NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	214070
Priority or Standard	Standard
Submit Date(s)	March 10, 2022
Received Date(s)	March 10, 2022
PDUFA Goal Date	January 10, 2023
Division/Office	Pulmonology, Allergy, and Critical Care (DPACC)/Immunology and Inflammation (OII)
Review Completion Date	January 9, 2023
Established/Proper Name	Albuterol sulfate/budesonide
(Proposed) Trade Name	AIRSUPRA
Pharmacologic Class	Short-acting beta$_2$-adrenergic agonist (SABA)/ (b) (4)
Applicant	Bond Avillion 2 Development LP
Dosage form	Metered dose inhaler (MDI)
Applicant proposed Dosing Regimen	Albuterol 180 µg and budesonide 160 µg (administered as 2 inhalations of albuterol/budesonide 90 µg/80 µg) as needed by oral inhalation. Do not take more than 6 doses (12 inhalations) in a 24-hour period.
Applicant Proposed Indication(s)/Population(s)	For the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	195967001 l Asthma (disorder)
Recommendation on Regulatory Action	Approval for ≥18 years of age (b) (4)
Recommended Indication(s)/Population(s) (if applicable)	For the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	195967001 l Asthma (disorder)
Recommended Dosing Regimen	AIRSUPRA 180 mcg/160 mcg (administered as 2 actuations of albuterol/budesonide 90 mcg/80 mcg) by oral inhalation as needed for asthma symptoms. Do not take more than 6 doses (12 inhalations) in a 24-hour period.

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

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Glossary

AC	advisory committee
ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
AZ	AstraZeneca
BDA	budesonide albuterol sulfate
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
ED	emergency department
eCTD	electronic common technical document
ePRO	electronic patient reported outcome
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	fixed dose combination
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GCP	good clinical practice
GINA	Global Initiative for Asthma
GRMP	good review management practice
ICH	International Conference on Harmonisation

IND	Investigational New Drug
IP	investigational product
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LABA	long acting beta-agonist
LAMA	long acting muscarinic-antagonist
LDP	listed drug product
LTRA	leukotriene receptor antagonist
MedDRA	Medical Dictionary for Regulatory Activities
MCID	minimally clinically important difference
MDI	metered dose inhaler
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OCS	oral corticosteroids
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAQLA	Pediatric Asthma Quality of Life Questionnaire
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PEF	peak expiratory flow
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PN	predicted normal
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRN	as needed
PRO	patient reported outcome
PSUR	Periodic Safety Update Report
QID	four times daily
REMS	risk evaluation and mitigation strategy
SABA	short-acting beta-agonist
SAE	serious adverse event
SAP	statistical analysis plan
SCS	systemic corticosteroids

SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

The Applicant, Bond Avillion 2 Development LP, in conjunction with AstraZeneca (AZ), submitted a 505(b)(2) NDA for a fixed dose combination (FDC) pressurized metered dose inhaler (MDI) for an oral inhalation aerosol containing an inhaled corticosteroid (ICS), budesonide, and a short-acting beta$_2$-adrenergic agonist (SABA), albuterol sulfate, herein referred to as BDA. The proposed indication was, "for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older." The Listed Drug Products (LDPs) for BDA include Pulmicort Flexhaler and Pulmicort Respules for budesonide and Proventil HFA for albuterol. Pulmicort Flexhaler has been approved since 2006 for the "maintenance treatment of asthma as prophylactic therapy" in patients down to 6 years of age, while Pulmicort Respules have been approved for the same indication since 2000 for patients 12 months to 8 years old. Albuterol has been approved since 1981 for the "treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm" (EIB) in patients down to 4 years old.

There are several unique features about this novel FDC product. BDA would be the first ICS/SABA combination product approved in the United States. Although albuterol is approved for the treatment and prevention of bronchospasm, the proposed indication and use to reduce the risk of exacerbations is novel. The rationale for BDA is to provide rapid symptom relief through bronchodilation via the SABA and to treat inflammation with the ICS in order to reduce the severity of exacerbations. FDA approval of an ICS-containing product as a reliever treatment for asthma (rather than as controller) would also be new.

