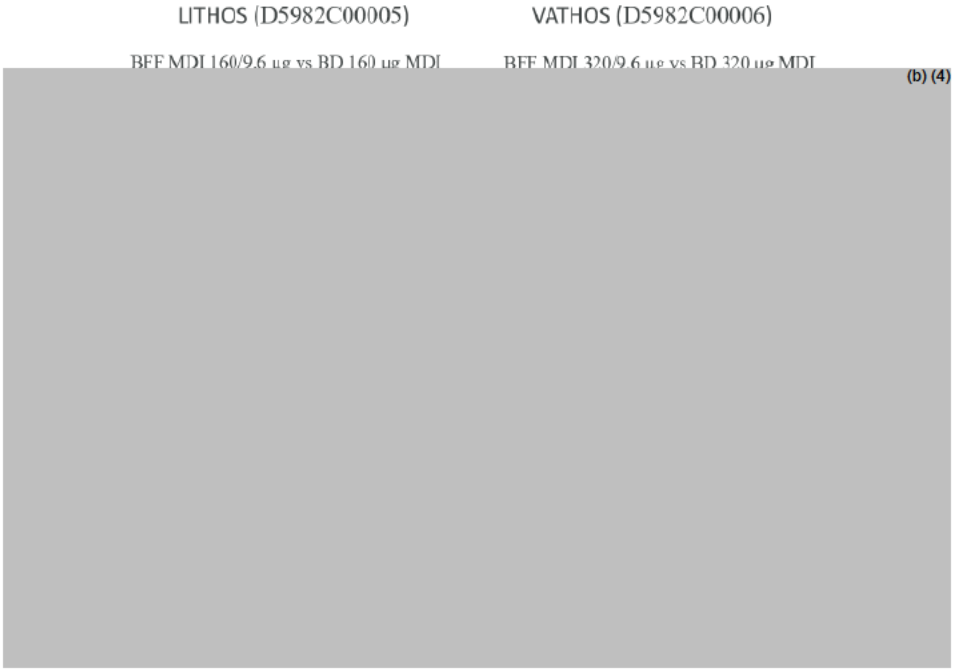
To investigate the interaction effect between subgroup and treatment comparison BFF 160/9.6 µg and BD MDI 160 µg for change from baseline in FEV_1 AUC_{0-3}, a similar model to the primary endpoint was fitted overall (combined subgroup categories) and also including subgroup, treatment by subgroup interaction, subgroup by visit interaction, and treatment by subgroup by visit interaction.

A contrast was computed at Week 12 to test the interaction effect between treatment and subgroup. A two-sided P-value was presented for the interaction effect of interest. Contrasts were used to obtain estimates of the treatment effect at Week 12 within each subgroup category. Point estimates with two-sided P-value and 95% CI were produced for each treatment difference.

Lithos and Vathos Control of Type I Error

The Applicant's multiplicity control is shown in Figure 5 for the comparison of BFF 160/9.6 µg vs BD 160 µg (Lithos) and BFF 320/9.6 µg versus BD 320 µg (Vathos). Note that after onset of action, Type I error of 0.05 is split into rescue use and PROs (0.025) and pooled severe exacerbation rates from both trials (0.025), with a final step of severe exacerbation rate within each trial (0.025).

Figure 5. Type I Error Control Procedure



Source: Lithos SAP, Figure 1
Abbreviations: ACQ-(X), X-item asthma control questionnaire (X=5 or 7); AQLQ(s)+12, asthma quality of life questionnaire(s) for 12 years of age and older; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; SAP, statistical analysis plan

Lithos Analysis of Secondary Endpoints

All secondary endpoints were assessed using the Efficacy Population. All continuous secondary endpoints used the same approach for ICE handling as for the primary endpoint.

Morning Pre-Dose Trough FEV_1 at Week 12

Change from baseline in morning pre-dose trough FEV_1 at Week 12 was the key secondary endpoint. For this endpoint the same choices for handling of ICEs, dropouts, missing data, and the primary analysis were used as for the primary endpoint.

Onset of Action

The Applicant evaluated onset of action on Day 1 by comparing BFF 160/9.6 µg versus BD MDI 160 µg in the mean change from baseline in FEV_1 at the 5 minutes post-dose timepoint. A repeated measures analysis of covariance was fitted to the Day 1 post-baseline data. This model included treatment, timepoint, prior maintenance medication (ICS versus ICS/LABA), and treatment-by-timepoint interaction as categorical covariates and baseline trough FEV_1 and percent reversibility as continuous covariates.

In the FDA review, we felt it was important to evaluate the full 12-hour time course of onset of action, which was done graphically over time for change from baseline in FEV_1 and for proportion of subjects who experienced at least a 100 mL increase from baseline in FEV_1.

Severe Asthma Exacerbation Rate

The rates of severe asthma exacerbations were analyzed using negative binomial regression in the Lithos and Vathos studies separately and with the pooled individual subject data from both studies (Lithos: BFF 160/9.6 µg, BD 160 µg treatment arms; Vathos: BFF 320/9.6 µg, BFF 160/9.6 µg, BD 320 µg treatment arms).

The negative binomial model for each study included treatment, baseline trough FEV_1, percent albuterol reversibility, baseline severe asthma exacerbation history (0, ≥1), prior maintenance medication (ICS versus ICS/LABA), and region as covariates. For the pooled analysis an additive model was used which also included study, and BD (1 if the BD dose is 320 µg, and 0 if the BD dose is 160 µg) and FF (1 if the FF dose is 9.6 µg, and 0 if no FF dose) instead of treatment as covariates. The comparison of interest was the FF effect. For the pooled analysis one dispersion parameter was estimated. Time at risk of experiencing a severe exacerbation was used as an offset variable in the model. Time during a severe exacerbation or in the 7 days following a severe exacerbation was not included in the calculation of exposure.

Change From Baseline in Average Daily Rescue Albuterol Use Over 12 Weeks

A repeated measures analysis of covariance model was used to analyze change from baseline in average daily rescue albuterol use. The model included treatment, the number of the relevant 4-week interval (interval 1 to 3), prior maintenance medication (ICS versus ICS/LABA), severe asthma exacerbation history (0, ≥1), and the treatment-by-4-week interval interaction as categorical covariates and baseline daily rescue albuterol use, baseline trough FEV_1 and percent albuterol reversibility as continuous covariates. Contrasts were used to obtain estimates of the treatment differences over 12 weeks. Two-sided p-values and point estimates with two-sided 95% CIs were produced for each treatment difference.

ACQ-7, ACQ-5, AQLQ(s)+12 at Week 12

Responder analysis was performed for these quality of life endpoints. Following the Treatment Policy estimand approach, all available data was utilized to determine response irrespective of any ICEs; subjects who withdrew from the study were considered non-responders. Missing data for reasons related to global/country situation were not be imputed, as those datapoints were considered to be missing completely at random and were excluded from the analysis. Intermittently missing data was classified as non-response.

Logistic regression was used to compare treatment groups, with treatment and prior maintenance medication (ICS versus ICS-LABA) as categorical covariates and baseline instrument score, baseline trough FEV_1, and percent albuterol reversibility as continuous covariates. ICEs were handled with all available data utilized to determine response irrespective of any ICEs except new asthma medication or administration of prohibited medication thought to impact efficacy in conjunction with premature study treatment discontinuation, where a subject was considered non-responder.

Vathos Statistical Analysis Plan

Vathos Analysis Populations

Screened, Randomized, Efficacy and Safety Sets for Vathos were defined as above for Lithos.

Additionally, Vathos had a rescue albuterol user population, defined as all subjects in the efficacy population with average baseline Rescue Albuterol use of ≥1 puff/day. This population was defined in order to represent the population of patients who may benefit from study treatment and reduce their use of rescue medication.

Vathos Primary Estimand

The Applicant described a primary estimand for this study:

- **Population**: Subjects age 12 to 80 years of age with inadequately controlled asthma (symptomatic on medium dose ICS or ICS-LABA)
- **Treatment**: Randomized treatment, BID adiminstration of BFF 160/9.6 µg, BFF 320/9.6 µg or BD MDI 320 µg, Symbicort TBH 320/9 µg
- **Endpoint**: Change from baseline in FEV_1 AUC_{0-3} (same as Lithos)
- **ICEs (strategy used)**: Identical to Lithos trial ICEs and estimand strategies.
- **Population summary measure**: Difference in mean change from baseline at Week 24

Vathos Analysis of Primary Endpoint

Change from baseline in FEV_1 AUC_{0-3} was analyzed using a repeated measures analysis of covariance model on the Efficacy Population using the same model as in the Lithos trial.

Contrasts were used to obtain estimates of the treatment differences at Week 24. Two-sided p-values and point estimates with 95% CIs were produced for each treatment difference.

Model-based statistics for other visits were also reported.

Vathos Missing Data Handling and Sensitvity Analysis of Primary Endpoint

Missing data was handled in the same manner as in the Lithos trial. Tipping point analysis was addressed in the same manner as in the Lithos trial as well.

Vathos Subgroup Analysis of Primary Endpoint

To explore the consistency of the overall treatment effect, subgroup analyses based on the primary analysis were performed for the same factors as the Lithos study, except that baseline pre-bronchodilator percent predicted FEV_1 (≤60%, >60%) was not analyzed. The race categories

for Vathos grouped American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander categories into 'Other.'

Interaction effect between subgroup and treatment comparison BFF 320/9.6 µg and BD MDI 320 µg for change from baseline in FEV_1 AUC_{0-3} was addressed similarly to how performed in the Lithos trial.

7.1.3. Study Results

The Applicant is proposing to market BFF 160/9.6 and BFF 320/9.6 and not Symbicort TBH in the United States; therefore, only efficacy results for BFF 160/9.6 and BFF 320/9.6, vs the respective BD monocomponents, are discussed in the following sections.

Compliance With Good Clinical Practices

All studies were conducted in accordance with good clinical practice (GCP), unless noted below, as required by the International Council for Harmonisation guidelines and in accordance with country-specific laws and regulations governing clinical studies of IPs and data protection.

GCP Noncompliance

Lithos and Vathos

- Site (b) (4) for Lithos and Site (b) (4) for Vathos (same site with different identifiers for each study, conducted in the United States) (b) (4) Following review of the data, the Applicant assessed the findings as having a direct impact on data integrity, although no safety concerns were identified. Data from this site was excluded from all analysis sets, except the Screened Set (AEs were included).

Lithos

- Site (b) (4) (Philippines) – As part of routine Centralized Statistical Monitoring activities conducted by the Applicant, (b) (4) . Following review of the data, the Applicant assessed the findings as having a direct impact on data integrity, although no safety concerns were identified. Data from this site was excluded from all analysis sets, except the Screened Set (AEs were included).
- Site (b) (4) (Czech Republic) and Site (b) (4) (United States)– (b) (4) . After review, the findings were assessed (b) (4) . These subjects were excluded from all analysis sets, except the Screened Set (AEs were included).

Financial Disclosure

Financial disclosures were submitted and reviewed. No significant conflicts of interest were identified that impacted the efficacy and safety assessment. See Section 12.2 in Appendices for more details.

Subject Disposition

In the Lithos trial, 357 subjects were randomized in a 1:1 ratio to BFF 160/9.6 µg or BD 160 µg (Table 11). Most subjects received study treatment (99%). A sizable majority completed the 12 week study period (96%). Of the 12 (3%) of subjects who prematurely discontinued study drug, 3 subjects were in the BFF arm and 9 in the BD arm. The most common reason was 'subject decision' (1% of subjects, with 1 subject in the BFF arm and 4 in the BD arm).

Lithos analysis sets were defined in the statistical analysis plan (SAP) section above (Section 7.1.2), with results in Table 12.

Table 11. Study Disposition, All Randomized Subjects, Lithos

Disposition Category	BFF 160/9.6 µg N=181 n (%)	BD MDI 160 µg N=176 n (%)	Total N=357 n (%)
All randomized	181 (100.0)	176 (100.0)	357 (100.0)
Subject started treatment	179 (98.9)	174 (98.9)	353 (98.9)
Subject completed study drug	176 (97.2)	165 (93.8)	341 (95.5)
Subject discontinued drug	3 (1.7)	9 (5.1)	12 (3.4)
Adverse event	0 (0.0)	1 (0.6)	1 (0.3)
Lost to follow-up	0 (0.0)	1 (0.6)	1 (0.3)
Other	1 (0.6)	2 (1.1)	3 (0.8)
Subject decision	1 (0.6)	4 (2.3)	5 (1.4)
Withdrawal of consent	1 (0.6)	1 (0.6)	2 (0.6)

Source: Statistical Reviewer Analysis; adsl.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_disposition table_2025.10.21.rtf
Abbreviations: BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified disposition; NDA, new drug application

Table 12. Analysis Sets, Lithos

Analysis Set	BFF 160/9.6 µg n	BD MDI 160 µg n	Total N
Randomized set	181	176	357
Safety set	179	174	353
Excluded from safety set	2	2	4
Subject did not receive study intervention	2	2	4
Efficacy set	177	169	346
Excluded from efficacy set	4	7	11
Subject did not receive study intervention	2	2	4
Subject randomized more than one time	2	5	7
Pulmonary function test sub-study set	57	57	114
Excluded from pulmonary function test sub-study set	131	129	260
Subject missing a postbaseline spirometry assessment	120	112	232
Subject did not receive study intervention	2	2	4
Subject randomized more than one time	2	5	7

Source: Statistical Reviewer Analysis; adsl.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_population table_2025.10.27.rtf
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects in analysis set; NDA, new drug application

In the Vathos trial, 585 subjects were randomized in a 1:2:2:2 ratio to BFF 160/9.6 µg, BFF 320/9.6 µg, BD 320 µg, or Symbicort 320/9 µg (Table 13). Most subjects received study treatment (99%). A majority completed the 24-week study period (90%). There were 53 (9%) of subjects who discontinued study drug. The most common reason was 'subject decision' (3% of subjects).

Vathos analysis sets were defined in the SAP section above (Section 7.1.2), with results in Table 14.

Table 13. Study Disposition, All Randomized Subjects, Vathos

Disposition Category	BFF 160/9.6 µg N=89 n (%)	BFF 320/9.6 µg N=166 n (%)	BD MDI 320 µg N=168 n (%)	Symbicort TBH 320/9 µg N=162 n (%)	Total N=585 n (%)
All randomized	89 (100.0)	166 (100.0)	168 (100.0)	162 (100.0)	585 (100.0)
Subject started treatment	88 (98.9)	163 (98.2)	168 (100.0)	162 (100.0)	581 (99.3)
Subject completed study drug	80 (89.9)	148 (89.2)	152 (90.5)	148 (91.4)	528 (90.3)
Subject discontinued drug	8 (9.0)	15 (9.0)	16 (9.5)	14 (8.6)	53 (9.1)
Adverse event	2 (2.2)	6 (3.6)	3 (1.8)	3 (1.9)	14 (2.4)
Development of study-specific discontinuation criteria	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Lack of efficacy	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Lost to follow-up	0 (0.0)	0 (0.0)	4 (2.4)	0 (0.0)	4 (0.7)
Other	2 (2.2)	1 (0.6)	1 (0.6)	2 (1.2)	6 (1.0)
Physician decision	1 (1.1)	2 (1.2)	0 (0.0)	0 (0.0)	3 (0.5)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Subject decision	3 (3.4)	4 (2.4)	3 (1.8)	6 (3.7)	16 (2.7)
Withdrawal of consent	0 (0.0)	1 (0.6)	4 (2.4)	1 (0.6)	6 (1.0)

Source: Statistical Reviewer Analysis; adsl.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_disposition table_2025.10.21.rtf
Abbreviations: BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified disposition; NDA, new drug application; TBH, Turbuhaler

Table 14. Analysis Sets, Vathos

Analysis Set	BFF 160/9.6 µg n	BFF 320/9.6 µg n	BD MDI 320 µg n	Symbicort TBH 320/9 µg n	Total N
Randomized set	89	166	168	162	585
Safety set	88	163	168	162	581
Excluded from safety set	1	3	0	0	4
Subject did not receive study intervention	1	3	0	0	4
Efficacy set	87	162	166	160	575
Excluded from efficacy set	2	4	2	2	10
Subject did not receive study intervention	1	3	0	0	4
Subject randomized more than one time	1	1	2	2	6
Per-protocol set	70	125	137	130	462
Excluded from per-protocol set	19	41	31	32	123
Subject did not receive study intervention	1	3	0	0	4
Subject had an IPD impacting efficacy at randomization visit	17	37	29	30	113
Subject randomized more than one time	1	1	2	2	6

Source: Statistical Reviewer Analysis; adsl.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_population table_2025.10.28.rtf
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; IPD, important protocol deviation; MDI, metered-dose inhaler; N, total number of subjects; n, number of subjects in analysis set; NDA, new drug application

Important Protocol Violations/Deviations

In Lithos, 13% of subjects had at least one important protocol deviation (IPD) (Table 15). The most common was deviations from an inclusion criteria IPD (6%), with 8% experienced in the BFF 160/9.6 µg arm and 4% in the BD 160 µg arm. There were 3% of subjects who were administered excluded medications, with similar frequencies on both treatment arms (3% on the BFF 160/9.6 µg and 4% on the BD 160 µg arm).

In Vathos, 24% of subjects had at least one IPD (Table 16). The most common was deviations related to study procedure (11%), with 6% experienced in the BFF 160/9.6 µg, 14% in BFF 320/9.6 µg, 11% in BD 320 µg arm and 9% in the Symbicort TBH 320 µg arm. There were 8% of subjects who were administered excluded medications, with similar frequencies on most treatment arms (12% on BFF 160/9.6 µg, 11% in BFF 320/9.6 µg, and 9% in the Symbicort TBH 320 µg arm) whereas the frequency of 4% was experienced in the BD 320 µg arm).

Table 15. Protocol Deviations, Randomized Set, Lithos

Protocol Deviations	BFF 160/9.6 µg N=181 n (%)	BD MDI 160 µg N=176 n (%)	Total N=357 n (%)
Subjects with at least one important protocol deviation	23 (12.7)	24 (13.6)	47 (13.2)
Inclusion criteria	15 (8.3)	7 (4.0)	22 (6.2)
Exclusion criteria	1 (0.6)	4 (2.3)	5 (1.4)
Discontinuation criteria for study product met but subject not withdrawn from study treatment	0	0	0
Discontinuation criteria for overall study withdrawal met but subject not withdrawn from study	0	0	0
Investigational product deviation	1 (0.6)	0	1 (0.3)
Excluded medications taken	5 (2.8)	7 (4.0)	12 (3.4)
Deviations related to study procedure	0	1 (0.6)	1 (0.3)
Other important deviations	3 (1.7)	5 (2.8)	8 (2.2)

Source: Lithos CSR, Table 6
Protocol deviations were defined by the Appliant as deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a subject's rights, safety or well-being.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CSR, clinical study report; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified protocol deviation

Table 16. Protocol Deviations, Randomized Set, Vathos

Protocol Deviation	BFF 160/9.6 µg N=89 n (%)	BFF 320/9.6 µg N=166 n (%)	BD MDI 320 µg N=168 n (%)	Symbicort TBH 320/9 µg N=162 n (%)	Total N=585 n (%)
Subjects with at least 1 IPD	21 (23.6)	47 (28.3)	37 (22.0)	38 (23.5)	143 (24.4)
Inclusion criteria	5 (5.6)	8 (4.8)	12 (7.1)	8 (4.9)	33 (5.6)
Exclusion criteria	0	1 (0.6)	4 (2.4)	5 (3.1)	10 (1.7)
Discontinuation criteria for study product met but subject not withdrawn from study treatment	0	1 (0.6)	0	0	1 (0.2)
Discontinuation criteria for overall study withdrawal met but subject not withdrawn from study	0	0	0	0	0
Investigation product deviation	0	3 (1.8)	2 (1.2)	4 (2.5)	9 (1.5)
Excluded medication taken	11 (12.4)	18 (10.8)	7 (4.2)	14 (8.6)	50 (8.5)
Deviations related to study procedure	5 (5.6)	24 (14.5)	19 (11.3)	14 (8.6)	62 (10.6)
Other IPDs	2 (2.2)	0	0	0	2 (0.3)
Subjects randomised multiple times at different sites or studies	1 (1.1)	1 (0.6)	2 (1.2)	2 (1.2)	6 (1.0)

Source: Vathos CSR, Table 6

Protocol deviations were defined by the Appliant as deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a subject's rights, safety or well-being.

Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CSR, clinical study report; IPD, important protocol deviation; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified protocol deviation; TBH, Turbuhaler

Intercurrent Events

Intercurrent events are those that occur after randomization and have potential to impact the interpretation of results. In Lithos, there were 3% of events where new asthma therapy was initiated in conjunction with study drug discontinuation, handled with Composite strategy: 1% in the BFF 160/9.6 arm and 5% in the BD 160 arm. The remainder of ICEs were handled with Treatment Policy. There were 8% of subjects that used systemic steroids for <14 days, 3% with study treatment discontinuation not associated with new asthma therapy, and 1% with prolonged exposure to systemic steroids or increased dose (Table 17).

In Lithos, there were 10 subjects evaluated by the Applicant that had imputed FEV_1 AUC_{0-3} value for records collected after ICE #1. Two subjects had a post-baseline record before ICE #1: (b) (6). When comparing the worst observed value versus the 12% decrease from subject's baseline value, the latter was worse for both. (b) (6) use a single-timepoint FEV_1 observed value that is worse than a 12% decrease.

In Vathos, there were 7% of events where new asthma therapy was initiated in conjunction with study drug discontinuation, handled with Composite strategy: 7% in BFF 160/9.6, 7% in BFF 320/9.6 µg, 8% in BD 320 µg arm and 7.5% in the Symbicort TBH 320 µg arm. The remainder of ICEs were handled with Treatment Policy. There were 10% of subjects that used systemic steroids for ≤14 days, 9% with study treatment discontinuation not associated with new asthma therapy, and <1% with prolonged exposure to systemic steroids or increased dose (Table 18).