The Applicant developed two doses for marketing: budesonide 160µg /albuterol sulfate 180µg, delivered as 2 actuations of 80µg/90µg (herein referred to as BDA 160/180) for patients ≥12 years old, and budesonide 80µg /albuterol sulfate 180µg, delivered as 2 actuations of 40µg/90µg (herein referred to as BDA 80/180) for patients ≥4 to <12 years old. As described below, since the development program supported substantial evidence of effectiveness only for subjects ≥18 years of age, only BDA 160/180 will be marketed.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is:

- **Approval** for BDA MDI 160/180, administered as 2 inhalations as needed for asthma symptoms, not to exceed 6 doses in 24 hours, for the "as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older."

- (b) (4)

Since there is no regulatory precedent for establishing substantial evidence of effectiveness (SEE) for an ICS/SABA product with PRN administration, the Applicant and FDA discussed a development program that could establish the efficacy and safety of BDA for the proposed indication and satisfy the 'combination rule' (*21CFR300.50a*). The Agency agreed that a large trial comparing BDA to AS, administered PRN, with asthma exacerbations as the primary endpoint, would provide the primary data to support the efficacy of BDA. This design would provide information on the contribution of the ICS and also provide data to evaluate the effect on asthma exacerbations. Since AS is already approved as a reliever therapy, the benefit of the ICS component was the greater concern; therefore, an ICS comparator arm was not necessary. The Agency agreed that a second factorial design trial with BDA administered scheduled would provide additional efficacy and safety data and data to satisfy the combination rule.

To support this application, the Applicant conducted three efficacy and safety trials, as well as six clinical pharmacology studies to assess pharmacokinetic (PK) interaction, bridging, and dose-ranging. The three efficacy trials were MANDALA (AV003), DENALI (AV004), and TYREE (AV005), with MANDALA and DENALI designed as adequate and well-controlled trials to provide the basis for demonstration of SEE.

- MANDALA was an event-driven, randomized, double-blind, comparator-controlled trial in subjects with moderate to severe asthma ≥4 years of age, in which the investigative product (IP) was administered as needed (PRN), with a primary endpoint of time to first severe asthma exacerbation. MANADLA was the primary trial used to support SEE given its exacerbation primary endpoint, large size, and design that reflected anticipated real-world use of BDA. Data from MANDALA supports the novel indication of "to reduce the risk of exacerbtions [of asthma]" and demonstrates the contribution of the ICS component to this benefit.
- DENALI was a 12-week, randomized, double-blind, placebo- and comparator-controlled trial that studied the effects of BDA 160/180 and BDA 80/180, compared to budesonide (BD) alone, albuterol (AS) alone, and placebo, on FEV1 when administered four times daily (QID) in patients with mild asthma. DENALI provided data to satisfy the 'combination rule,' information on the onset of action and duration of bronchodilation of BDA compared to the monocomponents, and safety data when used at a higher frequency in a milder population. The data from DENALI supports the "treatment and prevention of bronchoconstriction" indication.
- TYREE was a trial to evaluate the effects of BDA on exercise-induced bronchospasm; however, since the contribution of the ICS component of BDA to efficacy was not evaluated, as recommended by the Agency during the August 23, 2018 end-of-phase 2 meeting, the

trial does not contribute significant clinically meaningful data to support the proposed indication for BDA and is not used to demonstrate SEE.

As described in detail in Section 8.2.1, results from MANDALA demonstrated a significant delay in time to first severe acute exacerbation in the overall population. In subjects ≥18, MANDALA met the FDA-agreed upon primary endpoint of time to first severe exacerbation, as well as demonstrating benefit in the key secondary endpoints of reducing severe asthma exacerbations and reducing systemic corticosteroid use. As described in detail in Section 8.2.2, results from DENALI also met the agreed upon primary efficacy endpoints of change from baseline in FEV1 $AUC_{0\text{-}6hours}$ over 12 weeks and change from baseline in trough FEV1 at week 12, and satisfied the combination rule. Based on the results of the adequate and well-controlled MANDALA and DENALI trials, SEE has been established for the population ≥18 years of age.