For Vathos, there were 42 subjects with an imputed FEV_1 AUC_{0-3} value for records after an ICE #1. Nine subjects have a post-baseline record before ICE 4: (b) (6) Six of these subjects had the 12% decrease applied while the other 3 subjects use a single-timepoint FEV_1 observed value that is worse than a 12% decrease.

Table 17. Intercurrent Events, Efficacy Set, Lithos

Intercurrent Event	Strategy	BFF 160/9.6 µg N=177 n (%)	BD MDI 160 µg N=169 n (%)	Total N=346 n (%)
1. Initiation of new asthma therapy in conjunction with premature study drug discontinuation	Composite	2 (1.1)	8 (4.7)	10 (2.9)
2. Other premature study drug discontinuation	Treatment policy	3 (1.7)	9 (5.3)	12 (3.5)
3. Prolonged exposure to systemic steroids or increased dose	Treatment policy	1 (0.6)	0 (0.0)	1 (0.3)
4. Initiation of new asthma therapy	Treatment policy	0 (0.0)	0 (0.0)	0 (0.0)
5. Use of systemic steroids or increased dose for ≤14 days (PFT endpoints only)	Treatment policy	12 (6.8)	17 (10.1)	29 (8.4)

Source: Statistical Reviewer Analysis: adsl.xpt, adiceo.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_ICE table_2025.11.6.rtf
Percentages are calculated as n/N where N is the total number of subjects in each treatment group.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with intercurrent event; NDA, new drug application; PFT, pulmonary function test

Table 18. Intercurrent Events, Efficacy Set, Vathos

Intercurrent Event	Strategy	BFF 160/9.6 µg N=87 n (%)	BFF 320/9.6 µg N=162 n (%)	BD MDI 320 µg N=166 n (%)	Symbicort TBH 320/9 µg N=160 n (%)	Total n (%)
1. Initiation of new asthma therapy in conjunction with premature study drug discontinuation	Composite	6 (6.9)	11 (6.8)	13 (7.8)	12 (7.5)	42 (7.3)
2. Other premature study drug discontinuation	Treatment policy	7 (8.0)	15 (9.3)	16 (9.6)	14 (8.8)	52 (9.0)
3. Prolonged exposure to systemic steroids or increased dose	Treatment policy	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.5)
4. Initiation of new asthma therapy	Treatment policy	1 (1.1)	1 (0.6)	1 (0.6)	1 (0.6)	4 (0.7)
5. Use of systemic steroids or increased dose for ≤14 days (PFT endpoints only)	Treatment policy	4 (4.6)	17 (10.5)	15 (9.0)	24 (15.0)	60 (10.4)

Source: Statistical Reviewer Analysis: adsl.xpt, adiceo.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_ICE table_2025.11.6.rtf.
Percentages are calculated as n/N where N is the total number of subjects in each treatment group.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; ICE, intercurrent event; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects with intercurrent event; NDA, new drug application; PFT, pulmonary function test; TBH, Turbuhaler

Demographic Characteristics

There were more female than male subjects in the Lithos trial (70%), with more females in the BD 160 µg arm (76%). Most were either White (67%) or Asian (17%). Their mean age was 48.4 years. Aside from sex and race, demographic characteristics were generally well-balanced across treatment arms (Table 19).

Table 19. Demographics, Efficacy Set, Lithos

Demographic Characteristic	BFF 160/9.6 µg N=177	BD MDI 160 µg N=169	Total N=346
Age (years)			
Mean (SD)	48.8 (16.57)	48.0 (16.15)	48.4 (16.35)
Median	51.0	50.0	50.0
Min, max	12.0, 78.0	12.0, 79.0	12.0, 79.0
Age group (years), n (%)			
≥12 to <18 years	6 (3.4)	5 (3.0)	11 (3.2)
≥18 to <65 years	139 (78.5)	130 (76.9)	269 (77.7)
≥65 years	32 (18.1)	34 (20.1)	66 (19.1)
≥75 years	4 (2.3)	5 (3.0)	9 (2.6)
Sex, n (%)			
Female	113 (63.8)	128 (75.7)	241 (69.7)
Male	64 (36.2)	41 (24.3)	105 (30.3)
Race, n (%)			
Black or African American	15 (8.5)	19 (11.2)	34 (9.8)
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Asian	27 (15.3)	33 (19.5)	60 (17.3)
Other	9 (5.1)	5 (3.0)	14 (4.0)
White	123 (69.5)	110 (65.1)	233 (67.3)
Multiple	2 (1.1)	2 (1.2)	4 (1.2)
Ethnicity, n (%)			
Hispanic or Latino	45 (25.4)	34 (20.1)	79 (22.8)
Not Hispanic or Latino	132 (74.6)	135 (79.9)	267 (77.2)
BMI			
Mean (SD)	28.9 (5.11)	28.5 (5.51)	28.7 (5.30)
Median	29.0	28.0	28.0
Min, max	17.0, 39.0	15.0, 40.0	15.0, 40.0

Source: Statistical Reviewer Analysis; adsl.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_demographics table_2025.10.24.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; BMI, body mass index; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified characteristic; NDA, new drug application; SD, standard deviation

There were more female than male subjects in the Vathos trial (62%). Most were either White (73%), Black (11%) or Asian (12%). Their mean age was 49.9 years. Aside from sex and race, demographic characteristics were generally well-balanced across treatment arms (Table 20).

Table 20. Demographics, Efficacy Set, Vathos

Characteristic Statistic	BFF 160/9.6 µg N=87	BFF 320/9.6 µg N=162	BD MDI 320 µg N=166	Symbicort TBH 320/9 µg N=160	Total N=575
Age (years)					
Mean (SD)	49.4 (17.21)	49.7 (15.81)	49.0 (15.23)	51.3 (15.34)	49.9 (15.72)
Median	53.0	53.0	50.5	54.5	53.0
Min, max	15.0, 77.0	13.0, 77.0	13.0, 75.0	14.0, 78.0	13.0, 78.0
Age group (years), n (%)					
≥12 to <18 years	3 (3.4)	6 (3.7)	7 (4.2)	5 (3.1)	21 (3.7)
≥18 to <65 years	67 (77.0)	123 (75.9)	130 (78.3)	122 (76.3)	442 (76.9)
≥65 years	17 (19.5)	33 (20.4)	29 (17.5)	33 (20.6)	112 (19.5)
≥75 years	3 (3.4)	3 (1.9)	1 (<1)	3 (1.9)	10 (1.7)
Sex, n (%)					
Female	48 (55.2)	101 (62.3)	108 (65.1)	101 (63.1)	358 (62.3)
Male	39 (44.8)	61 (37.7)	58 (34.9)	59 (36.9)	217 (37.7)
Race, n (%)					
Black or African American	9 (10.3)	16 (9.9)	17 (10.2)	24 (15.0)	66 (11.5)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (<1)	1 (<1)
American Indian or Alaska Native	0	0	1 (<1)	0	1 (<1)
Asian	9 (10.3)	22 (13.6)	18 (10.8)	19 (11.9)	68 (11.8)
White	64 (73.6)	119 (73.5)	122 (73.5)	112 (70.0)	417 (72.5)
Other	5 (5.7)	5 (3.1)	8 (4.8)	4 (2.5)	22 (3.8)
Ethnicity, n (%)					
Hispanic or Latino	14 (16.1)	40 (24.7)	38 (22.9)	31 (19.4)	123 (21.4)
Not Hispanic or Latino	73 (83.9)	122 (75.3)	128 (77.1)	129 (80.6)	452 (78.6)

Characteristic Statistic	BFF 160/9.6 µg N=87	BFF 320/9.6 µg N=162	BD MDI 320 µg N=166	Symbicort TBH 320/9 µg N=160	Total N=575
BMI					
Mean (SD)	28.6 (5.32)	28.5 (5.12)	29.2 (5.50)	28.9 (5.34)	28.8 (5.32)
Median	28.3	28.2	29.3	28.8	28.7
Min, max	16.5, 39.7	18.7, 39.6	17.8, 39.8	16.4, 39.6	16.4, 39.8

Source: Statistical Reviewer Analysis; adsl.xpt, adscre.xpt, adqsacq.xpt, adqsast.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_demographics table_2025.10.23.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; BMI, body mass index; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects with specified characteristic; NDA, new drug application; SD, standard deviation; TBH, Turbuhaler

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The important baseline characteristics were generally balanced in the Lithos trial (Table 21) and Vathos trial (Table 22).

Table 21. Baseline Disease Characteristics, Efficacy Set, Lithos

Disease Characteristic Statistics	BFF 160/9.6 µg N=177	BD MDI 160 µg N=169	Total N=346
Blood eosinophil count (cells per mm^3)			
Mean (SD)	189.9 (121.12)	188.2 (138.85)	189.1 (129.92)
Median	170.0	150.0	160.0
Min, max	20.0, 650.0	20.0, 1070.0	20.0, 1070.0
Missing	1	0	1
Prebronchodilator % predicted FEV_1			
Mean (SD)	69.7 (10.70)	70.4 (9.35)	70.1 (10.05)
Median	70.6	71.6	71.2
Min, max	50.2, 90.0	50.2, 89.6	50.2, 90.0
Rescue med use (puffs/day)			
Mean (SD)	1.1 (1.82)	1.2 (1.62)	1.2 (1.72)
Median	0.1	0.3	0.3
Min, max	0.0, 10.3	0.0, 6.7	0.0, 10.3
Missing	6	2	8
Asthma meds (≥8 weeks prior to Visit 1), n (%)			
ICS	43 (24.3)	42 (24.9)	85 (24.6)
ICS/LABA	134 (75.7)	127 (75.1)	261 (75.4)
Smoking status, n (%)			
Former smoker	38 (21.5)	25 (14.8)	63 (18.2)
Non-smoker	139 (78.5)	144 (85.2)	283 (81.8)
Smoking pack years			
Mean (SD)	4.4 (3.07)	4.0 (2.92)	4.3 (2.99)
Median	5.0	4.0	4.0
Min, max	0.0, 10.0	0.0, 10.0	0.0, 10.0
Missing	139	144	283

Disease Characteristic Statistics	BFF 160/9.6 µg N=177	BD MDI 160 µg N=169	Total N=346
ACQ-7			
Mean (SD)	2.4 (0.59)	2.4 (0.54)	2.4 (0.57)
Median	2.3	2.3	2.3
Min, max	0.6, 5.3	1.6, 4.6	0.6, 5.3

Source: Statistical Reviewer Analysis; adsl.xpt, adscre.xpt, adqsacq.xpt, adqsast.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_baseline characteristics table_2025.10.24.rtf
Abbreviations: ACQ-7, 7-item asthma control questionnaire; BD, budesonide; BFF, budesonide/formoterol fumarate; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified disease characteristic; NDA, new drug application; SD, standard deviation

Table 22. Baseline Disease Characteristics, Efficacy Set, Vathos

Disease Characteristic Statistics	BFF 160/9.6 µg N=87	BFF 320/9.6 µg N=162	BD MDI 320 µg N=166	Symbicort TBH 320/9 µg N=160	Total N=575
Blood eosinophil count (cells per mm^3)					
Mean (SD)	196.8 (132.57)	201.7 (276.26)	216.5 (255.65)	200.7 (155.24)	205.0 (222.30)
Median	160.0	150.0	155.0	150.0	150.0
Min, max	40.0, 720.0	30.0, 3180.0	0.0, 2650.0	20.0, 730.0	0.0, 3180.0
Missing	0	3	0	0	3
Prebronchodilator % predicted FEV_1					
Mean (SD)	72.2 (9.79)	70.7 (9.69)	71.3 (9.60)	70.4 (9.79)	71.0 (9.70)
Median	72.7	71.0	70.8	70.9	71.1
Min, max	50.6, 89.4	50.8, 86.7	51.7, 88.5	50.2, 88.5	50.2, 89.4
Missing	0	1	0	1	2
Rescue med use (puffs/day)					
Mean (SD)	1.1 (1.53)	1.0 (1.45)	1.2 (1.60)	1.3 (1.69)	1.1 (1.58)
Median	0.3	0.3	0.4	0.6	0.3
Min, max	0.0, 5.9	0.0, 8.9	0.0, 6.9	0.0, 8.0	0.0, 8.9
Missing	2	4	3	5	14
Asthma meds (≥8 weeks prior to Visit 1), n (%)					
ICS	11 (12.6)	17 (10.5)	20 (12.0)	19 (11.9)	67 (11.7)
ICS/LABA	76 (87.4)	145 (89.5)	145 (87.3)	141 (88.1)	507 (88.2)
ICS/LAMA/LABA	0	0	1 (<1)	0	1 (<1)
Smoking status, n (%)					
Former smoker	19 (21.8)	34 (21.0)	48 (28.9)	34 (21.3)	135 (23.5)
Non-smoker	68 (78.2)	128 (79.0)	118 (71.1)	126 (78.8)	440 (76.5)

Disease Characteristic Statistics	BFF 160/9.6 µg N=87	BFF 320/9.6 µg N=162	BD MDI 320 µg N=166	Symbicort TBH 320/9 µg N=160	Total N=575
Smoking pack years					
Mean (SD)	4.3 (3.19)	3.9 (3.23)	4.6 (3.16)	5.4 (3.08)	4.6 (3.17)
Median	3.0	2.0	4.0	5.0	4.0
Min, max	0.0, 9.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0
Missing	68	129	119	126	442
ACQ-7					
Mean (SD)	2.2 (0.53)	2.3 (0.48)	2.4 (0.56)	2.3 (0.48)	2.3 (0.52)
Median	2.1	2.3	2.3	2.3	2.3
Min, max	1.6, 4.7	1.6, 3.9	1.3, 4.0	1.3, 3.9	1.3, 4.7

Source: Statistical Reviewer Analysis; adsl.xpt, adscre.xpt, adqsacq.xpt, adqsast.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_baseline characteristics table_2025.10.24.rtf.
Abbreviations: ACQ-7, 7-item asthma control questionnaire; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler; NDA, new drug application; SD, standard deviation; TBH, Turbuhaler

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In Lithos, treatment compliance measured by eDiary was high (mean 89.55%, median 94.08%) and was well balanced between both treatment arms. In Vathos, compliance was also high (mean 88.27%, median 93.13%) and well balanced between all four treatment arms.

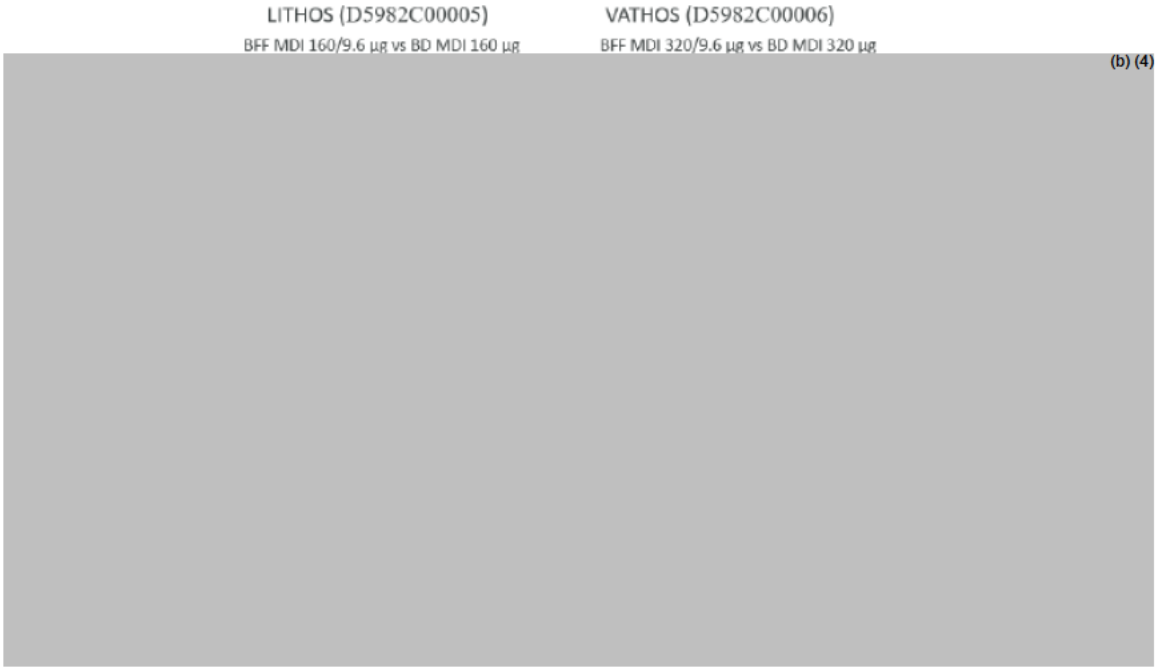
Concomitant medication was defined as any medication that was taken on or after the first dose of IP after randomization. In Lithos, use of concomitant medications was well balanced between both treatment arms (93.8% in BFF 160/9.6 vs 94.1% in BD 160) during the treatment period; the most commonly used asthma-related medications were salbutamol (72%), cetirizine hydrochloride (5.8%) and fluticasone propionate (4.6%). In Vathos, the use of all concomitant medications was fairly well balanced between treatment arms (98.9% in BFF 160/9.6. 96.3% in BFF 320/9.6 and 94.6% in BD 320). The most commonly used asthma-related medications in Vathos were the same as in Lithos: salbutamol (70.1%), cetirizine hydrochloride (7.1%) and fluticasone propionate (5.7%).

Overall, treatment compliance and concomitant medication use in Lithos and Vathos were well balanced between the individual study treatment arms and are unlikely to impact evaluation of efficacy.

Efficacy Results

Efficacy results were controlled for multiplicity as noted in the SAP section (Section 7.1.2, Figure 5). Results of these multiplicity-controlled endpoints are shown in Figure 6. The Lithos trial achieved significance through all of the quality of life endpoints. Conversely, the Vathos trial was not statistically significant for ACQ-5 or ACQ-7. Pooled results for severe exacerbations were also not statistically significant. See specific endpoint sections below for details.

Figure 6. Overview of Efficacy Results Regarding Type I Error Control, Efficacy Set



Source: Lithos CSR, Figure 3
Abbreviations: ACQ-5, 5-item asthma control questionnaire; ACQ-7, 7-item asthma control questionnaire; AQLQ(s)+12, asthma quality of life questionnaire for 12 years of age and older; AUC_{0-3}, area under the curve from 0 to 3 hours; BFF, budesonide/formoterol fumarate; CSR, clinical study report; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler

Primary Endpoint

Lithos Primary Endpoint Results

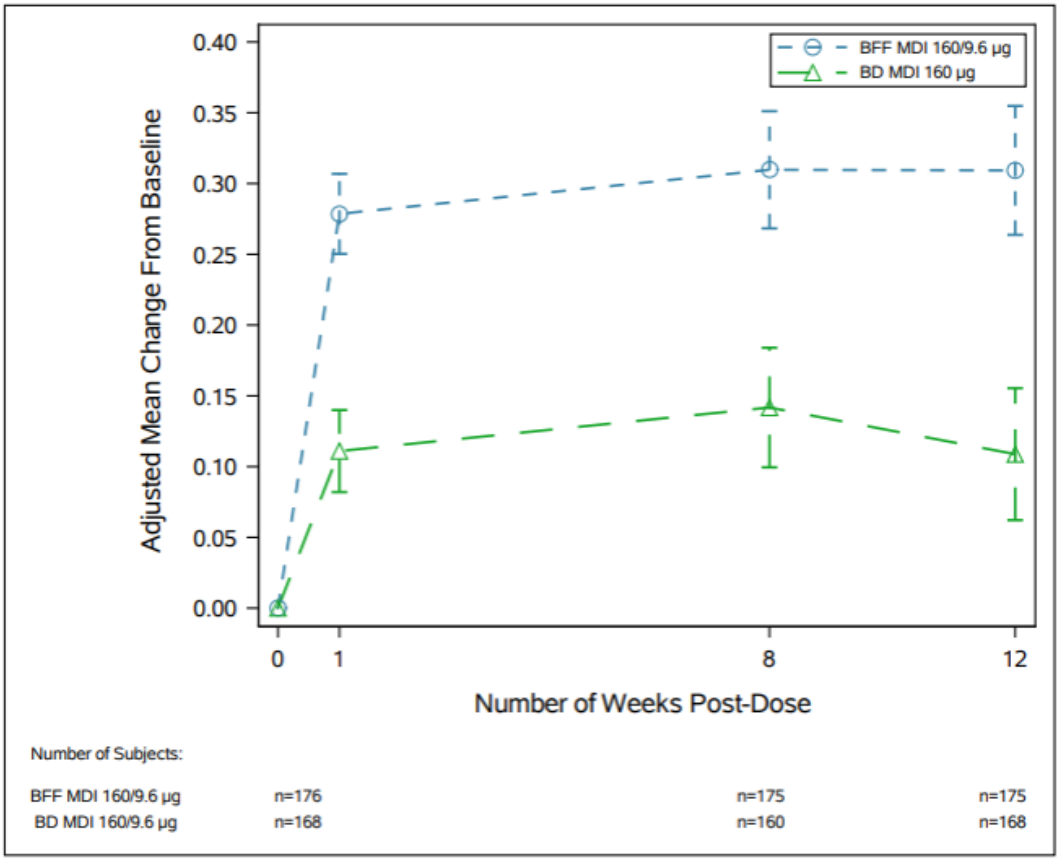
The primary endpoint was change from baseline in FEV_1 AUC_{0-3} at Week 12 comparing BFF 160/9.6 µg vs. BD 160 µg, based on the Efficacy Set. Results are shown in Table 23 and Figure 7. Change from baseline to Week 12 means for BFF 160/9.6 µg and BD 160 µg were 0.31 L and 0.11 L, respectively. with a mean change from baseline of 0.20 L (95% CI: 0.13 to 0.27; p-value<0.0001).

Table 23. Change From Baseline in FEV_1 AUC_{0-3} (L) at Week 12, Efficacy Set, Lithos

					Comparison With BD MDI 160 µg			
Timepoint	**Group**	**n**	**Estimate**	**SE**	**Estimate**	**SE**	**95% CI**	**p-Value**
Week 12	BFF 160/9.6 µg N=177	175	0.309	0.0235	0.200	0.0337	(0.134, 0.267)	<0.0001
Week 12	BD MDI 160 µg N=169	168	0.109	0.0241				

Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_primary endpoint FEV1 AUC0-3 table_2025.11.17.rtf.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; NDA, new drug application; SE, standard error

Figure 7. Change From Baseline in FEV_1 AUC_{0-3} (L) Over Time, Efficacy Set, Lithos



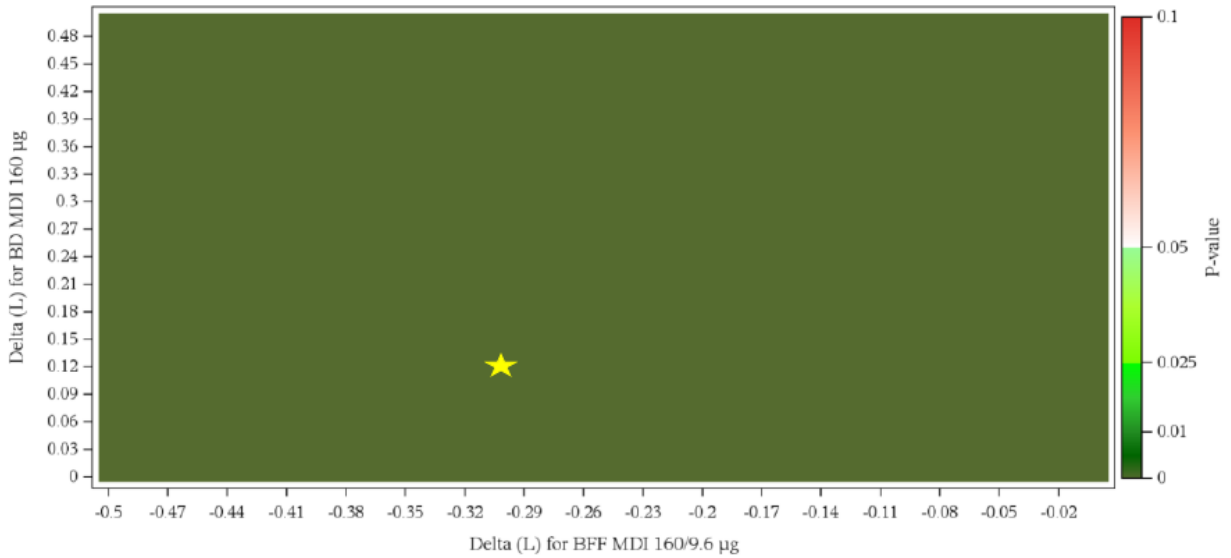
Source: Statistcal Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_primary endpoint FEV1 AUC0-3 figure_2026.3.18.rtf.
95% confidence intervals are reported.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; NDA, new drug application

Lithos Primary Endpoint Sensitivity Analysis

Tipping-point analysis was conducted to examine the impact of missing data assumption using multiple imputation to impute values for missing data by varying the mean using the same model as the primary analysis. Missing data since study discontinuation and until the last planned study day were imputed.

The heat map in Figure 8 displays the relationship between assumed differences from baseline and the corresponding nominal p-values. The treatment effect remains statistically significant (indicated by green) across a wide range of plausible assumptions, including scenarios where the mean for the BFF 160/9.6 µg treatment effect for the unobserved observations is reduced by up to 500 mL, and the mean for the BD 9.6 µg treatment effect for the unobserved observations is increased by up to 500 mL. These findings suggest that the conclusions for the endpoint, change from baseline in FEV_1 AUC at Week 12, is robust to reasonable deviations in assumptions about missing data.

Figure 8. Tipping Point Analysis for Primary Endpoint, FEV_1 AUC_{0-3} (L) at Week 12, Efficacy Set, Lithos



Source: Response to information request date February 24, 2026, received March 2, 2026.
Center of the yellow star is approximate location of results for primary analysis. Note the analysis tips and is no longer significant at the white area seen in the color-coded panel for the associated nominal p-value on the left.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler

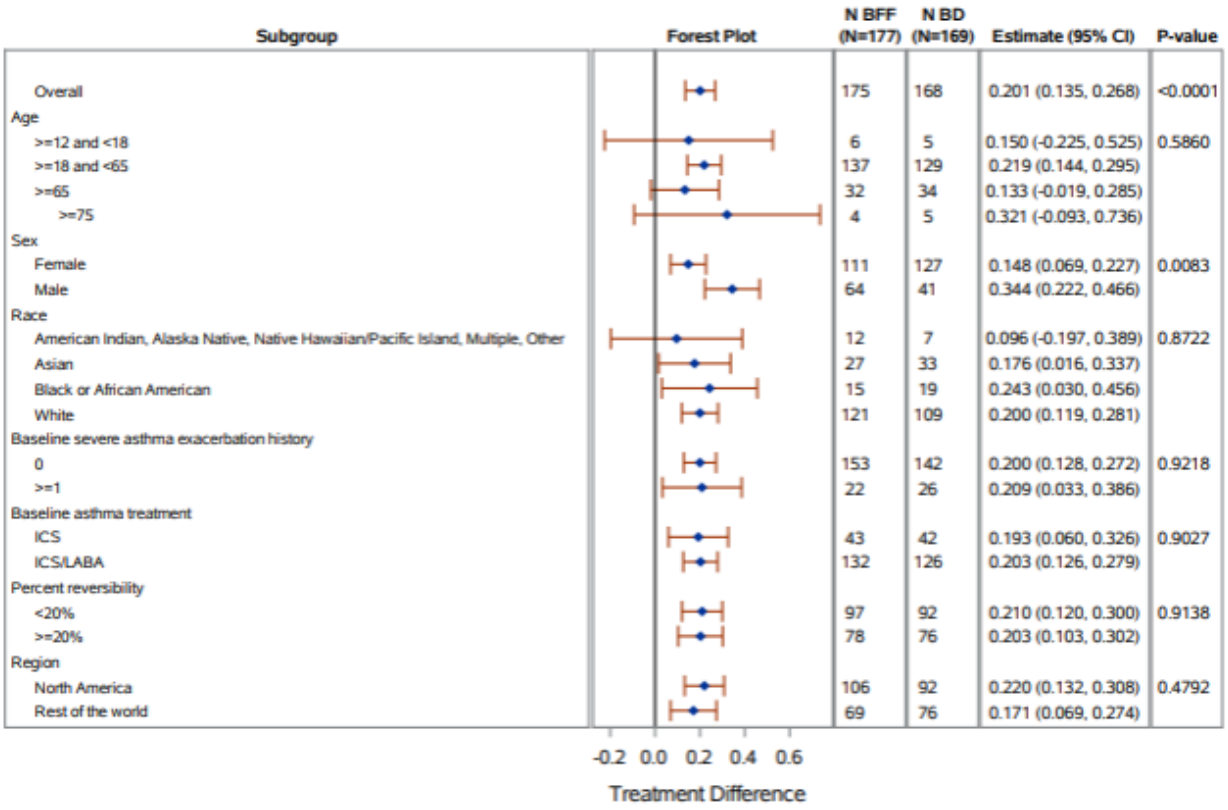
Lithos Primary Endpoint Subgroup Analysis

Subgroup analyses were conducted on adjusted mean FEV_1 AUC_{0-3} (L) comparing BFF 160/9.6 µg vs BD 160 µg. The Applicant assessed the subgroups of age, sex, race, baseline asthma exacerbation history, baseline asthma treatment (ICS or ICS/LABA), percent reversibility and region. Results are shown in Figure 9.

One subgroup showed CIs that included the possibility of no treatment difference: subjects >65 years within the age category. However, this subgroup had relatively small sample sizes, which limits the interpretability of these findings. P-values reported are for interaction between subgroup factor and treatment arm. Most p-values were not significant, indicating no heterogeneity of treatment effect, except for sex, where the effect was higher for males than females, but effect in both subgroups trends in the same direction and is not likely to be clinically concerning.

No notable differences were observed; the subgroup analyses do not change the overall assessment of effectiveness.

Figure 9. Subgroup Analysis for Change From Baseline in FEV_1 AUC_{0-3} (L) Treatment Comparisons at Week 12, Efficacy Set, Lithos



Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_subgroup analysis forest plot_2026.3.6.rtf.
Analysis was performed using a repeated measures analysis of covariance model. The model included treatment, subgroups, visit, prior maintenance medication (ICS versus ICS/LABA), treatment-by-visit, treatment-by-subgroup interaction, subgroup-by-visit interaction, and treatment-by-subgroup-by-visit interaction as categorical covariates and baseline trough FEV_1 and percent albuterol reversibility as continuous covariates. For each subgroup analysis, if the subgroup parameter was same as covariate, the model factors were reduced by removing that covariate. The interaction p-value refers to the difference in difference joint/F-test based on the subgroup interaction.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; NDA, new drug application

Vathos Primary Endpoint Results

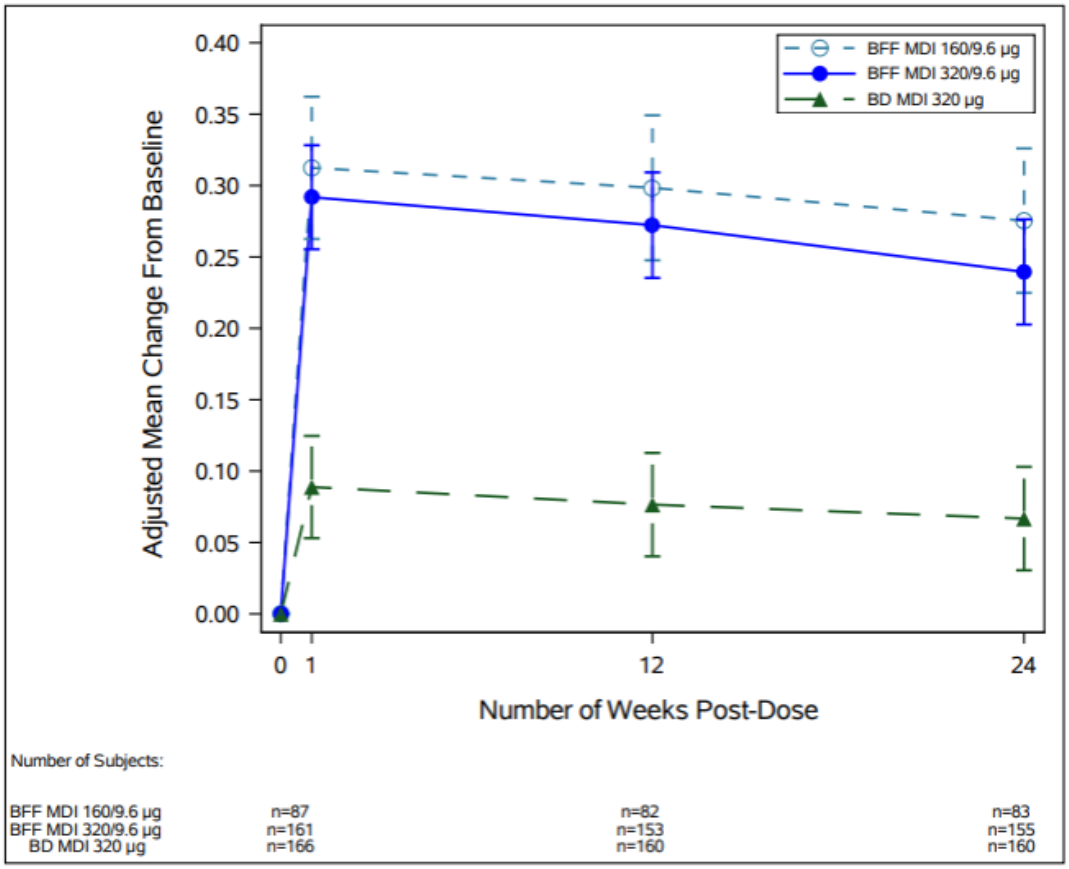
The primary endpoint was change from baseline in FEV_1 AUC_{0-3} at Week 24 comparing BFF 320/9.6 µg vs. BD 320 µg, based on the Efficacy Set. Results are shown in Table 24 and Figure 10. Change from baseline to Week 24 means for BFF 320/9.6 µg and BD 320 µg were 0.24 L and 0.07 L, respectively. with a mean change from baseline of 0.17 L (95% CI: 0.11 to 0.23; p-value<0.0001). Note in Figure 10 that the mean change from baseline in BFF 160/9.6 µg was higher than in the BFF 320/9.6 µg dose arm.

Table 24. Change From Baseline in FEV_1 AUC_{0-3} (L) at Week 24, Efficacy Set, Vathos

					Comparison With BD MDI 320 µg			
Timepoint	**Group**	**n**	**Estimate**	**SE**	**Estimate**	**SE**	**95% CI**	**p-Value**
Week 24	BFF 320/9.6 µg N=162	155	0.240	0.0219	0.173	0.0308	(0.112, 0.233)	<0.0001
Week 24	BD MDI 320 µg N=166	160	0.067	0.0216				

Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_primary endpoint FEV1 AUC0-3 table_2025.12.1.rtf.
Estimates include all 4 treatment groups in the calculations, although only 2 treatment groups are displayed.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects in analysis; NDA, new drug application; SE, standard error

Figure 10. Change From Baseline in FEV_1 AUC_{0-3} (L) Over Time, Efficacy Set, Vathos

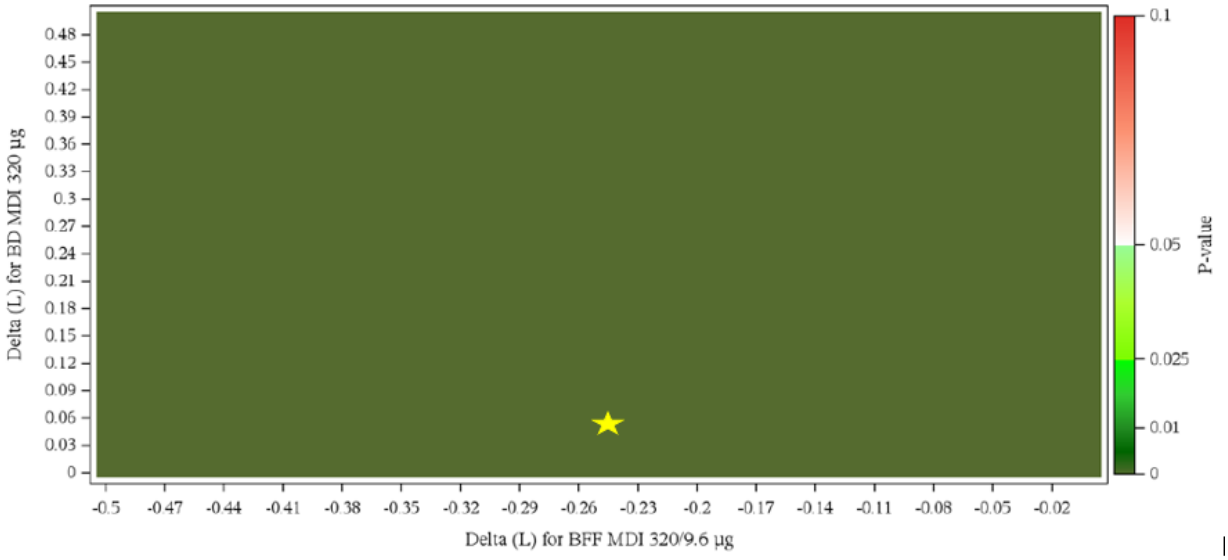


Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_primary endpoint FEV1 AUC0-3 figure_2026.3.18.rtf.
95% confidence intervals are reported.
Estimates include all 4 treatment groups in the calculations, although only 3 treatment groups are displayed.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; n, number of subjects in analysis; NDA, new drug application

Vathos Primary Endpoint Sensitivity Analysis

Similar to Lithos, a tipping point analysis was conducted on the primary endpoint for Vathos FEV_1 AUC_{0-3}, at Week 24. The heat map in Figure 11 displays the relationship between assumed differences from baseline and the corresponding nominal p-values. The treatment effect remains statistically significant (indicated by green) across a wide range of plausible assumptions, including scenarios where the mean for the BFF 320/9.6 µg treatment effect for the unobserved observations is reduced by up to 500 mL, and the mean for the BD 9.6 µg treatment effect for the unobserved observations is increased by up to 500 mL. These findings suggest that the conclusions for the endpoint, change from baseline in FEV_1 AUC at Week 24, is robust to reasonable deviations in assumptions about missing data.

Figure 11. Tipping Point Analysis for Primary Endpoint, FEV_1 AUC_{0-3} (L) at Week 24, Efficacy Set, Vathos



Source: Response to information request date December 5, 2025, received December 15, 2025.
Center of the yellow star is approximate location of results for primary analysis. Note the analysis tips and is no longer significant at the white area seen in the color-coded panel for the associated nominal p-value on the left.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler

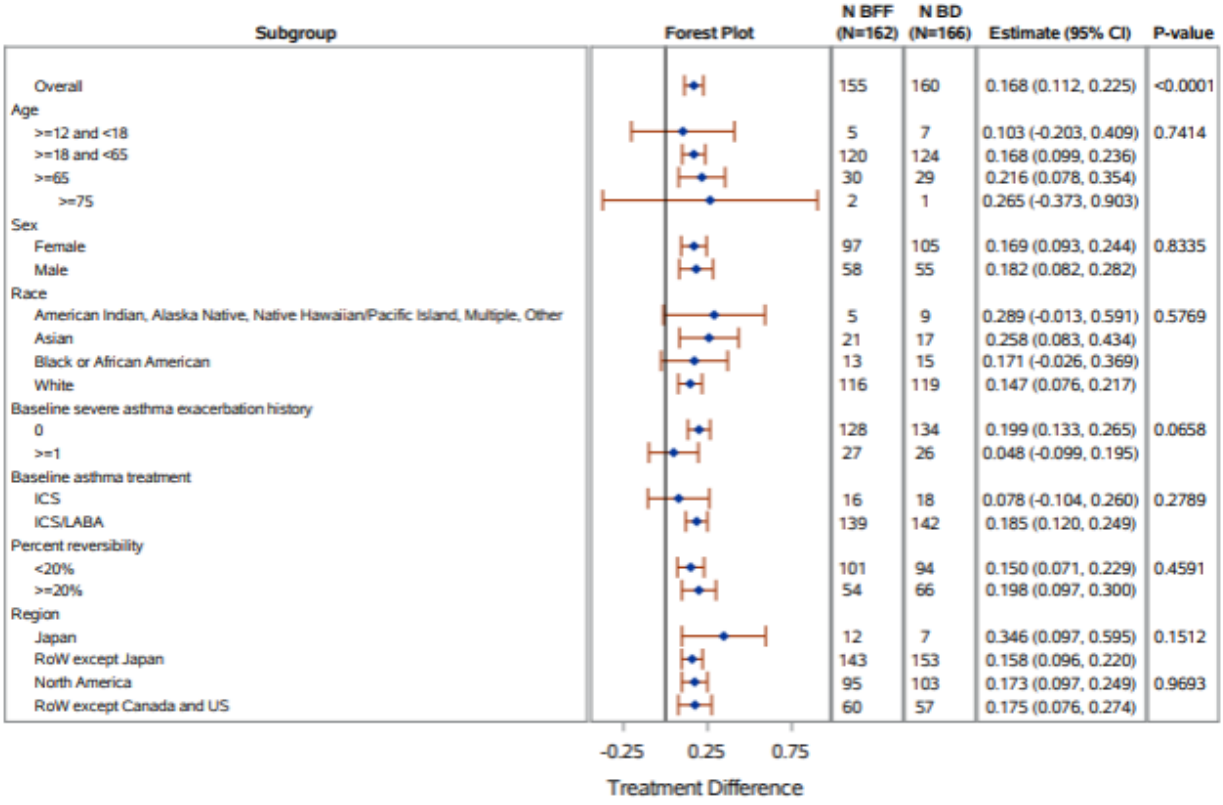
Vathos Primary Endpoint Subgroup Analysis

Subgroup analyses were conducted on adjusted mean FEV_1 AUC_{0-3} (L) comparing BFF 320/9.6 µg vs BD 320 µg. The Applicant assessed the subgroups of age, sex, race, baseline asthma exacerbation history, baseline asthma treatment (ICS or ICS/LABA), percent reversibility and region. Results are shown in Figure 12.

Three subgroups showed CIs that included the possibility of no treatment difference: American Indian and Black subjects within the race category, subjects with one or more severe exacerbations at baseline, and subjects receiving ICS monotherapy at baseline. However, each of these subgroups had relatively small sample sizes, which limits the interpretability of these findings. P-values reported are for interaction between subgroup factor and treatment arm. None of these p-values were significant.

No other notable differences were observed; the subgroup analyses do not change the overall assessment of effectiveness.

Figure 12. Subgroup Analysis for Change From Baseline in FEV_1 AUC_{0-3} (L) Treatment Comparisons at Week 24, Efficacy Set, Vathos



Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Vathos_subgroup analysis forest plot_2026.3.6.rtf.
Analysis was performed using a repeated measures analysis of covariance model. The model included treatment, subgroups, visit, prior maintenance medication (ICS versus ICS/LABA), treatment-by-visit, treatment-by-subgroup interaction, subgroup-by-visit interaction, and treatment-by-subgroup-by-visit interaction as categorical covariates and baseline trough FEV_1 and percent albuterol reversibility as continuous covariates. For each subgroup analysis, if the subgroup parameter was same as covariate, the model factors were reduced by removing that covariate. The interaction p-value refers to the difference in difference joint/F-test based on the subgroup interaction.
Abbreviations: AUC_{0-3}, area under the curve from 0 to 3 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; N, number of subjects in treatment group; NDA, new drug application

<u>Effect of Using 'Only Subjects With Non-Missing Covariates'</u>

SAPs for both Lithos and Vathos note the primary and key secondary analyses would include only subjects with non-missing covariates. We confirmed there were no missing covariate values by comparing the Study Data Tabulation Model (SDTM) "raw" data and Analysis Data Model (ADaM) datasets for these variables.

Efficacy Results – Key Secondary Endpoints

Lithos Morning Pre-Dose Trough FEV_1 at Week 12

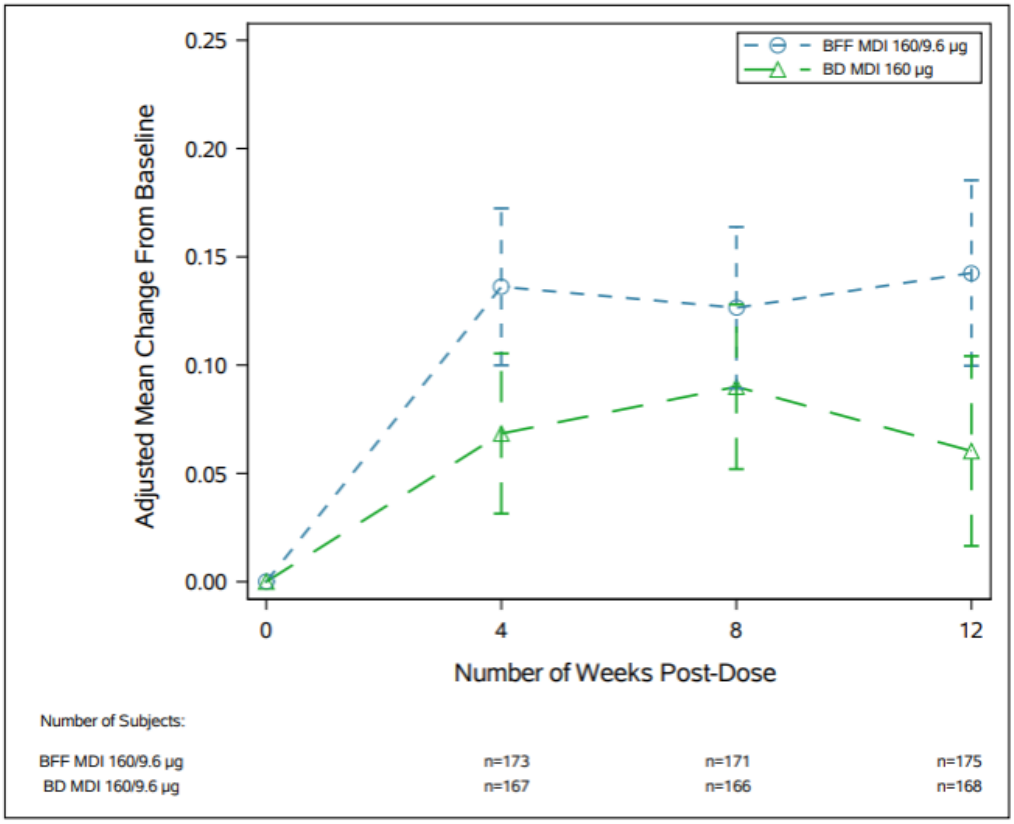
The key secondary endpoint was change from baseline in trough FEV_1 at Week 12 comparing BFF 160/9.6 µg vs. BD 160, based on the Efficacy Set. Results are shown in Table 25 and Figure 13. Change from baseline to Week 12 means for BFF 160/9.6 µg and BD 160 µg were 0.14 L and 0.06 L, respectively. with a mean change from baseline of 0.03 L (95% CI: 0.02 to 0.14; p-value 0.01).

Table 25. Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) at Week 12, Efficacy Set, Lithos

					Comparison With BD MDI 160 µg			
Timepoint	**Group**	**n**	**Estimate**	**SE**	**Estimate**	**SE**	**95% CI**	**p-Value**
Week 12	BFF 160/9.6 µg N=177	175	0.143	0.0221	0.082	0.0316	(0.020, 0.144)	0.0096
Week 12	BD MDI 160 µg N=169	168	0.060	0.0226				

Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_secondary endpoint pre-dose trough FEV1 table_2025.12.9.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects in analysis; NDA, new drug application; SE, standard error

Figure 13. Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) Over Time, Efficacy Set, Lithos



Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_secondary endpoint pre-dose trough FEV1 figure_2026.3.18.rtf.
95% confidence intervals are reported.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; n, number of subjects; NDA, new drug application

Vathos Trough FEV_1 at Week 24

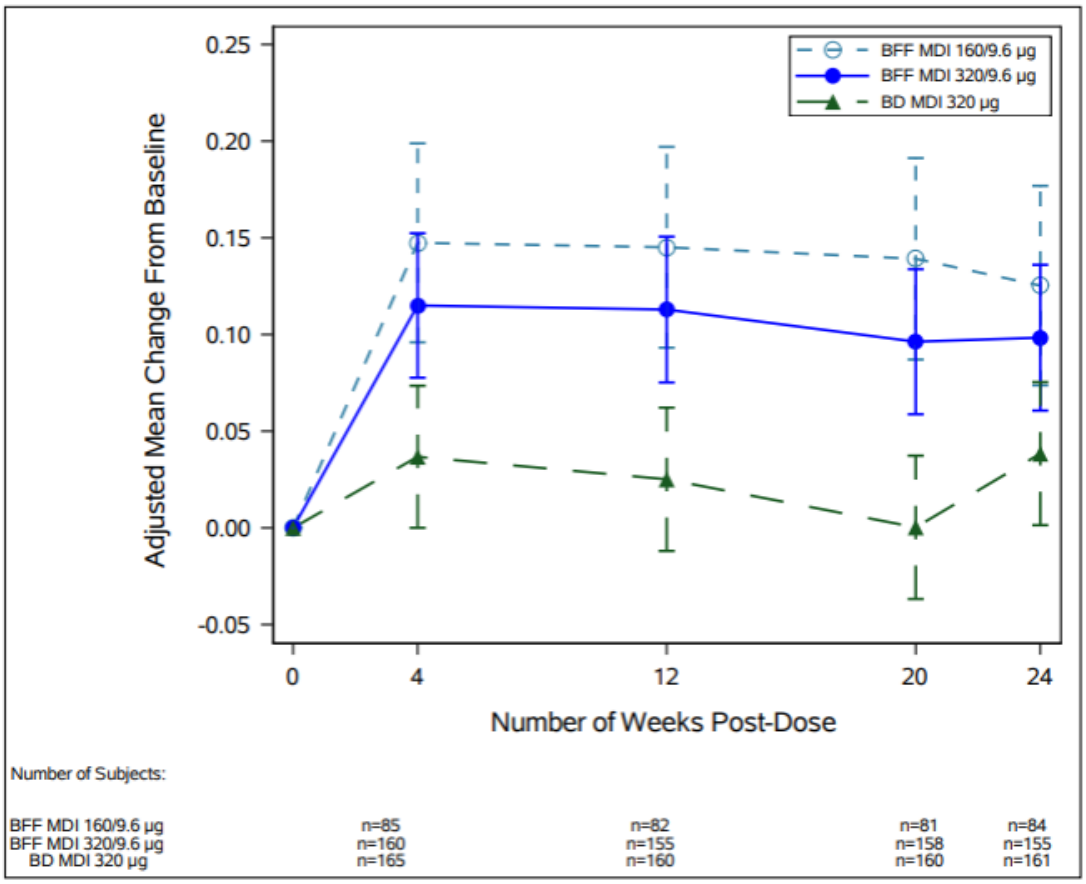
The key secondary endpoint was change from baseline in trough FEV_1 at Week 24 comparing BFF 320/9.6 µg vs. BD 320/9.6 µg, based on the Efficacy Set. Results are shown in Table 26 and Figure 14. Change from baseline to Week 24 means for BFF 320/9.6 µg and BD 320 µg were 0.10 L and 0.04 L, respectively. with a mean change from baseline of 0.06 L (95% CI: 0.001 to 0.12; p-value 0.05). Note in Figure 14 that the mean change from baseline in BFF 160/9.6 µg was higher than in the BFF 320/9.6 µg dose arm.

Table 26. Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) at Weeks 12 and 24, Efficacy Set, Vathos

					Comparison With BD MDI 320 µg			
Timepoint	**Group**	**n**	**Estimate**	**SE**	**Estimate**	**SE**	**95% CI**	**p-Value**
Week 12	BFF 320/9.6 µg N=162	155	0.113	0.0195	0.088	0.0274	(0.034, 0.141)	0.0015
Week 12	BD MDI 320 µg N=166	160	0.025	0.0192				
Week 24	BFF 320/9.6 µg N=162	155	0.099	0.0215	0.061	0.0302	(0.001, 0.120)	0.0447
Week 24	BD MDI 320 µg N=166	161	0.038	0.0211				

Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_secondary endpoint pre-dose trough FEV1 table_2025.12.11.rtf
Estimates include all 4 treatment groups in the calculations, although only 2 treatment groups are displayed.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects in analysis; NDA, new drug application; SE, standard error

Figure 14. Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) Over Time, Efficacy Set, Vathos



Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_secondary endpoint pre-dose trough FEV1 figure_2026.3.18.rtf.
95% confidence intervals are reported.
Estimates include all 4 treatment groups in the calculations, although only 3 treatment groups are displayed.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; n, number of subjects in analysis; NDA, new drug application

Efficacy Results – Secondary Endpoints

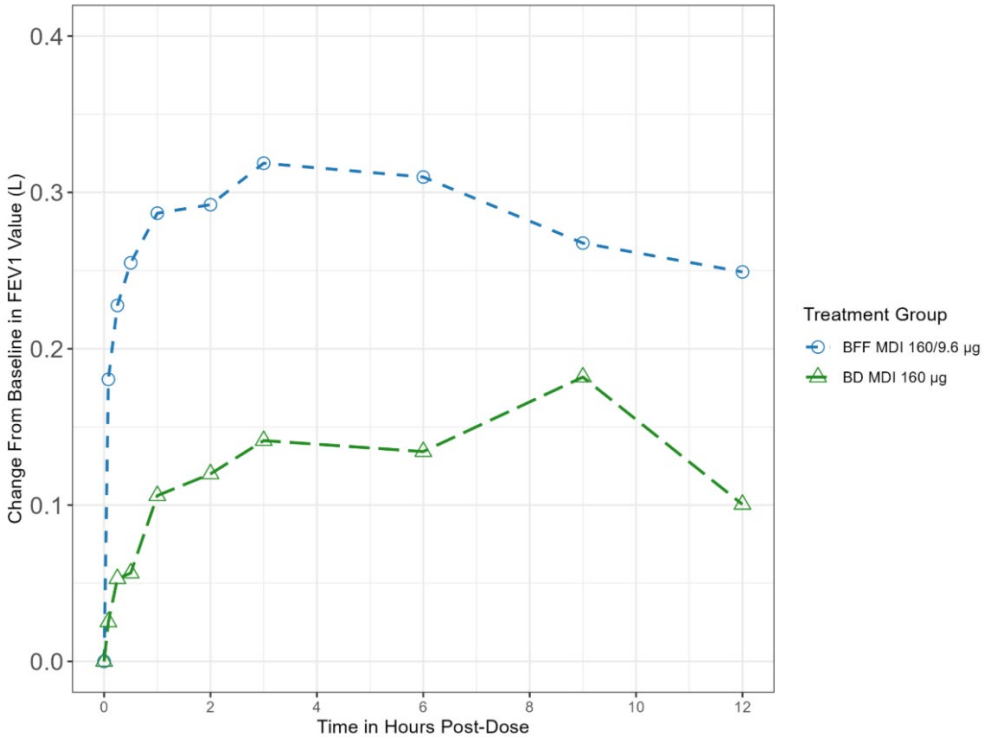
Onset of Action

In Lithos, onset of action was evaluated descriptively for the full 12-hour time course for change from baseline in FEV_1 (Figure 15) and for proportion of subjects who experienced at least a 100 mL increase from baseline in FEV_1 (Figure 16). In both assessments, the BFF 160/9.6 µg arm had a stronger and faster response than the BD 160 µg arm.

In Vathos, onset of action was evaluated descriptively for a 3-hour time course for change from baseline in FEV_1 (Figure 17) and for proportion of subjects who experienced at least a 100 mL increase from baseline in FEV_1 (Figure 18). In both assessments, the BFF 320/9.6 µg and 160/9.6 µg arm had stronger and faster responses than the BD 320 µg arm.

In both Lithos and Vathostrials, whether onset of action occurred within 5 minutes of the first dose was also evaluated, as defined by absolute change in FEV_1 at 5 minutes post-dose on Day 1 compared to BD 320 µg. In Lithos, BFF 160 µg /9.6 µg demonstrated 153 mL in absolute change in FEV_1 at 5 minutes post-dose at Day 1 compared to BD 160 µg (95% CI: 114, 192). In Vathos, BFF 320 µg/9.6 µg demonstrated 144 mL in absolute change in FEV_1 at 5 minutes post-dose at Day 1 compared to BD 320 µg (95% CI: 110, 177).[2]

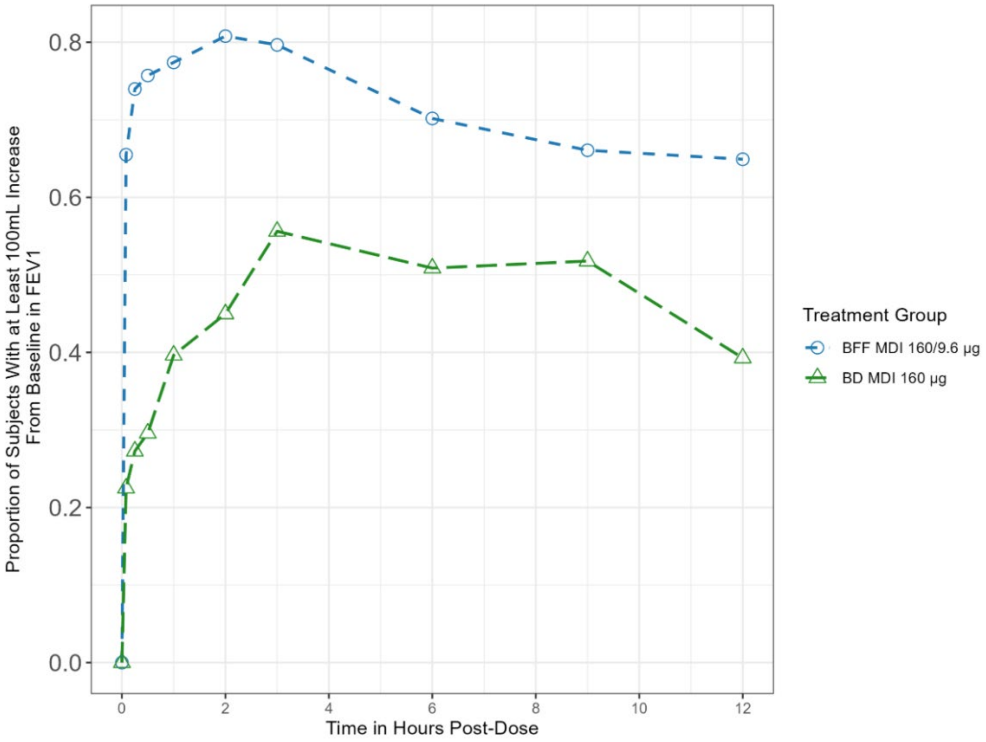
Figure 15. Onset of Action Based on Change From Baseline in FEV_1 (L), Efficacy Set, Lithos



Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_onset of action change from baseline figure_2026.3.18.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; NDA, new drug application

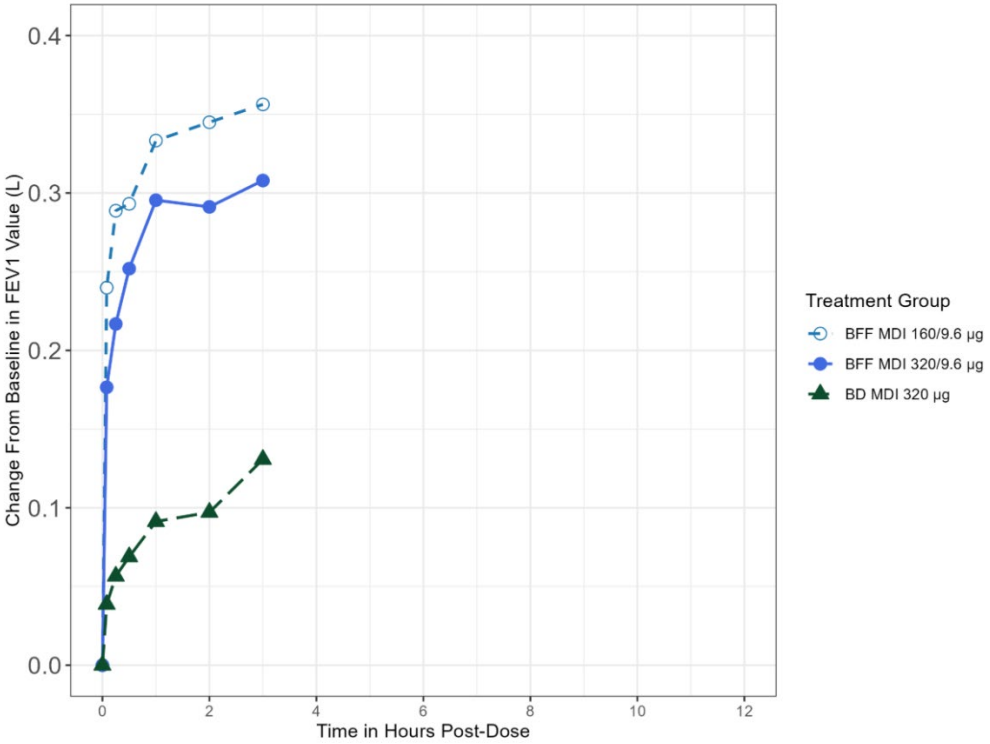
[2] Source: LITHOS: CSR, Table 15; VATHOS: CSR, Table 15.

Figure 16. Onset of Action Proportion of Subjects With at Least 100 mL Increase From Baseline in FEV_1, Efficacy Set, Lithos



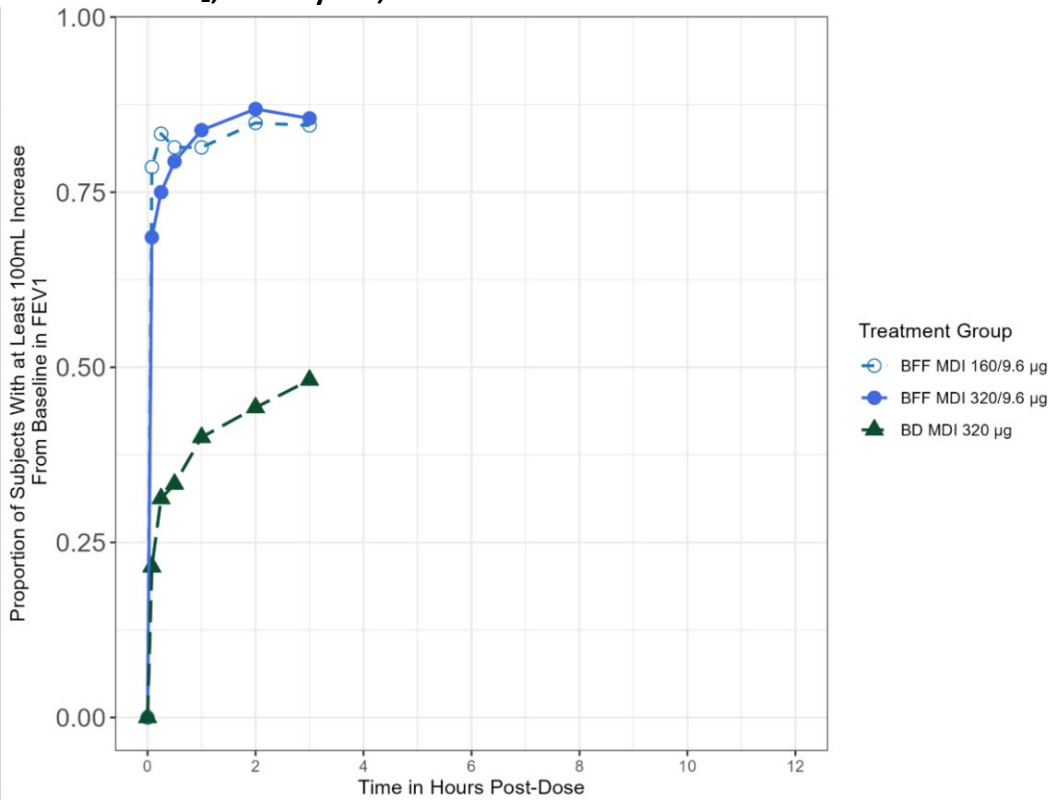
Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_onset of action proportion of patients figure_2026.3.18.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; NDA, new drug application

Figure 17. Onset of Action Based on Change From Baseline in FEV_1 (L), Efficacy Set, Vathos



Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Vathos/Lithos_onset of action change from baseline figure_2026.3.18.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; NDA, new drug application

Figure 18. Onset of Action Proportion of Subjects With at Least 100 mL Increase From Baseline in FEV_1, Efficacy Set, Vathos



Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Vathos_ onset of action proportion of patients figure_2026.3.18.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; NDA, new drug application

Quality of Life Assessments

For Lithos, all three quality of life endpoint percent responder results at Week 12 were significantly better in the BFF 160/9.6 µg arm compared to the BD 160 µg arm (Table 27).

Conversely for Vathos at Week 24, percent responder results for AQLQ(s)+12 were nominally significantly better in the BFF 320/9.6 µg arm compared to the BD 320 µg arm but not for the ACQ-5 or ACQ-7 endpoints (Table 28).

Table 27. Percentage of Responders for ACQ-7, ACQ-5, and AQLQ(s)+12 at Week 12, Efficacy Set, Lithos

		Subjects Responding			Comparison With BD MDI 160 µg		
Assessment	**Group**	**n**	**Number**	**%**	**Odds Ratio**	**95% CI**	**p-Value**
ACQ-7 average score	BFF 160/9.6 µg, N=177	175	130	74.3	1.851	(1.158, 2.958)	0.0101
	BD MDI 160 µg, N=169	168	104	61.9			
ACQ-5 average score	BFF 160/9.6 µg, N=177	175	135	77.1	2.114	(1.302, 3.432)	0.0025
	BD MDI 160 µg, N=169	168	105	62.5			
AQLQ(S) +12 average score	BFF 160/9.6 µg, N=177	173	106	61.3	1.873	(1.175, 2.985)	0.0084
	BD MDI 160 µg, N=169	162	77	47.5			

Source: Statistical Reviewer Analysis: adsl.xpt, adqsacq.xpt, adqsaqlq.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_Percentage of responders in ACQ7 ACQ5 and AQLQ_2026.2.26.rtf.
The analysis was performed using a logistic regression model to compare the treatment groups with treatment and prior maintenance medication (ICS versus ICS/LABA) as categorical covariates and baseline instrument score, percent albuterol reversibility, and baseline trough FEV_1 as continuous covariates.
Only subjects with non-missing covariates were included in the analysis.
Baseline was defined as the last non-missing value before randomization.
An odds ratio >1 for the comparison favoured BFF 160/9.6 µg.
Abbreviations: ACQ-(X), X-item asthma control questionnaire (X=5 or 7); AQLQ(s)+12, asthma quality of life questionnaire for 12 years and older; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICE, intercurrent event; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; MDI, metered dose inhaler; N, number of subjects in treatment group; n, number of subjects in analysis; NDA, new drug application

Table 28. Percentage of Responders for ACQ-7, ACQ-5, and AQLQ(s)+12 at Week 24, Efficacy Set, Vathos

		Subjects Responding			Comparison With BD MDI 320 µg		
Assessment	**Group**	**n**	**Number**	**%**	**Odds Ratio**	**95% CI**	**p-Value**
ACQ-7 average score	BFF 320/9.6 µg, N=162	155	106	68.4	1.283	(0.803, 2.052)	0.2977
	BD MDI 320 µg, N=166	161	101	62.7			
ACQ-5 average score	BFF 320/9.6 µg, N=162	155	111	71.6	1.332	(0.819, 2.166)	0.2477
	BD MDI 320 µg, N=166	161	106	65.8			
AQLQ(S) +12 average score	BFF 320/9.6 µg, N=162	150	86	57.3	1.770	(1.097, 2.858)	0.0194
	BD MDI 320 µg, N=166	157	74	47.1			

Source: Statistical Reviewer Analysis: adsl.xpt, adqsacq.xpt, adqsaqlq.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos_Percentage of responders in ACQ7 ACQ5 and AQLQ_2026.1.22.rtf.
The analysis was performed using a logistic regression model to compare the treatment groups with treatment and prior maintenance medication (ICS versus ICS/LABA) as categorical covariates and baseline instrument score, percent albuterol reversibility, and baseline trough FEV_1 as continuous covariates.
Only subjects with non-missing covariates were included in the analysis.
Baseline was defined as the last non-missing value before randomization.
An odds ratio >1 for the comparison favoured BFF 160/9.6 µg.
Abbreviations: ACQ-(X), X-item asthma control questionnaire (X=5 or 7); AQLQ(s)+12, asthma quality of life questionnaire for 12 years and older; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICE, intercurrent event; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; MDI, metered dose inhaler; N, number of subjects in treatment group; n, number of subjects in analysis; NDA, new drug application

Rescue Medication Use

For Lithos, the BFF 160/9.6 µg treatment group rescue medication use over 12 weeks demonstrated a statistically significant improvement in mean change from baseline in rescue medication use by a reduction in rescue medication of 0.28 puffs/day (95% CI: -0.48 to -0.08) over 12 weeks compared with the BD MDI 160 µg treatment group (Table 29).

For Vathos, the BFF 320/9.6 µg treatment group rescue medication use over 24 weeks demonstrated a nominally significant improvement in mean change from baseline in rescue medication use by a reduction in rescue medication of 0.27 puffs/day (95% CI: -0.48 to -0.05) over 24 weeks compared with the BD MDI 320 µg treatment group (Table 30).

Table 29. Change From Baseline in Mean Daily Number of Puffs of Rescue Medication Use (Puffs/Day) Over 12 Weeks, Efficacy Set, Lithos

				Comparison With BD MDI 160 µg			
Group	**n**	**Estimate**	**SE**	**Estimate**	**SE**	**95% CI**	**p-Value**
BFF 160/9.6 µg, N=177	171	-0.589	0.0708	-0.280	0.1008	(-0.478, -0.082)	0.0058
BD MDI 160 µg, N=169	167	-0.309	0.0721				

Source: Statistical Reviewer Analysis: adsl.xpt, adqsast.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos rescue medication use over 12 weeks table_2026.2.9.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects in analysis; NDA, new drug application; SE, standard error

Table 30. Change From Baseline in Mean Daily Number of Puffs of Rescue Medication Use (Puffs/Day) Over 24 Weeks, Efficacy Set, Vathos

				Comparison With BD MDI 320 µg			
Group	**n**	**Estimate**	**SE**	**Estimate**	**SE**	**95% CI**	**p-Value**
BFF 320/9.6 µg, N=162	157	-0.481	0.0781	-0.268	0.1092	(-0.482, -0.053)	0.0146
BD MDI 320 µg, N=166	163	-0.213	0.0764				

Source: Statistical Reviewer Analysis: adsl.xpt, adqsast.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos rescue medication use over 24 weeks table_2026.2.10.rtf.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects in analysis; NDA, new drug application; SE, standard error

Pooled and Individual Trial Severe Exacerbation Rate

Rate of severe asthma exacerbations pooled across both trials was prespecified as a multiplicity-controlled endpoint higher in the hierarchical consideration of either of the trial results individually. The rate was numerically lower in those treated with a BFF-containing regimen compared with those treated with a BD only-containing regimen with a rate ratio of 0.79 and 95% CI of 0.53 to 1.17 (Table 31).

A similar analysis was conducted for Lithos and Vathos individual studies. The rate ratio for Lithos (0.48, 95% CI, 0.23 to 0.97; Table 32) was appreciably lower than the pooled rate for both studies. For Vathos, the rate ratio favored the control arm (1.02; 95% CI: 0.61 to 1.72; Table 33). Because of the difference in results between Lithos and Vathos, this calls into question the appropriateness of pooling results for these trials.

It should be noted that the Applicant's and Agency's results did not match exactly. The reviewer's analysis yielded consistent results with minor numerical differences attributable to rounding and computational precision. Both analyses demonstrated no statistically significant difference in severe exacerbation rates between BFF and BD treatment groups for the pooled analysis and the Vathos analysis. Both analyses demonstrated nominally significant results for Lithos.

Table 31. Rate of Severe Asthma Exacerbations, Efficacy Set, Pooled Lithos and Vathos

Parameter	Statistic	BFF 160/9.6 µg or 320/9.6 µg (N=426; n=425)	BD MDI 160 µg or 320 µg (N=335; n=335)
Exacerbations	Severe n1 (%) [#]	48 (11.3) [53]	48 (14.3) [51]
Total follow-up time (years)	Subject-years	153.3	114.1
Exacerbations rate per year	Severe rate	0.35	0.45
	Adjusted rate (SE)	0.34 (0.05)	0.44 (0.06)
Dispersion parameter	Estimate (SE)	0.26 (0.428)	
	95% CI	(0.01, 6.33)	
Comparison of treatment groups for severe exacerbations	Treatment incidence BFF 160/9.6 µg or 320/9.6 µg		
	Rate ratio		0.79
	95% CI		(0.53, 1.17)
	p-value		0.2335

Source: Statistical Reviewer Analysis: adsl.xpt, adxacsum.xpt
NDA 216579 Symbicort/Output/Pooled Lithos and Vathos Rate of Exacerbation_2026.2.11.rtf.
Analysis was performed with the pooled individual subject data from Vathos and Lithos studies (Vathos: BFF 320/9.6 µg, BFF 160/9.6 µg, BD 320 µg. Lithos: BFF 160/9.6 µg, BD 160 µg treatment arms. The BFF treatment arm in the Vathos study was not included).
The analysis for rate ratio was performed using negative binomial regression. The model included treatment (budesonide [1 if the budesonide dose was 320 µg and 0 if the budesonide dose was 160 µg] and formoterol (1 if the formoterol dose was 9.6 µg and 0 if no formoterol dose), study, baseline trough FEV_1, percent reversibility, baseline severe asthma exacerbation history (0, ≥1), prior maintenance medication (ICS versus ICS/LABA), and region. The comparison of interest was the formoterol effect. The logarithm of time at risk of experiencing a severe exacerbation was used as an offset variable in the model.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; N, number of subjects in treatment group; n, number of subjects in analysis; NDA, new drug application; n1, number of events; SE, standard error; #, total number of events

Table 32. Rate of Severe Asthma Exacerbations, Efficacy Set, Lithos

Parameter	Statistic	BFF 160/9.6 µg (N=177)	BD MDI 160 µg (N=169)
Exacerbations	Severe n (%) [#]	12 (6.8) [12]	21 (12.4) [22]
Total follow-up time (years)	Subject-years	41.1	38.6
Exacerbations rate per year	Severe rate	0.29	0.57
	Adjusted rate (SE)	0.25 (0.08)	0.52 (0.12)
Dispersion parameter	Estimate (SE)	<0.0001 (<0.0001)	
Comparison of treatment groups for severe exacerbations	Treatment incidence BFF 160/9.6 µg		
	Rate ratio		0.48
	95% CI		(0.23, 0.97)
	p-value		0.0424

Source: Statistical Reviewer Analysis: adsl.xpt, adxacsum.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_rate of exacerbation_2026.2.6.rtf.
The analysis for rate ratio and 95% CI was performed using negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, ≥1), prior maintenance medication (ICS versus ICS/LABA), and region. The logarithm of time at risk of experiencing a severe exacerbation is used as an offset variable in the model.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; MDI, metered-dose inhaler; n, number of subjects with at least one severe exacerbation; NDA, new drug application; SE, standard error; #, total number of events

Table 33. Rate of Severe Asthma Exacerbations, Efficacy Set, Vathos

Parameter	Statistic	BFF 160/9.6 µg (N=87)	BFF 320/9.6 µg (N=162)	BD MDI 320 µg (N=166)
Exacerbations	Severe n (%) [#]	11 (12.6) [11]	25 (15.5) [30]	27 (16.3) [29]
Total follow-up time (years)	Subject-years	39.5	72.6	75.5
Exacerbations rate per year	Severe rate	0.28	0.41	0.38
	Adjusted rate (SE)	0.26 (0.08)	0.36 (0.07)	0.35 (0.07)
Dispersion parameter	Estimate (SE)		<0.0001 (<0.0001)	
Comparison of treatment groups for severe exacerbations	Treatment incidence BFF 320/9.6 µg			
	Rate ratio			1.02
	95% CI			(0.61, 1.72)
	p-value			0.9368

Source: Statistical Reviewer Analysis: adsl.xpt, adxacsum.xpt
NDA 216579 Symbicort/Output/Vathos/Vathos rate of exacerbation_2026.2.11.rtf.
The analysis for rate ratio and 95% CI was performed using negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, ≥1), prior maintenance medication (ICS versus ICS/LABA), and region. The logarithm of time at risk of experiencing a severe exacerbation is used as an offset variable in the model.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects with at least one severe exacerbation; NDA, new drug application; SE, standard error; #, total number of events

FEV_1 AUC_{0-12} at Day 1 and Week 12

Improvements were demonstrated in FEV_1 AUC_{0-12} at Day 1 and Week 12 in the BFF 160/9.6 µg compared with BD MDI 160 µg using the Primary Strategy for Handling ICEs (Table 34). Although not included in the Type I error control plan, these data were nominally significant and supportive of the change from baseline in FEV_1 AUC_{0-3} conclusions.

Table 34. FEV_1 AUC_{0-12} at Day 1 and Week 12, PFT Sub-Study Set, Lithos

					Comparison With BD MDI 160 µg			
Timepoint	**Group**	**n**	**Estimate**	**SE**	**Estimate**	**SE**	**95% CI**	**p-Value**
Day 1	BFF 160/9.6 µg, N=57	56	0.292	0.0312	0.149	0.0440	(0.062, 0.237)	0.0010
	BD MDI 160 µg, N=57	57	0.143	0.0310				
Week 12	BFF 160/9.6 µg, N=57	57	0.308	0.0465	0.195	0.0661	(0.064, 0.326)	0.0039
	BD MDI 160 µg, N=57	56	0.113	0.0468				

Source: Statistical Reviewer Analysis: adsl.xpt, adre.xpt
NDA 216579 Symbicort/Output/Lithos/Lithos_PFT Subset FEV1 AUC0-12 table_2026.3.10.rtf
Abbrevations: AUC_{0-12}, area under the curve from 0 to 12 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects in analysis; NDA, new drug application; PFT, pulmonary function test; SE, standard error

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (PRO) Endpoints

Results for ACQ-5, ACQ-7, and AQLQ(s)+12 for both trials are noted above in the secondary efficacy section, where they are discussed in the context of multiplicity control for each trial.

7.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

The primary endpoint for both Lithos and Vathos was the change from baseline in FEV_1 AUC_{0-3} at 12 and 24 weeks, respectively. Data from Lithos provided sufficient evidence of the efficacy for BFF 160/9.6 compared with BD 160 by demonstrating a statistically significant treatment difference on the change from baseline in FEV_1 AUC_{0-3} observed at the 12 week timepoint (difference in LS means = 200 mL; 95% CI: 134 to 267; p<0.0001). The improvement in mean change from baseline in FEV_1 AUC_{0-3} for BFF 320/9.6 compared to BD 320 at Week 24 in Vathos was statistically significant (difference in LS means = 173 mL; 95% CI: 112 to 233; p<0.0001).

Secondary and Other Endpoints

The key secondary endpoint for both Lithos and Vathos was the change from baseline in pre-dose trough FEV_1 at Weeks 12 and 24, respectively. Statistically significant differences in improvements in pre-dose trough FEV_1 in the BFF compared to BD arms for both Lithos and Vathos provided further evidence of the efficacy of BFF on lung function. In Lithos, a stastistically significant treatment difference was observed for BFF 160/9.6 compared to BD 160 at the 12-week timepoint (difference in LS means = 82 mL; 95% CI: 20 to 144; p=0.0096). The improvement in mean change from baseline in pre-dose trough FEV_1 was greater for BFF 320/9.6 compared to BD 320 at Week 24 in Vathos (difference in LS means = 61 mL; 95% CI: 1 to 120; p=0.0447).

Subpopulations

For the adolescent population (N=27), efficacy was supported with Applicant's post hoc Bayesian analysis of the pooled Lithos and Vathos data (Table 10 of Clinical Overview). Because of similar disease pathophysiology and expected treatment response between the adult and adolescent asthma populations, Bayesian analysis was considered appropriate for the proposed indication.

In the post hoc analysis, Bayesian borrowing from the adult population was used to estimate the effect in adolescents. The results showed numerical improvements in FEV_1 AUC_{0-3} for adolescents for the BFF treatment group compared to the BD MDI treatment group (0.189 L, 95% credible interval [0.000 L. 0.246 L]).

7.1.5. Integrated Assessment of Effectiveness

The Applicant submitted results from two pivotal clinical trials as the primary support for efficacy: Lithos and Vathos. We considered Lithos and Vathos to represent adequate and well-controlled trials that contributed to SEE.

For both Lithos and Vathos, the primary and key secondary endpoints were lung function-based endpoints (mean change from baseline in FEV_1 AUC_{0-3} and mean change from baseline in morning pre-dose trough FEV_1, respectively) evaluating treatment of subjects ≥12 years of age and older with asthma that was not adequately controlled despite treatment with low dose ICS or ICS/LABA (Lithos) or medium dose ICS or ICS/LABA (Vathos). Lithos demonstrated that treatment with BFF 160/9.6 over 12 weeks led to statistically significant improvements in both mean change from baseline in FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1 compared to BD 160 alone. Vathos demonstrated that treatment with BFF 320/9.6 over 24 weeks led to statistically significant improvements in both mean change from baseline in FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1 compared to BD 320 alone.

Efficacy results from both trials provided support for the indication of "treatment of asthma." Other claims made in Section 14 of the label include improvements in health-related quality of life, based on statistically significant improvements in the AQLQ+12 scores for Lithos and nominal significance for Vathos, due to the placement in the statistical hierarchy. Vathos did not achieve statistical significance for two other health-related quality of life tools (ACQ-5 and ACQ-7), and both were higher in the pre-specified statistical hierarchy. Lithos met statistical significance for all of the study-specific mutiplicity-controlled endpoints,which included all health-related quality of life tools (ACQ-5, ACQ-7 and AQLQ+12).

In both Lithos and Vathos, treatment with BFF statistically significantly reduced the use of rescue medication compared to BD (measured as mean change from baseline in puffs per day). The reduction was similar for both trials–0.28 puff/day for Lithos and -0.27 puffs/day for Vathos).

The pre-specified pooled asthma exacerbation endpoint did not meet statistical significance. The rate of asthma exacerbations was statistically significantly lower for subjects treated with BFF 160/9.6 compared to BD when data from only Lithos was evaluated, however, a statistically significant difference between BFF 320/9.6 and BD was not detected when data from only Vathos was evaluated. This could possibly reflect the difference in study populations between the two trials, as inclusion criteria for Vathos specified that subjects with asthma were not adequately controlled on medium dose ICS or ICS/LABA as opposed to low dose ICS or ICS/LABA for subjects in Lithos.

In conclusion, the Applicant has demonstrated SEE for the (b) (4) treatment of asthma in patients ≥12 years of age and older. This is based on statistically and clinically persuasive results on the lung function-based primary and key secondary endpoints, and many of the other multiplicity controlled secondary endpoints from both Lithos and Vathos. The results from both

trials also supported the contribution of FF to the overall treatment effect of BFF, satisfying the combination rule.

7.2. Review of Safety

7.2.1. Safety Review Approach

The Applicant submitted data from Lithos and Vathos as the primary support for safety of BFF 320/9.6 and BFF 160/9.6. Because of the differences in the study design of these trials, including the study population, dosages, and treatment duration, the trials were not pooled for safety analyses. Given the limited comparative value of Symbicort TBH to a U.S. market, data from the TBH arm are not presented in the main safety analyses. This reviewer analyzed these results and will note pertinent findings when applicable.

Safety analyses were performed by the clinical reviewer to verify Applicant analyses or to initiate other related safety analyses, using Analysis Studio. The safety population was defined as all randomized subjects given at least one dose of study treatment.

7.2.2. Review of the Safety Database

Overall Exposure

Table 35 and Table 36 show the population of subjects exposed to BFF and BD in the development program for asthma. The mean exposure of study drug in Vathos was longer than Lithos, as expected given the longer trial duration of Vathos. The majority of subjects in all arms in Lithos completed ≥12 weeks and ≥24 weeks in Vathos. There was no imbalance in exposure between BFF 160/9.6 compared to BD 160 in Lithos or between BFF 320/9.6 compared to BD 320 in Vathos.

Table 35. Exposure, Safety Population, Lithos

Exposure, Days	BFF 160/9.6 (N=179)	BD 160 (N=174)
Mean (SD)	85.0 (6.8)	83.4 (9.7)
Median	85.0	85.0
Min, max	20, 116	9, 98
Total person-years exposure	42	40

Source: Clinical Reviewer, modified from Lithos CSR, page 98
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CSR, clinical study report; N, number of subjects in treatment group; SD, standard deviation

Table 36. Exposure, Safety Population, Vathos

Exposure, days	BFF 160/9.6 (N=88)	BFF 320/9.6 (N=162)	BD 320 (N=168)	Symbicort TBH 320/9 (N=162)
Mean (SD)	158.4 (36.7)	162.6 (27.3)	160.8 (31.0)	161.0 (32.3)
Median	169.0	169.0	169.0	169.0
Min, max	1, 188	7, 193	27, 185	1, 190
Total person-years exposure	38.2	72.1	74	71.4

Source: Clinical Reviewer, modified from Vathos CSR, page 127
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; CSR, clinical study report; N, number of subjects in treatment group; SD, standard deviation; TBH, Turbuhaler

Adequacy of the Safety Database

In the context of the known safety profiles of BD and FF and the current understanding of these drug classes (ICS and LABAs) in asthma, the size of the BFF safety database is adequate.

Categorization of Adverse Events

In Lithos and Vathos, The Applicant used definitions of AEs and SAEs that were consistent with requirements outlined in 21 CFR 312.32. The definition of an AE was the development of any untoward medical occurrence in a subject administered a medicinal product, whether or not considered related to the study treatment. AEs were collected during the entire study period (run-in, treatment period, follow up).

AEs included in the safety set included AEs with an onset date on or after the date of first dose of IP, up to and including 1 day following the date of last IP dose. Changes in vital signs or laboratory test results were reported as AEs only if they met SAE criteria, caused discontinuation of treatment with the IP or were adjudicated as clinically relevant by the Investigator.

7.2.3. Safety Results

Deaths

There were no treatment emergent deaths in either Lithos or Vathos. There were two deaths that occurred during the pre-randomization (run-in) period when all subjects were treated with BD, one occurring in Lithos and one in Vathos.

In Lithos, a subject experienced a fatal cardiopulmonary arrest reportedly due to the toxic effects of fentanyl and alcohol, and the death was not considered related to study drug. In Vathos, a subject experienced a fatal cardiopulmonary arrest during a dental procedure. The AE was not considered related to study drug by the Investigator.

No deaths were reported during the treatment or post-treatment period for either trial.

Serious Adverse Events

No SAEs were reported for subjects in Lithos in the BFF 160 treatment group. There were SAEs in Vathos, which is not unexpected given the differences in study population and treatment duration between studies.

A summary of SAEs in Vathos are outlined in Table 37. In Vathos, SAEs were generally rare but were more common in the BFF 160/9.6 (3.4%) and BFF 320/9.6 arms (1.8%) compared to BD 320 alone (0.6%). SAEs were more common in the BFF 160/9.6 arm compared to the BFF 320/9.6 arm, but all SAEs were isolated events with no greater than one subject experiencing an SAE for any individual preferred term. Overall, SAEs were uncommon and these data did not raise new safety concerns.

Although Symbicort TBH 320 data are not included in the table, total SAEs were more common than in any other arm (4.3%). The following SAEs were reported for the Symbicort TBH arm (all at a frequency of 0.6% [one subject]): asethenia, asthma, acute cholecystitis, decreased appetite, diverticulitis, large intestinal polyp and localized infection.

Table 37. Summary of Subjects With SAEs, Vathos

System Organ Class Preferred Term	BFF 160/9.6 µg N=88 n (%)	BFF 320/9.6 µg N=163 n (%)	BD MDI 320 µg N=168 n (%)
Subjects with any SAE	3 (3.4)	3 (1.8)	1 (0.6)
COVID-19 pneumonia	0 (0.0)	1 (0.6)	0 (0.0)
Asthma	0 (0.0)	1 (0.6)	0 (0.0)
Skin ulcer	0 (0.0)	1 (0.6)	0 (0.0)
Myocardial ischemia	0 (0.0)	0 (0.0)	1 (0.6)
Gastric ulcer	1 (1.1)	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	1 (0.6)
Inguinal hernia	1 (1.1)	0 (0.0)	0 (0.0)
Clavicle fracture	1 (1.1)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "BFF MDI 160/9.6 µg" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A = "BFF MDI 320/9.6 µg" and SAFFL = Y (BFF MDI 320/9.6 µg); TRT01A = "BD MDI 320 µg" and SAFFL = Y (BD MDI 320 µg); TRTEMFL = "Y" and AESER = "Y" (Adverse Events)
Abbreviations: AESER, adverse event classified as serious; BD, budesonide; BFF, budesonide/formoterol fumarate; COVID-19, coronavirus disease of 2019; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects with specified SAE; SAE, serious adverse event; SAFFL, safety population flag; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

Discontinuations Due to Adverse Events

Overall, AEs that led to discontinuation were uncommon for both trials. In Lithos, no AEs led to discontinuation in the BFF 160 arm and only one subject (0.6%) experienced an AE (asthma) that led to discontinuation in the BD 160 arm.

A summary of AEs leading to discontinuation in Vathos are outlined in Table 38. In Vathos, AEs most commonly occurred in the BFF 320/9.6 arm (3.7%) and were <2% in the BFF 160/9.6 and BD 320 arms. The most common etiology that led to discontinuation for both trials was asthma. It was not unexpected that more asthma AEs would be reported in Vathos, given the more severe baseline disease of the enrolled population. All other AEs leading to discontinuation were isolated events with a frequency of only 0.6% (one subject), and these data did not raise any new safety concerns.

Although not shown in the table, only 3 AEs led to discontinuation in the Symbicort TBH arm (asthma, nasal polyps and palpitations).

Table 38. Summary of Subjects With AEs Leading to Discontinuation, Vathos

System Organ Class Preferred Term	BFF 160/9.6 µg N=88 n (%)	BFF 320/9.6 µg N=163 n (%)	BD MDI 320 µg N=168 n (%)
Subjects with any AE	1 (1.1)	6 (3.7)	3 (1.8)
Asthma	1 (1.1)	4 (2.5)	1 (0.6)
Dysphonia	0 (0.0)	1 (0.6)	0 (0.0)
Blood pressure increased	0 (0.0)	1 (0.6)	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	1 (0.6)
Eczema	0 (0.0)	0 (0.0)	1 (0.6)

Source: OCS Analysis Studio, Safety Explorer
Filters: TRT01A = "BFF MDI 160/9.6 µg" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A = "BFF MDI 320/9.6 µg" and SAFFL = Y (BFF MDI 320/9.6 µg); TRT01A = "BD MDI 320 µg" and SAFFL = Y (BD MDI 320 µg); TRTEMFL = "Y" and AEACN = ("DRUG WITHDRAWN") (Adverse Events)
Abbreviations: AE, adverse event; AEACN, actions taken with study treatment; BD, budesonide; BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; SAFFL, safety population flag; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

Significant Adverse Events

Severity was assessed independently of seriousness and describes the intensity of signs or symptoms. The majority of AEs in both trials were mild or moderate. In Lithos, there were no AEs rated by investigators as severe in intensity.

Table 39 summarizes the AEs rated as severe during the randomized treatment period in Vathos. In Vathos, severe AEs were more common in the BFF 320/9.6 arm (3.1%) compared to BFF 160/9.6 or BD 320 (1.1% and 1.2% respectively). However, severe AEs for all three arms were isolated events and these data did not raise any new safety concerns.

Table 39. Number of Subjects With an AE Rated as Severe, Vathos

Preferred Term	BFF 160/9.6 µg N=88 n (%)	BFF 320/9.6 µg N=163 n (%)	BD MDI 320 µg N=168 n (%)
Subjects with any severe AE	1 (1.1)	5 (3.1)	2(1.2)
Pneumonia bacteria	0 (0)	1 (0.6)	0 (0)
COVID-19 pneumonia	0 (0)	1 (0.6)	0 (0)
Clavicle fracture	1 (1.1)	0 (0)	0 (0)
Fall	0 (0)	1 (0.6)	0 (0)
Spinal compression fracture	0 (0)	1 (0.6)	0 (0)
Asthma	0 (0)	1 (0.6)	0 (0)
Tendon pain	0 (0)	0 (0)	1 (0.6)
Myocardial ischemia	0 (0)	0 (0)	1 (0.6)
Gastritis	0 (0)	0 (0)	1 (0.6)
Esophageal food impaction	0 (0)	1 (0.6)	0 (0)

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: TRT01A = "BFF MDI 160/9.6 µg" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A = "BFF MDI 320/9.6 µg" and SAFFL = Y (BFF MDI 320/9.6 µg); TRT01A = "BD MDI 320 µg" and SAFFL = Y (BD MDI 320 µg); TRT01A = "Symbicort TBH 320/9 µg" and SAFFL = Y (Symbicort TBH 320/9 µg); TRTEMFL = "Y" and ASEV = ("Mild", "Moderate", or "Severe") (Adverse Events)
Abbreviations: AE, adverse event; ASEV, analysis severity; BD, budesonide; BFF, budesonide/formoterol fumarate; COVID-19, coronavirus disease of 2019; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified AE; SAFL, safety population flag; TBH, Turbuhaler; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

Treatment Emergent Adverse Events and Adverse Reactions

Table 40 summarizes the most common (occurring in ≥1% of the population) AEs in Lithos during the randomized treatment period. The total incidence of AEs was low and balanced between treatment arms. The most common AEs were nasopharyngitis and upper respiratory tract infections; respiratory tract infections were more common in BFF 160/9.6 (3.4% vs 2.3%), and nasopharyngitis was more common in the BD 160 arm (2.3% vs 1.7%). These findings are not unexpected based on known class effects and described in the U.S. prescribing information (USPI) of related products. In Lithos, upper respiratory tract infection was the only AE that occurred at an incidence of ≥2% and more frequently in BFF 160/9.6 compared to BD 160 (3.4% vs 2.9%).

Table 40. Summary of Subjects With ≥1% TEAEs in Any Arm, Lithos

Preferred Term	BFF 160/9.6 µg N=179 n (%)	BD MDI 160 µg N=174 n (%)
Subjects with any AE	33 (18.4)	34 (19.5)
Back pain	2 (1.1)	2 (1.1)
COVID-19	3 (1.7)	3 (1.7)
Fall	2 (1.1)	2 (1.1)
Influenza	2 (1.1)	0 (0.0)
Influenza like illness	0 (0.0)	2 (1.1)
Ligament sprain	1 (0.6)	2 (1.1)
Nasopharyngitis	3 (1.7)	4 (2.3)
Upper respiratory tract infection	6 (3.4)	5 (2.9)

Source: OCS Analysis Studio, Safety Explorer
Filters: TRT01A = "BFF MDI 160/9.6 µg" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A = "BD MDI 160 µg" and SAFFL = Y (BD MDI 160 µg); TRTEMFL = "Y" (Adverse Events)
Percent threshold: Any column ≥1%
Abbreviations: AE, adverse event; BD, budesonide; BFF, budesonide/formoterol fumarate; COVID-19, coronavirus disease of 2019; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified TEAE; SAFFL, safety population flag; TEAE, treatment-emergent adverse event; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

Table 41 summarizes the most common (occurring in ≥2% of the population) AEs in Vathos during the randomized treatment period. Total AEs were well balanced between both BFF arms (approximately 50%), and AEs were less frequent in the BD arm (38.1%). The most common AEs overall were nasopharyngitis, COVID-19, and upper respiratory tract infections. Infection, including respiratory infection, is a known risk of ICS described in the label for all drugs in class.

When comparing BFF 320/9.6 to BD 320, the following were more common in the BFF arm: asthma, COVID-19, gout, nasopharyngitis, and allergic rhinitis. Hypertension was not consistently more common in the arms treated with LABA compared to BD alone. Based on these data, no new safety concerns were identified.

Table 41. Summary of Subjects With ≥2% TEAEs in Any Arm, Vathos

Preferred Term	BFF 160/9.6 µg N=88 n (%)	BFF 320/9.6 µg N=163 n (%)	BD MDI 320 µg N=168 n (%)
Subjects with any AE	44 (50.0)	82 (50.3)	64 (38.1)
COVID-19	3 (3.4)	15 (9.2)	8 (4.8)
Nasopharyngitis	12 (13.6)	15 (9.2)	15 (8.9)
Upper respiratory tract infection	3 (3.4)	8 (4.9)	12 (7.1)
Asthma	2 (2.3)	4 (2.5)	1 (0.6)
Rhinitis allergic	1 (1.1)	4 (2.5)	0 (0.0)
Bronchitis bacterial	2 (2.3)	2 (1.2)	2 (1.2)
Arthralgia	3 (3.4)	1 (0.6)	1 (0.6)
Gout	2 (2.3)	1 (0.6)	0 (0.0)
Hypertension	3 (3.4)	1 (0.6)	3 (1.8)
Diarrhea	2 (2.3)	0 (0.0)	1 (0.6)
Influenza like illness	2 (2.3)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer
Filters: TRT01A = "BFF MDI 160/9.6 µg" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A = "BFF MDI 320/9.6 µg" and SAFFL = Y (BFF MDI 320/9.6 µg); TRT01A = "BD MDI 320 µg" and SAFFL = Y (BD MDI 320 µg); TRTEMFL = "Y" (Adverse Events)
Percent threshold: Any column ≥2%
Abbreviations: AE, adverse event; BD, budesonide; BFF, budesonide/formoterol fumarate; COVID-19, coronavirus disease of 2019; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified TEAE; SAFFL, safety population flag; TEAE, treatment-emergent adverse event; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

Table 42 describes AEs that occurred in ≥2% of the safety population and were more common in either BFF arm compared to BD. These data will be included in Section 6 of the USPI.

Table 42. Summary of Subjects With AEs ≥2% and More Common in Either BFF Arm Compared to BD 320, Vathos

Preferred Term	BFF 160/9.6 µg N=88 n (%)	BFF 320/9.6 µg N=163 n (%)	BD MDI 320 µg N=168 n (%)
Subjects with any AE	44 (50.0)	82 (50.3)	64 (38.1)
COVID-19	3 (3.4)	15 (9.2)	8 (4.8)
Nasopharyngitis	12 (13.6)	15 (9.2)	15 (8.9)
Asthma	2 (2.3)	4 (2.5)	1 (0.6)
Rhinitis allergic	1 (1.1)	4 (2.5)	0 (0.0)
Bronchitis bacterial	2 (2.3)	2 (1.2)	2 (1.2)
Arthralgia	3 (3.4)	1 (0.6)	1 (0.6)
Gout	2 (2.3)	1 (0.6)	0 (0.0)
Hypertension	3 (3.4)	1 (0.6)	3 (1.8)
Diarrhea	2 (2.3)	0 (0.0)	1 (0.6)
Influenza like illness	2 (2.3)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer
Filters: TRT01A = "BFF MDI 160/9.6 µg" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A = "BFF MDI 320/9.6 µg" and SAFFL = Y (BFF MDI 320/9.6 µg); TRT01A = "BD MDI 320 µg" and SAFFL = Y (BD MDI 320 µg); TRTEMFL = "Y" (Adverse Events)
Percent threshold: Any Column ≥2%
Abbreviations: AE, adverse event; BD, budesonide; BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects in treatment arm; n, number of subjects with specified adverse event; SAFFL, safety population flag; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

Laboratory Findings

The Applicant conducted analyses of clinical laboratory results including changes in mean values and changes in individual subjects over time. Across both trials, laboratory findings did not demonstrate clinically meaningful trends in the mean change from baseline within or between treatment groups in terms of the parameters of hematology, clinical chemistry, renal function or liver function. Overall, there were no safety concerns identified from the safety laboratory analyses for either Lithos or Vathos.

Vital Signs

Vital Signs (heart rate and blood pressure) over time were recorded in Lithos and Vathos. There were no clinically meaningful findings related to mean change in vital signs over time or differences between treatment arms for either Lithos or Vathos.

Electrocardiograms

ECGs were only performed at screening for Lithos and Vathos; therefore, changes in ECG assessments over time is not applicable.

Immunogenicity

Not applicable.

7.2.4. Safety Analyses by Demographic Subgroups

Demographic subgroup analyses conducted by this reviewer included analyses by age, and race. Subgroups based on and race showed that the most common AEs were consistent with the overall population and did not reveal any new safety concerns. The focus of this section will be the review of safety in the adolescent age group, as these subjects may be more vulnerable to the side effects of ICS or LABAs.

Per the Applicant's analyses and an independent analyses conducted by this reviewer, there were no clinically meaningful differences in AEs when assessed by age group (12 to <18 and ≥18 years of age; <65 and ≥65 years of age). In the geriatric age group, there were no deaths and the incidence of overall AEs were not meaningfully different than the entire population.

In the small adolescent population, the overall incidence of AEs were low and the most common AEs (nasopharyngitis and upper respiratory tract infections) were consistent with the adult population and no new safety findings were identified (see Table 43 and Table 44). In the adolescent population for both Lithos and Vathos, no serious AEs, AEs leading to discontinuation, severe AEs or deaths were reported.

Table 43. Summary of Adolescent Subjects With AEs, Lithos

Preferred Term	BFF 160/9.6 µg N=6 n (%)	BD MDI 160 µg N=5 n (%)
Any AE	2 (33.3)	1 (20.0)
Pharyngitis streptococcal	1 (16.7)	0 (0.0)
Bronchitis bacterial	0 (0.0)	1 (20.0)
Skin laceration	1 (16.7)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer
Filters: TRT01A = "BFF MDI 160/9.6 µg" and AGEGR1 = ">=12 to <18" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A="BD MDI 160 µg" and AGEGR1 = ">=12 to <18" and SAFFL = Y (BD MDI 160 µg); TRTEMFL = "Y" (Adverse Events)
Abbreviations: AE, adverse event; AGEGR1, pooled age group 1; BD, budesonide; BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; N, number of subjects in treatment group; n, number of subjects with specified adverse event; SAFFL, safety population flag; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

Table 44. Summary of Adolescent Subjects With AEs, Vathos

System Organ Class Preferred Term	BFF 160/9.6 µg N=3 n (%)	BFF 320/9.6 µg N=6 n (%)	BD MDI 320 µg N=7 n (%)	Symbicort TBH 320/9 µg N=5 n (%)
Any AE	3 (100.0)	3 (50.0)	4 (57.1)	3 (60.0)
Nasopharyngitis	1 (33.3)	1 (16.7)	1 (14.3)	1 (20.0)
Upper respiratory tract infection	1 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)
Rhinovirus infection	0 (0.0)	0 (0.0)	1(14.3)	0 (0.0)
Arthralgia	1 (33.3)	0 (0.0)	1 (14.3)	0 (0.0)
Bone pain	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Pain in jaw	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Hand fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Scratch	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Epistaxis	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Throat clearing	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer
Filters: TRT01A = "BFF MDI 160/9.6 µg" and AGEGR1 = ">=12 to <18" and SAFFL = Y (BFF MDI 160/9.6 µg); TRT01A="BFF MDI 320/9.6 µg" and AGEGR1 = ">=12 to <18" and SAFFL = Y (BFF MDI 320/9.6 µg); TRT01A = "BD MDI 320 µg" and AGEGR1 = ">=12 to <18" and SAFFL = Y (BD MDI 320 µg); TRT01A = "Symbicort TBH 320/9 µg" and AGEGR1 = ">=12 to <18" and SAFFL = Y (Symbicort TBH 320/9 µg); TRTEMFL = "Y" (Adverse Events)
Abbreviations: AE, adverse event; AGEGR1, pooled age group 1; BD, budesonide; BFF, budesonide/formoterol fumarate; MDI, metered-dose inhaler; SAFFL, safety population flag; TBH, Turbuhaler; TRTEMFL, treatment-emergent analysis flag; TRT01A, treatment for period 01

7.2.5. Additional Safety Explorations

Pediatrics and Assessment of Effects on Growth

The effect of BFF on the HPA axis function is expected to be similar between BFF, BGF, and Symbicort MDI. Refer to the discussion regarding the evaluation of the effect of BFF on HPA axis under Section 5.2.1 for details.

7.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There are currently no new safety concerns regarding BFF from the postmarketing experience noted in the Periodic Benefit-Risk Evaluation Report (October 2025). The postmarketing experience of BFF is described in the product label (SYMBICORT AEROSPHERE USPI, Section 6.2).

Expectations on Safety in the Postmarket Setting

Based on the extensive experience with ICS, LABA, and combination products, as well as the extensive experience specifically with BD, FF, and Symbicort MDI, it is not expected that new major safety concerns will be discovered in the postmarket setting. The expected safety is likely to be consistent with drug class and will be monitored through routine pharmacovigilance.

7.2.7. Integrated Assessment of Safety

The safety data submitted from two randomized, double-blind, active controller trials (Lithos and Vathos) were adequate for review. Differences between the two trials, such as a more severe asthma population, different dosages and longer treatment duration in Vathos, made pooling of safety data not appropriate for this review.

Overall, the safety profile based on the major safety categories (SAEs, AEs leading to drug discontinuation, common AEs), as well as vital signs and clinical laboratory testing, did not raise new safety concerns. There were no deaths in either Lithos or Vathos during the treatment or post-treatment periods. Common AEs in both trials, such as nasopharyngitis and upper respiratory tract infections, were consistent with known risks associated with ICS/LABA use.

No new safety signals were identified in either trial that would outweight the potential benefit of BFF when used as indicated, and the safety data submitted for review were sufficient to support a new indication for asthma.

7.3. Statistical Issues

Based on the primary clinical question for these trials, the Agency agreed with the Applicant's primary estimand for this application. The Agency's thinking has evolved from use of Treatment Policy for treatment discontinuation regardless of the reason to composite strategy for ICE1 (see next paragraph) and treatment policy strategy for treatment discontinuation due to other reasons (ICE2). This evolution was discussed with Agency clinical colleagues and conveyed to the Applicant during IND stage, and they accepted and implemented.

Subjects who (1) discontinued study medication and also began new asthma therapy were distinguished from (2) those subjects who only discontinued study medication. This is an important distinction because study drug discontinuation related to treatment arm could be due to lack of efficacy (LOE) in the BD control arm, or could be due to toxicity in the BFF active arm. Therefore, ICE1, with the addition of new asthma therapy, would have a higher frequency in the control arm if confounded with treatment arm due to LOE. ICE2 would have a higher frequency in the active arms if confounded with treatment arm.

These two ICEs in Lithos (Table 17) were predominantly in the BD 160 µg arm for both ICE1 and ICE2 (1-2% in the BFF 160/9.6 µg arm versus 5% for both ICEs in the BD 160 µg arm). This may indicate that if there was confounding with treatment, it was due to LOE on the control arm.

These two ICEs in Vathos (Table 18) were similar across all treatment arms for both ICE1 and ICE2 (7-8% in the BFF and Symbicort TBH arms for ICE1 versus 8% for the BD arm; 8-9% in the BFF and Symbicort TBH arms for ICE2 versus 10% for the BD arm). This may indicate there was no confounding with treatment, due to either LOE or toxicity in this study.

It does not appear that GCP violations described in the Lithos and Vathos study reports and summarized in Section 7.1.3 had influence on study results or interpretation.

7.4. Conclusions and Recommendations

The data submitted by the Applicant demonstrated SEE and safety for BFF 160/9.6 and BFF 320/9.6 for the (b) (4) treatment of asthma in patients 12 years of age and older. Therefore, the recommended regulatory action for this population and proposed dose is Approval.

Regarding the SEE framework, Lithos and Vathos were adequate and well-controlled trials and both provided support for effectiveness. Both trials met their prespecified primary and key secondary endpoints, mean change from baseline in FEV_1 AUC_{0-3} and mean change from baseline in morning pre-dose trough FEV_1, respectively. Both trials also demonstrated a lung function benefit with efficacy findings that were generally consistent across various demographic and baseline characteristic subgroups. The data also supported that the combination of BD and FF was superior to BD alone, thus characterizing the contribution of to the combination product and satisfying the combination rule.

Regarding safety, the submitted trials were adequate for evaluation and the review did not raise any new safey concerns, as the overall safety analysis was consistent with known safety profiles for inhaled ICS/LABA therapies.

8 Pediatrics

The safety and efficacy of BFF 160/9.6 and BFF 320/9.6 in patients 12 years of age and older was established during this sNDA review (see Sections 7.2.4 and 7.1.4, respectively). The Applicant has an agreed upon pediatric study plan that includes deferred pediatric studies in patients 4 to <12 years of age and a waiver of studies in children <4 years of age.

For children 4 to <12 years of age, the Applicant has agreed to conduct the following studies under the Pediatric Research Equity Act:

1. A randomized, open-label, single-dose, 2-period crossover phase 1 study to compare the pharmacokinetics of BD and FF delivered with BFF and Symbicort pressurized MDI
2. A 6-week randomized, double-blind, active-controlled, parallel group phase 3 efficacy and safety study of BFF 160/9.6 compared to BD 160

The Pediatric Research Equity Act postmarketing requirements (PMRs) to be issued are also discussed in Section 10.

9 Labeling Recommendations

9.1. Prescription Drug Labeling

Table 45. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes Incorporated Into the Finalized PI
1 INDICATIONS AND USAGE	The supplement proposed for a new indication with the following indication statement: SYMBICORT AEROSPHERE is indicated for the treatment of asthma in adult and pediatric patients aged 12 years and older. *"(b) (4)" was removed from the indication statement consistent with the Symbicort MDI labeling.*
2 DOSAGE AND ADMINISTRATION	The Recommended Dosage for asthma provides for two different dosages, dependent on asthma severity or level of asthma symptom control. The section was revised to provide the recommended dose of the fixed-combination product with parenthetical information of number of actuations and strength of each component.
4 CONTRAINDICATIONS	A contraindication of SYMBICORT AEROSPHERE for "primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required" was added consistent with class labeling.
5 WARNINGS AND PRECAUTIONS	This section was updated consistent with class labeling.
6 ADVERSE REACTIONS	In the *Clinical Trials Experience* subsection, the safety data of SYMBICORT AEROSPHERE for Asthma was based on two trials, Lithos and Vathos. The safety data from the Vathos trial informs the common adverse reaction table because Vathos evaluated the two different dosages (SYMBICORT AEROSPHERE 320 µg /9.6 µg and 160 µg /9.6 µg twice daily) compared to an active comparator (budesonide MDI 320 µg twice daily). Adverse reactions from the Lithos trial is provided in text below the common adverse reaction table to provide adverse reaction(s) that differed from Vathos.

Full PI Sections[1]	Rationale for Major Changes Incorporated Into the Finalized PI
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	**8.1 Pregnancy** the *Disease-Associated Maternal and/or Embryo/Fetal Risk* language was added consistent with class labeling for products indicated for asthma. **8.4 Pediatric Use** The Pediatric Use subsection was provided to include the pediatric use statement and the supporting evidence for use of SYMBICORT AEROSPHERE in pediatric patients 12 years of age and older. Additionally, the language regarding the effect on growth among pediatric patients with the use of orally inhaled corticosteroid was added to inform healthcare providers of this risk. **8.5 Geriatric Use** The subsection was updated with information of geriatric exposure from Lithos and Vathos and included the regulatory statement of no observed differences in safety and/or effectiveness between geriatric and young adult patients.
10 OVERDOSAGE	Added Poison Help line language.
12 CLINICAL PHARMACOLOGY	The Applicant proposed language regarding the ratio between topical anti-inflammatory activity and systemic corticosteroid effects. Although the language is in the SYMBICORT MDI, it was not retained in SYMBICORT AEROSPHERE labeling because language is too general and vague by current therapeutic standard. *Recommend removal of this statement. Although this "* (b) (4) *" statement is true, the language was copied from Symbicort (NDA 021929) approved 20 years ago when there were only a few inhaled corticosteroid available. None of the recently approved corticosteroid-containing inhaled products, including the label of the original approved SYMBICORT AEROSHERE back in 2023 included this statement*.

Full PI Sections[1]	Rationale for Major Changes Incorporated Into the Finalized PI
14 CLINICAL STUDIES	A new subsection for the Asthma indication was added to provide the efficacy of SYMBICORT AEROSPHERE for treatment of asthma in adults and pediatric patients 12 years of age and older. This subsection provides the description of the two trials, Lithos and Vathos, and includes demographics and baseline characteristics of the study population. The efficacy results for the primary and key secondary endpoints of lung function (FEV_1 area under the curve from 0-3 hours and trough FEV_1 at Week 12 and 24) were presented in a table and figures. Clinically meaningful efficacy for exacerbations, use of rescue medication, and health-related quality of life was provided in text following the primary efficacy results.
17 PATIENT COUNSELING INFORMATION	• Added Serious-Asthma Related Events counseling discussion language consistent with updates in Section 5 in the labeling. • Added language for effect on growth so that HCP will discuss the effect of ICS on growth among pediatric patients.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	• Sections 3, 11, and 16 were updated with information of a new strength of SYMBICORT AEROSPHERE 80 µg /4.8 µg. • Section 16 was reformatted to provide package information in a table.

Source: Associate Director of Labeling and Clinical Reviewer
[1] Labeling Discussion Comments dated February 13, April 8, and 21, 2026

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; NDA new drug application; PI, prescribing information

10 Postmarketing Requirements and Commitment

Agreed-upon PMRs include the following:

- **PMR-1**: Conduct a randomized, open-label, single-dose, crossover study to compare the pharmacokinetics of BD and FF delivered with BFF and Symbicort pressurized MDI in children 4 to less than 12 years of age with asthma

  Final Report Submission: July 2027

- **PMR-2**: Conduct a phase 3, randomized, active-controlled, double-blind, parallel group, 6-week efficacy and safety lung function study of BFF compared to BD MDI in children 4 to less than 12 years of age with asthma

  Final Protocol Submission: July 2026
  Study Completion: October 2029
  Final Report Submission: = February 2030

11 Associate Director for Therapeutic Review Comments

I concur with the contents of this review and with the multi-disciplinary review team's recommendation for approval of this supplemental NDA.

12 Appendices

12.1. Bioanalytical Assay Assessment

Determinations of FF and BD concentrations in human plasma samples collected from Kalos were performed using the same liquid chromatography with tandem mass spectrometry methods developed in the COPD program. Details on the development and validation of bioanalytical methodology were provided in the original NDA 212122 for COPD program. Analytical site was also the same as that in the original NDA: (b) (4) . The performance of these methods is deemed acceptable.

- Bioanalytical assay for measuring FF plasma concentrations obtained from Kalos

  Bioanalytical assay for measuring FF plasma concentrations obtained from Kalos used the same method (TSLM14053) developed in the COPD program (updated with Addendum 2). After that, four additional addendums (Addendums 3, 4, 5, and 6) were updated for the same method.

- Addendum 3 (December 2019) included the results for method modification to update the standard curve regression (changed from 1/x to $1/x^2$ weighting) for FF in human plasma. The performance of FF bioanalytical assay from Addendum 3 is summarized below. The performance of the assay is acceptable.

Table 46. Performance of Formoterol Bioanalytical Assay TSLM14053 Addendum 3

Formoterol Validation Results	
Internal Standard:	Formoterol-d_6
LLOQ and ULOQ:	1.00 pg/mL and 200 pg/mL
Calibration Standard Concentrations:	1.00, 2.00, 5.00, 10.0, 60.0, 120, 180 and 200 pg/mL
Inter-Assay Accuracy (%Bias): Inter-Assay Precision (%CV):	-1.4% to 3.0% 1.6% to 11.1%
Regression and Weighting:	Linear $1/x^2$
Quality Control Levels:	1.00, 3.00, 15.0, 80.0 and 160 pg/mL
LLOQ QC	
Intra-Assay Accuracy (%Bias): Intra-Assay Precision (%CV): Inter-Assay Accuracy (%Bias): Inter-Assay Precision (%CV):	-8.3% to 0.0% 1.6% to 8.9% -4.5% 7.7%
Intra-Assay results are reported as ranges from the A/P runs. Inter-Assay results are reported as the result from the ANOVA calculations.	
Low, Low-Medium, Medium and High QC	
Intra-Assay Accuracy (%Bias): Intra-Assay Precision (%CV): Inter-Assay Accuracy (%Bias): Inter-Assay Precision (%CV):	-4.7% to 2.3% 1.0% to 4.2% -2.3% to -0.3% 2.3% to 4.1%
Intra-Assay results are reported as ranges from the A/P runs. Inter-Assay results are reported as ranges from the ANOVA calculations.	
Ability to Dilute:	800 pg/mL (DF=10)
Dilution Linearity:	8,000 pg/mL (DF=100)
Matrix Effects	
LLOQ Reproducibility in Matrix:	Accuracy (%Bias): 11.0% Precision (%CV): 3.8%
Interference	
Analyte Only:	No significant interference found at the retention time of interest for Analyte Only samples.

Continued

Table 46, continued

Internal Standard Only:	No significant interference found at the retention time of interest for IS Only samples.
Additional Compounds:	Budesonide (500 pg/mL) Quantitation of formoterol is not impacted by the co-administered compounds when present at the concentrations described above.
Stability in Matrix	
Freeze-Thaw:	6 Cycles; stored at -70 °C and thawed in an ice bath
Bench-Top:	6 Hours at room temperature; 7 Hours at 5 °C
Long-Term:	42 Days at -20 °C and 1,138 Days at -70 °C*
Reinjection Reproducibility:	167 Hours at 5 °C
Extract Stability:	67 Hours at 5 °C
Batch Size Evaluation:	Sample analysis runs may include up to 192 samples (including Standards, QCs, Blanks, Unknowns, etc.)

Source: tslr14-053-method-validation-report-addendum-3.pdf
Abbreviations: ANOVA, analysis of variance; A/P, accuracy/precision; CV, coefficient of variation; DF, dilution factor; IS, internal standard; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

- Addendum 4 (February 2022) was to complete hemolysis and solution stability evaluations of FF. The results showed the low quality control (QC) and high QC samples in blank plasma containing 2% lysed whole blood had precision ≤15% and mean concentration values were within ±15% bias of the normal concentration for each QC sample concentration.
- Addendum 5 (July 2023) was to complete a method qualification evaluation to include the low-binding plate ((b) (4)), used in sample extraction due to the supply shortage of salinized well plates ((b) (4)), from the vendor for FF in human plasma. The results indicate that low-binding plate was acceptable for measuring FF in human plasma over the calibration range of 1.00 to 200 pg/mL.
- Addendum 6 (May 2024, tslr07-043-method-validation-report-amendment-memo-1.pdf) was to update solution stability evaluations of FF in human plasma prepared in a dimethylformamide (DMF)-containing intermediate solution. The motivation for conducting this assay is unclear. The assay failed to establish stability of the DMF-containing FF samples stored at 5°C for (b) (4) days (and thus the stability is established only for 125 days based on previous results from TSLS14-017).
- Bioanalytical assay for measuring BD plasma concentrations obtained from Kalos

  Bioanalytical assay for measuring BD plasma concentrations obtained from Kalos used the same method (TSLS13-225) developed in the COPD program (updated with Addendum 2). The performance of BD bioanalytical assay from Addendum 2 is summarized below.

Table 47. Performance of Budesonide Bioanalytical Assay TSLS13-225 Addendum 2

Bioanalytical method validation report name and amendments	TSLR13-225: Assay Validation Report: Quantitative Determination of Budesonide in Human Plasma (EDTA) by LC/MS/MS TSLR13-225 Addendum 1: Assay Validation Addendum Report: Quantitative Determination of Budesonide in Human Plasma (EDTA) by LC/MS/MS TSLR13-225 Addendum 2: Assay Validation Addendum Report: Quantitative Determination of Budesonide in Human Plasma (EDTA) by LC/MS/MS		
Method description	TSLM13-225 (Appendix A in validation report) SPE followed by LC-MS/MS		
Materials used for calibration curve & concentration	Human Plasma, K_3EDTA Reference material: Budesonide Calibration standard concentrations: Budesonide: 3, 6, 12.5, 50, 100, 250, 450 and 500 pg/mL		
Validated assay range	Budesonide: 3 pg/mL- 500 pg/mL		
Material used for QCs & concentration	Human Plasma, K_3EDTA Reference material: Budesonide Quality Control levels: Budesonide: 3, 9, 40, 200 and 400 pg/mL		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	NA		
Regression model & weighting	Budesonide: Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ Budesonide:	8	TSLR13-225 Section 7.1
	Cumulative accuracy (%bias) from LLOQ to ULOQ Budesonide:	-2.0 to 4.0 %	TSLR13-225 Section 7.1
	Cumulative precision (%CV) from LLOQ to ULOQ Budesonide:	≤ 9.0%	TSLR13-225 Section 7.1
QCs performance during accuracy & precision	**Cummulative accuracy (%bias) in 5 QCs** QCs Budesonide:	-5.0 to -0.4%	TSLR13-225 Section 7.2
	Inter-batch %CV QCs Budesonide: :	≤ 8.1%	TSLR13-225 Section 7.2
	Total error QCs:	NA	NA
Selectivity & matrix effect	*Number of total lots tested. Range of observed bias. State any issue* 6 different lots tested No interference greater than acceptable limits detected at the retention times of interest.		TSLR13-225 Section 6.1 Section 7.5 Section 7.6

Continued

Table 47, continued

	Matrix Factor (MF) Budesonide low: MF=0.688, IS=0.691, IS Normalized MF:1.00 Budesonide high: MF=0.736, IS=0.744, IS Normalized MF:0.991	
Interference & specificity	*Number of total lots tested. Range of observed bias. State any issue* Single lot. No significant interference found at the retention time of analyte or IS. Interference test for Formoterol and Glycopyrrolate met acceptance criteria.	TSLR13-225 Section 7.7
Hemolysis effect	*Number of total lots tested. Range of observed bias. State any issue* Single lot. No significant impact in samples evaluated with up to 2 % hemolysis.	TSLR13-225 Section 7.13
Lipemic effect	*Number of total lots tested. Range of observed bias. State any issue* Single Lot. No significant impact in samples with hyperlipidemia.	TSLR13-225 Section 7.14
Dilution linearity & hook effect	NA	
Bench-top/process stability	Budesonide: Bench-top: 6 hours at 5 °C Extract stability: 47 hours at RT Extract stability: 115 hours at RT Reinjection reproducibility: 147 h at RT	TSLR13-225 Section 7.9-7.11 TSLR13-225 Addendum 1

Source: Clinical-information-amendment.pdf dated March 12, 2019, and tslr13-225-method-validation-report-addendum-2.pdf
Abbreviations: CV, coefficient of variation; EDTA, ethylenediaminetetraacetic acid; IS, internal standard; LC/MS/MS, liquid chromatography tandem-mass spectrometry; LLOQ, lower limit of quantification; NA, not applicable; QC, quality control; RT, room temperature; ULOQ, upper limit of quantification

- After that, Addendum 3 (September 2019) was to complete to update an interference, solution stability, matrix bench-top stability, matrix freeze-thaw stability, and matrix frozen stability (in the presence of albuterol) evaluation of BD in human plasma. The updated results are displayed below:

Table 48. Results of Budesonide Bioanalytical Assay TSLS13-225 Addendum 3

Analyte	Budesonide
Species	Human
Analytical Matrix	K_3EDTA Plasma
Internal Standard (ISTD)	Budesonide-d_8
Validated Method	TSLM13225
Validated Range	3.00 to 500 pg/mL
Quality Control (QC) levels	9.00 pg/mL, 40.0 pg/mL, 200 pg/mL, 400 pg/mL
Analytical technique/method of detection	Solid-Phase Extraction / LC/MS/MS
Sample Volume	500 µL
Calibration Model	Linear regression
Weighting Factor	$1/x^2$
Effect of Analytes Not Measured with the Assay	Albuterol – 20,000 pg/mL Passes acceptance criteria
Hemolysis	Passes acceptance criteria
Solution Stability – Bench-Top	Primary standard solutions Budesonide at 600,000 ng/mL prepared in DMF: 24 hours at room temperature Budesonide-d_8 at 5.00 ng/mL prepared in H20:MeCN (50:50 v/v): 24 hours at room temperature Intermediate solutions Budesonide at 0.240 ng/mL prepared in DMF: 24 hours at room temperature
Matrix Bench-Top Stability	Budesonide: 25 hours at room temperature
Matrix Freeze-Thaw Stability	Budesonide: 8 cycles at -70°C
Matrix Frozen Stability(in the presence of albuterol)	Budesonide: 91 days at -20°C

Source: tsls13-225-method-validation-report-addendum-3.pdf
Abbreviations: DMF, dimethylformamide; EDTA, ethylenediaminetetraacetic acid; LS/MS/MS, liquid chromatography tandem-mass spectrometry

The runs to support these new results all had precision ≤15% and mean concentration values were within ±15% bias of the normal concentration for each QC sample concentration.

In-Study Performance (Kalos Study 8451-340)

The in-study performance of bioanalytical assays for measuring FF and BD plasma concentrations are acceptable.

FF

- Assay passing rate: 17 of 20 runs (85%)
- Total number of samples analyzed: 1670
- Total number of samples re-assayed: 224 (13.4%)
- Total duration of sample storage was 1399 days (from first sample collection on April 6, 2021, to the last sample extracted on February 3, 2025). However, the study samples were analyzed in multiple subsets which resulted in the analysis of all samples within 912 days of collection.
- Calibration curve performance: Cumulative bias -2.2% to 2.6%; coefficient of variation (CV) ≤8.7%
- QC performance: Cumulative bias -0.8% to 2.0%; CV ≤12.2%

BD

- Assay passing rate: 17 of 19 runs (89%)
- Total number of samples analyzed: 1731
- Total number of samples re-assayed: 264 (15.3%)
- Total duration of sample storage was 1400 days (from first sample collection on April 6, 2021, to the last sample extracted on February 4, 2025). However, the study samples were analyzed in multiple subsets which resulted in the analysis of all samples within 724 days of collection.
- Calibration curve performance: Cumulative bias -2.8% to 2.2%; CV ≤8.0%
- QC performance: Cumulative bias -4.3% to 1.5%; CV ≤9.6%

In conclusion, the bioanalytical methods used to measure FF, and BD plasma concentrations from PK samples collected from are acceptable and meet the FDA guidance for industry *Bioanalytical Method Validation* (May 2018) requirements.

12.2. Financial Disclosure

Table 49. Clinical Investigator Financial Disclosure, Lithos and Vathos

Was a list of clinical investigators provided:		Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 978		
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 3 investigators		
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
	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: 3 Lithos and Vathos: (b) (6) received payments totaling $30,235, including compensation for research activities ($25,000) and consulting and speaking ($5,235). (b) (6) site for Lithos enrolled 5 subject and 3 were randomized. (b) (6) site for Vathos enrolled 17 subjects and 11 were randomized. Because a small number of subjects at Dr (b) (6) sites for Lithos and Vathos were randomized, the study sites are unlikely to have had an impact on the study outcome. Lithos: (b) (6) received $67,604.48 as compensation for advisory services and as an honorary speaker for the Applicant. (b) (6) site enrolled 3 subjects and 2 were randomized. Because a small number of subjects at (b) (6) sites were randomized, the study site is unlikely to have had an impact on the study outcome. Vathos: (b) (6) received $34,359 honoraria for speaking roles. In the Vathos study, (b) (6) enrolled 3 subjects and none were randomized. There are no randomized subjects in this site, therefore, impact on the study outcome is unlikely. 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) Not Applicable

12.3. Trials Lithos and Vathos: Additional Information

Table 50. Schedule of Activities, Lithos

	Screening				Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	1	2	3	3a	4	4a	5	5a	6	6a	7		2 weeks (± 2 days) after last dose	
Week					Rand	2	4	6	8	10	12			
Study Day[c]	-21	-14 (+ 2)	-7 (± 2)	-3 (± 2)	1	15 (± 2)	29 (± 2)	43 (± 5)	57 (± 5)	71 (± 5)	85 (± 5)			
Virtual Televisual Visit for Home-coached Spirometry Sub-Study				X		X		X		X				
Informed consent/assent	X													Section 4.1, Section 5.1, Appendix A 3
Inclusion/exclusion criteria	X	X	X		X									Section 5.1, Section 5.2
Verify continuing eligibility							X		X		X			Section 7.1
Calculate FEV_1 stability limit	X													Section 5.1
Calculate PEF stability limit					X									Section 8.1.2.5
Routine clinical procedures														
Demography and medical/surgical history	X													Section 5.1, Section 8.2.1
Prior/concomitant medication review	X	X	X		X		X		X		X	X	X	Section 6.5
Dispense and collect eDiary	X[d]										X	X		Section 8.1.2

Continued

Table 50, continued

	Screening				Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**3a**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**		**2 weeks (± 2 days) after last dose**	
Week					**Rand**	**2**	**4**	**6**	**8**	**10**	**12**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**-3 (± 2)**	**1**	**15 (± 2)**	**29 (± 2)**	**43 (± 5)**	**57 (± 5)**	**71 (± 5)**	**85 (± 5)**			
Virtual Televisual Visit for Home-coached Spirometry Sub-Study				**X**		**X**		**X**		**X**				
Dispense and collect home-coached spirometer/peak flow meter	X[d]										X	X		Section 8.1.1.4, Section 8.1.2.5
eDiary training and review	X[d]	X	X		X		X		X		X	X		Section 8.1.2
Peak flow meter training and review	X[d]	X	X		X		X		X		X	X		Section 8.1.2.5
Dispense/collect albuterol (as needed)	X[d]	X	X		X		X		X		X	X		Section 4.1, Section 6, Section 6.5.1
Reversibility to albuterol		X[e]	X[e]											Table 2, Section 8.1.1.3
Discontinue ICS or ICS/LABA	X[d]													Section 4.1, Section 6
Dispense/collect Run-in BD MDI	X[d]				X									Section 4.1, Section 6
Dispense/collect blinded study intervention					X		X		X		X	X		Section 4.1, Section 6

Continued

Table 50, continued

	Screening				Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**3a**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**		**2 weeks (± 2 days) after last dose**	
Week					**Rand**	**2**	**4**	**6**	**8**	**10**	**12**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**-3 (± 2)**	**1**	**15 (± 2)**	**29 (± 2)**	**43 (± 5)**	**57 (± 5)**	**71 (± 5)**	**85 (± 5)**			
Virtual Televisual Visit for Home-coached Spirometry Sub-Study				**X**		**X**		**X**		**X**				
Dispense and collect home-coached spirometer/peak flow meter	X[d]										X	X		Section 8.1.1.4, Section 8.1.2.5
eDiary training and review	X[d]	X	X		X		X		X		X	X		Section 8.1.2
Peak flow meter training and review	X[d]	X	X		X		X		X		X	X		Section 8.1.2.5
Dispense/collect albuterol (as needed)	X[d]	X	X		X		X		X		X	X		Section 4.1, Section 6, Section 6.5.1
Reversibility to albuterol		X[e]	X[e]											Table 2, Section 8.1.1.3
Discontinue ICS or ICS/LABA	X[d]													Section 4.1, Section 6
Dispense/collect Run-in BD MDI	X[d]				X									Section 4.1, Section 6
Dispense/collect blinded study intervention					X		X		X		X	X		Section 4.1, Section 6

Continued

Table 50, continued

	Screening				Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**3a**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**		**2 weeks (± 2 days) after last dose**	
Week					**Rand**	**2**	**4**	**6**	**8**	**10**	**12**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**-3 (± 2)**	**1**	**15 (± 2)**	**29 (± 2)**	**43 (± 5)**	**57 (± 5)**	**71 (± 5)**	**85 (± 5)**			
Virtual Televisual Visit for Home-coached Spirometry Sub-Study				X		X		X		X				
Routine safety measurements (pre-dose)														
Adverse event assessments[f]	X	X	X		X		X		X		X	X	X	Section 8.3, Appendix B
Asthma exacerbation assessment	X	X	X		X		X		X		X	X	X	Section 8.2.1, Section 8.2.7
Pregnancy testing[f]	X	X	X		X		X		X		X	X		Section 5.1, Section 8.3.10
Safety laboratory assessments (blood)	X										X	X		Section 8.2.6
Physical examination	X				X						X	X		Section 8.2.2
Height and weight	X										X			Section 8.2.3
Vital signs (blood pressure and pulse)	X				X						X	X		Section 8.2.4
12-lead ECG	X													Section 8.2.5
Genomics Initiative, optional exploratory genetic sample					X									Section 8.7, Appendix C

Continued

Table 50, continued

	Screening				Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**3a**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**		**2 weeks (± 2 days) after last dose**	
Week					**Rand**	**2**	**4**	**6**	**8**	**10**	**12**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**-3 (± 2)**	**1**	**15 (± 2)**	**29 (± 2)**	**43 (± 5)**	**57 (± 5)**	**71 (± 5)**	**85 (± 5)**			
Virtual Televisual Visit for Home-coached Spirometry Sub-Study				X		X		X		X				
Efficacy measurements[g]														
In-clinic serial spirometry[h]					X				X		X	X		Table 2, Section 8.1.1
In-clinic pre-dose spirometry[h]	X[i]	X	X		X		X		X		X	X		Table 2, Section 8.1.1
Home-coached pre-dose spirometry (sub-study only)			X[j]	X		X		X		X				Section 8.1.1.4
ACQ (pre-dose)	X				X		X		X		X	X		Section 8.1.2.7
AQLQ(s)+12 (pre-dose)					X		X		X		X	X		Section 8.1.2.7
EQ-5D (pre-dose)					X		X		X		X	X		Section 8.1.2.7
AIRQ (pre-dose)	X				X						X			Section 8.1.2.7
Healthcare resource utilization			X				X		X		X	X		Section 8.8
Serial spirometry 12-hours post-dose (sub-study)					X						X			Table 2, Section 8.1.1

Continued

Table 50, continued

	Screening				Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**3a**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**		**2 weeks (± 2 days) after last dose**	
Week					**Rand**	**2**	**4**	**6**	**8**	**10**	**12**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**-3 (± 2)**	**1**	**15 (± 2)**	**29 (± 2)**	**43 (± 5)**	**57 (± 5)**	**71 (± 5)**	**85 (± 5)**			
Virtual Televisual Visit for Home-coached Spirometry Sub-Study				X		X		X		X				
Study intervention administration														
Check of inhalation device technique and training	X[d]	X	X		X		X		X					Section 6
Administer Run-in BD MDI in clinic[k]		X	X											Section 4.1, Section 6
Administer blinded study intervention in clinic[k]					X		X		X		X			Section 4.1, Section 6

Abbreviations: ACQ=Asthma Control Questionnaire; AEs=adverse events; AIRQ=Asthma Impairment and Risk Questionnaire; AQLQ(s)+12=Asthma Quality of Life Questionnaire for 12 years and older; BD=budesonide; CSP=Clinical Study Protocol; ECG=electrocardiogram; eDiary=electronic diary; PRO=Patient Reported Outcome; EQ-5D=European Quality-of-Life-5 Dimensions; F/U=follow-up; ICS/LABA=inhaled corticosteroid/long-acting beta$_2$-agonist; MDI=metered-dose inhaler; PEF=peak expiratory flow; Rand=randomization; SAE=serious adverse event; TC=telephone call

[a] Risk assessments for the SARS-CoV-2 pandemic must be made prior to every in-clinic visit in-line with the Study Disruption Mitigation Instructions.

[b] Sites should call participants 1 to 2 days before each scheduled visit to remind the participant of the visit and the required medication washouts (6 hours for short-acting bronchodilators and 12 hours for run-in BD MDI and blinded study intervention). Participants will be required to return to the clinic at approximately the same time ± 1 hour as Visit 1 throughout the study. For all visits after Visit 1, if albuterol and study intervention have not been withheld for the specified timeframes, the visit should be rescheduled and conducted within the specified visit window.

[c] Site should make every effort to maintain participants within the scheduled visit windows. Participants who fall outside the visit window should be placed in the protocol-defined window at the next scheduled visit.

[d] At Visit 1, issue/train participants on eDiary/peak flow meter use/in-home spirometers, discontinue ICS or ICS/LABA, and dispense albuterol and run-in BD MDI **only** after the participant has been found eligible to proceed to Visit 2.

[e] If reversibility criteria is not met at Visit 2, participants may continue to Visit 3. Reversibility criteria must be met at either Visit 2 or Visit 3, otherwise the participant will be screen failed

Continued

Reference ID: 5786374

Table 50, continued

f For all screen failures, an assessment of AEs and highly sensitive urine pregnancy testing (for women of childbearing potential) must be performed within 7 days of the screen failure date.
g The suggested order of assessments is vital signs, AE/SAE assessments, -60 minute spirometry, PRO questionnaires, -30 minute spirometry, ECG, blood draw, and then study intervention administration. **Spirometry MUST be performed in accordance with the specified timing.**
h All pre-dose (trough) spirometry will be required to be collected in the morning (0800 ± 2 hours).
i Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry inclusion criteria at Visit 1 should return to the clinic to repeat spirometry testing within 2 days. If repeat spirometry failed to meet the inclusion criteria, then the participant must be screen failed.
j The first home-coached spirometry measurement at Visit 3, for training purposes, will be conducted at the site in a separate room, including remote televisual coaching.
k All in-clinic dosing must occur prior to 1000 (+ 1 hour allowance)

Source: Lithos Clinical Study Protocol, page 13-18

Table 51. Timing of In-Clinic Spirometry Measurements, Lithos

Visits	Pre-dose		Post-dose								
	Minutes		Minutes			Hours					
	-60 (±10)	-30 (±10)	5 (±2)	15 (±5)	30 (±5)	1 (±10 min)	2 (±10 min)	3 (±10 min)	6 (±10 min)	9 (±10 min)	12 (±10 min)
1 and 5	X	X									
2 (reversibility to albuterol) and 3 (reversibility to albuterol, if needed)	X	X			X	X[a]					
4	X	X	X	X	X	X	X	X			
6 and 7 or Study Intervention Discontinuation/Withdrawal	X	X		X	X	X	X	X			
12-hour spirometry sub-study at Visits 4 and 7	X	X	X[b]	X	X	X	X	X	X	X	X

a. For reversibility, 1-hour post-dose spirometry may be assessed if not reversible at 30 minutes post-dose
b. Only applies at Visit 4

Source: Lithos Clinical Study Protocol, page 18

Table 52. Schedule of Activities, Vathos

	Screening			Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**2 weeks (± 2 days) after last dose**	
Week	**-3**	**-2**	**-1**	**Rand**	**4**	**8**	**12**	**16**	**20**	**24**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**1**	**29 (± 2)**	**57 (± 5)**	**85 (± 5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**			
Telemedicine Visit (telephone or video)						X		X					
Informed consent/assent[d]	X												Section 4.1, Section 5.1, Appendix A 3
Inclusion/exclusion criteria	X	X	X	X									Section 5.1, Section 5.2
Verify continuing eligibility					X	X	X	X	X	X			Section 7.1
Calculate FEV_1 stability limit	X												Section 5.1
Calculate PEF stability limit				X									Section 8.1.2.5
Routine clinical procedures													
Demography and medical/surgical history	X												Section 8.2.1
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Dispense and collect eDiary	X[e]									X	X		Section 8.1.2
eDiary/peak flow meter training and review	X[e]	X	X	X	X	X	X	X	X	X	X		Section 8.1.2, Section 8.1.2.5
Peak flow meter dispensed/collected	X[e]									X	X		Section 8.1.2.5

Continued

Table 52, continued

	Screening			Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**2 weeks (± 2 days) after last dose**	
Week	**-3**	**-2**	**-1**	**Rand**	**4**	**8**	**12**	**16**	**20**	**24**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**1**	**29 (± 2)**	**57 (± 5)**	**85 (± 5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**			
Telemedicine Visit (telephone or video)						X		X					
Dispense/collect albuterol (as needed)	X[e]	X	X	X	X		X		X	X	X		Section 4.1, Section 6, Section 6.5.1
Reversibility to albuterol		X[f]	X[f]										Table 2, Section 8.1.1.3
Discontinue ICS or ICS/LABA	X[e]												Section 4.1, Section 6
Dispense/collect Run-in BD MDI	X[e]			X									Section 4.1, Section 6
Dispense/collect blinded/open-label study intervention				X	X		X		X	X	X		Section 4.1, Section 6
Routine safety measurements (pre-dose)													
Adverse event assessments[g]	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3, Appendix B
Asthma exacerbations assessment	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.1, Section 8.2.7
Pregnancy testing[g]	X	X	X	X	X		X		X	X	X		Section 5.1, Section 8.3.10
Safety laboratory assessments (blood)	X									X	X		Section 8.2.6
Physical examination	X			X						X	X		Section 8.2.2

Continued

Table 52, continued

	Screening			Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**2 weeks (± 2 days) after last dose**	
Week	**-3**	**-2**	**-1**	**Rand**	**4**	**8**	**12**	**16**	**20**	**24**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**1**	**29 (± 2)**	**57 (± 5)**	**85 (± 5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**			
Telemedicine Visit (telephone or video)						X		X					
Height and weight	X									X	X		Section 8.2.3
Vital signs (blood pressure and pulse)	X			X						X	X		Section 8.2.4
12-lead ECG	X												Section 8.2.5
Genomics Initiative, optional exploratory genetic sample				X									Section 8.7, Appendix C
Efficacy measurements[h]													
Serial spirometry[i]				X			X			X	X		Table 2, Section 8.1.1
Pre-dose spirometry[i]	X[j]	X	X	X	X		X		X	X	X		Table 2, Section 8.1.1
ACQ (pre-dose)	X			X	X		X		X	X	X		Section 8.1.2.7
AQLQ(s)+12 (pre-dose)				X	X		X		X	X	X		Section 8.1.2.7
EQ-5D (pre-dose)				X	X		X		X	X	X		Section 8.1.2.7
AIRQ (pre-dose)	X			X			X			X	X		Section 8.1.2.7
Healthcare resource utilization			X		X		X		X	X	X		Section 8.8
Study intervention administration													
Check of inhalation device technique and training	X[e]	X	X	X	X		X		X				Section 6

Continued

Table 52, continued

	Screening			Treatment Period							Study Intervention Discontinuation or Study Withdrawal	F/U TC	Details in CSP Section or Appendix
Visit[a,b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**2 weeks (± 2 days) after last dose**	
Week	**-3**	**-2**	**-1**	**Rand**	**4**	**8**	**12**	**16**	**20**	**24**			
Study Day[c]	**-21**	**-14 (+ 2)**	**-7 (± 2)**	**1**	**29 (± 2)**	**57 (± 5)**	**85 (± 5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**			
Telemedicine Visit (telephone or video)						**X**		**X**					
Administer Run-in BD MDI in clinic[j]	X	X	X										Section 4.1, Section 6
Administer blinded/open-label study intervention in clinic[k]				X	X[l]		X[l]		X	X			Section 4.1, Section 6

Abbreviations: ACQ=Asthma Control Questionnaire; AEs=adverse events; AIRQ=Asthma Impairment and Risk Questionnaire; AQLQ(s)+12=Asthma Quality of Life Questionnaire for 12 years and older; BD=budesonide; CSP=Clinical Study Protocol; ECG=electrocardiogram; eDiary=electronic diary; EQ-5D=European Quality of Life-5 Dimensions; F/U=follow-up; ICS/LABA=inhaled corticosteroid/long-acting beta$_2$-agonist; MDI=metered dose inhaler; PEF=peak expiratory flow; PRO=Patient Reported Outcome; Rand=randomization; SAE=serious adverse event; TC=telephone call

[a] Risk assessments for the SARS-CoV-2 pandemic must be made prior to every in-clinic visit in line with the Study Disruption Mitigation Instructions.

[b] Sites should call participants one to 2 days before each scheduled visit to remind the participant of the visit and the required medication washouts (6 hours for short-acting bronchodilators and 12 hours for run-in BD MDI and blinded/open-label study intervention). Participants will be required to return to the clinic at approximately the same time ± 1 hour as Visit 1 throughout the study for all in-clinic visits. For all visits after Visit 1, if albuterol and study intervention have not been withheld for the specified timeframes, the visit should be rescheduled and conducted within the specified visit window.

[c] Site should make every effort to maintain participants within the scheduled visit windows. Participants who fall outside the visit window should be placed in the protocol-defined window at the next scheduled visit.

[d] Informed consent form may be signed at or prior to Visit 1.

[e] At Visit 1, issue/train participants on eDiary/peak flow meter use, discontinue ICS or ICS/LABA, and dispense albuterol and run-in BD MDI **only** after the participant has been found eligible to proceed to Visit 2. Should there be any concern that the ICS or ICS/LABA was taken prior to Visit 1, this visit can be rescheduled within 2 days.

[f] If reversibility criterion is not met at Visit 2, participants may continue to Visit 3. Reversibility criterion must be met either in the 12 months prior to Visit 1 or at Visit 2 or Visit 3, otherwise the participant will be screen failed.

[g] For all screen failures, an assessment of AEs and highly sensitive urine pregnancy testing (for women of childbearing potential) must be performed within 7 days of the screen failure date.

[h] The suggested order of assessments is vital signs, AE/SAE assessments, -60-minute spirometry, PRO questionnaires, -30-minute spirometry, ECG, blood draw, and then study intervention administration. **Spirometry MUST be performed in accordance with the specified timing.**

[i] All pre-dose (trough) spirometry will be required to be collected in the morning (0800 ± 2 hours).

[j] Participants who have not withheld asthma medications prior to Visit 1 and failed spirometry inclusion criteria at Visit 1 should return to the clinic to repeat spirometry testing (or have the spirometry postponed if it is known in advance that the participant has not washed out) within 2 days. If repeat spirometry fails to meet the inclusion criteria, then the participant must be screen failed.

[k] All dosing occurring during study visits must occur prior to 1000 (+ 1 hour allowance)

[l] Sufficient blinded/open-label study intervention should be provided to account for next physical visit.

Source: Vathos Clinical Study Protocol, page 25-28

Table 53. Timing of Spirometry Measurements, Vathos

Visits	Pre-dose		Post-dose					
	Minutes		Minutes			Hours		
	-60 (±10)	-30 (±10)	5 (±2)	15 (±5)	30 (±5)	1 (±10 min)	2 (±10 min)	3 (±10 min)
1, 5, and 9	X	X						
2 (reversibility to albuterol) and 3 (reversibility to albuterol, if needed)	X	X			X	X[a]		
4	X	X	X	X	X	X	X	X
7 and 10, or Study Intervention Discontinuation/Withdrawal	X	X		X	X	X	X	X

a. For reversibility, 1-hour post-dose spirometry may be assessed if not reversible at 30 minutes post-dose

Source: Vathos Clinical Study Protocol, page 29

Table 54 through Table 56 list medications that were prohibited throughout the study as well as the minimum cessation period of these medications to enroll in Lithos or Vathos.

Table 54. Prohibited Medications Throughout the Study and Required Cessation Periods Prior to Visit 1, Lithos

Medication	Minimum Cessation Period Prior to Visit 1
Long-acting beta$_2$-agonist as reliever (LABA)	8 weeks
Long-acting muscarinic antagonist (LAMA)	12 months
Leukotriene antagonists/modifiers (eg, Zileuton®)	3 months
Oral beta$_2$-agonist	3 months
Theophylline	7 days
Oral and IV corticosteroids[a]	8 weeks
Injectable systemic corticosteroids (eg, depot formulation, intra-articular, intraocular, intradermal, intramuscular)	12 months
Any marketed (eg, omalizumab, mepolizumab, benralizumab, reslizumab) or investigational biological therapy for asthma or any other condition	6 months or 5 half-lives, whichever is longer
Prophylactic antibiotics	8 weeks
Roflumilast	30 days
Any immunomodulators or immunosuppressives[b]	3 months or 5 half-lives, whichever is longer
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	30 days
Any drug with potential to significantly prolong the QT interval[c]	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccines	30 days
Non-selective non-ocular β-blocking agents (except carvedilol)	7 days
Monoamine oxidase inhibitors	14 days
Systemic treatment with strong CYP3A4-inhibitors (eg, ketoconazole, itraconazole, and ritonavir)	30 days
Systemic anticholinergics[d]	7 days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases (eg, Chinese complementary and alternative bronchodilatory medicines)	10 days

a. Use of systemic corticosteroids for any other reason except for the acute treatment of a severe asthma exacerbation is prohibited for the duration of the study.
b. Topical administration of immunosuppressive medication maybe allowed at the discretion of the Investigator after discussion with the Study Physician.
c. Participants who are on medications that have the potential to prolong the QTc interval may be enrolled provided the dose has remained stable for at least 3 months prior to Visit 1, the participant meets all of the ECG inclusion criteria and none of the ECG exclusion criteria, and if, in the opinion of the Investigator, there are not safety concerns for the participant to participate in the study.
d. If systemic anticholinergics are used for the treatment of irritable bowel syndrome or overactive bladder and the treatment has been constant for at least 1 month, they are allowed.

Source: Lithos Clinical Study Protocol, Table 8, page 53
Abbreviations: CYP, cytochrome P450; ECG, electrocardiogram; IV, intravenous; QTc, corrected QT

Table 55. Prohibited Medications Throughout the Study and Required Cessation Periods Prior to Visit 1, Vathos

Medication	Minimum Cessation Period Prior to Visit 1
Long-acting beta$_2$-agonist as reliever (LABA)	8 weeks
Long-acting muscarinic antagonist (LAMA)	12 months
Leukotriene antagonists/modifiers (eg, Zileuton®)	3 months
Oral beta$_2$-agonist	3 months
Theophylline	7 days
Oral and IV corticosteroids[a]	8 weeks
Injectable systemic corticosteroids (eg, depot formulation, intra-articular, intraocular, intradermal, intramuscular)	12 months
Any marketed (eg, omalizumab, mepolizumab, benralizumab, reslizumab) or investigational biological therapy for asthma or any other condition	6 months or 5 half-lives, whichever is longer
Prophylactic antibiotics	8 weeks
Roflumilast	30 days
Any immunomodulators or immunosuppressives[b]	3 months or 5 half-lives, whichever is longer
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	30 days
Any drug with potential to significantly prolong the QT interval[c]	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccines	30 days
Non-selective non-ocular β-blocking agents (except carvedilol)	7 days
Monoamine oxidase inhibitors	14 days
Systemic treatment with strong CYP3A4-inhibitors (eg, ketoconazole, itraconazole, and ritonavir)	30 days
Systemic anticholinergics[d]	7 days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases (eg, Chinese complementary and alternative bronchodilatory medicines)	10 days

a. Use of systemic corticosteroids for any other reason except for the acute treatment of a severe asthma exacerbation is prohibited for the duration of the study.
b. Topical administration of immunosuppressive medication maybe allowed at the discretion of the Investigator after discussion with the Study Physician.
c. Participants who are on medications that have the potential to prolong the QTc interval may be enrolled provided the dose has remained stable for at least 3 months prior to Visit 1, the participant meets all of the ECG inclusion criteria and none of the ECG exclusion criteria, and if, in the opinion of the Investigator, there are not safety concerns for the participant to participate in the study.
d. If systemic anticholinergics are used for the treatment of irritable bowel syndrome or overactive bladder and the treatment has been constant for at least 1 month, they are allowed.

Source: Vathos Clinical Study Protocol, Table 7, page 46
Abbreviations: CYP, cytochrome P450; ECG, electrocardiogram; IV, intravenous; QTc, corrected QT

Table 56. Prohibited Asthma and Allergy Medications and Required Washout Period Prior to Visit 2, Lithos and Vathos

Medication	Minimum Washout Period Prior to Visit 2
ICS other than sponsor-provided[a]	7 days
ICS/LABA other than sponsor-provided[a]	7 days
Cromoglycate[b]	7 days
Nedocromil[b]	7 days
Ketotifen[b]	7 days
Short-acting muscarinic antagonists and/or short-acting beta$_2$-agonists alone, loose, or fixed combination other than sponsor-provided albuterol	7 days

a. Administration as fixed or loose combinations
b. Cromoglycate, nedocromil, and ketotifen eye drops are allowed for allergic conjunctivitis; no washout period

Source: Lithos Clinical Study Protocol Table 9 (page 54) and Vathos Clinical Study Protocol Table 8 (page 47)
Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist

12.4. References

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