As specified in the Agreed initial Pediatric Study Plan (iPSP), the Applicant included children down to 4 years of age in the BDA development program. Of the 3,132 subject randomized in MANDALA, 100 subjects were ≥12 to <18 years of age and 83 subjects were ≥4 to <12 years of age; subjects <12 years of age were not randomized to high dose BDA treatment. In DENALI, 25 adolescents 12 to <18 years of age were enrolled and only 10 children 4 to <12 years of age were enrolled. To evaluate efficacy in children in the MANDALA trial, we performed a *post hoc* analysis of age cohort subgroups, described in detail in Sections 8.2.1 and Appendix 14.4 and results shown in Figure 10. Results from the subgroup analyses show that efficacy for the proposed doses in the two pediatric subgroups (≥12 to <18 years and ≥4 to <12 years) is uncertain. The confidence intervals are wide and the upper confidence limits for the hazard ratios exceed 1 and are skewed towards benefit of AS (HR >1). To address this uncertainty, we conducted post-hoc Bayesian analyses, presented in Sections 8.2.1 and Appendix 14.4. The conclusions of these analyses were that borrowing of approximately 95% of adult data would be necessary to achieve meaningful results to demonstrate the benefit of BDA among pediatric subjects. The high degree of Bayesian borrowing required to achieve meaningful results in the pediatric subgroups requires that near complete extrapolation would be necessary to demonstrate efficacy.

Pediatric extrapolation can extend what is known about the adult population (e.g., efficacy) to pediatric subjects based upon an assessment of the relevant similarities of disease and response to therapy between the two populations. Extrapolation is a tool that can reduce the pediatric data requirements for pediatric development programs. Pediatric extrapolation should be based on careful clinical and pharmacological evaluations to determine how similar children are to adults in the course of disease and in response to treatment. Such evaluations should include the quality of available data, as well as important knowledge gaps and uncertainties. Figure 14, from the recent FDA Draft Guidance for Industry: E11A Pediatric Extrapolation (FDA 2022), provides a visualization of key considerations for pediatric extrapolation.

A high degree of extrapolation (e.g. >95%) should be supported by high confidence not only in the similarity of disease and its response to treatment across age groups, but also in the quality of supportive evidence. After reviewing the available literature relevant to the novel indication, focused on increasing ICS doses in children to reduce the risk of severe exacerbations, and discussions at the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting held on November 8, 2022, we concluded the quality and certaintity of the available evidence did not support such a high degree of extrapolation for pediatric patients for this novel combination product and novel indication. As a result, SEE has not been adequately demonstrated for children 4 to <18 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

BDA (tradename AIRSUPRA) is the first oral inhalation FDC of an ICS and SABA developed for the treatment and prevention of bronchoconstriction and to reduce the risk of severe asthma exacerbations. The recommendation is *approval* for adults ≥18 years of age (b) (4) , based on the efficacy and safety data submitted in support of this 505(b)(2) NDA.

Asthma is a serious and common disease, characterized by airway inflammation, airway hyperresponsiveness, and bronchoconstriction. Asthma is a heterogenous disease with a spectrum of phenotypes and range of severities; however, all patients with asthma are vulnerable to severe acute exacerbations. With a current global estimate of 235 million people affected by asthma and a US prevalence of 8% among both children and adults, acute asthma exacerbations account for a large portion of healthcare utilization. Many exacerbations may be managed with PRN SABA or systemic corticosteroids (SCS)—which may, themselves, be associated with morbidity—but severe exacerbations may require hospitalization, higher or prolonged doses of SCS, and may result in death. The rationale for BDA development was to provide rapid symptom relief through bronchodilation via the SABA and to treat inflammation with the ICS in order to reduce the risk of and severity of exacerbations. Although there are many marketed controller (maintenance) treatments for asthma, there is only one class of inhaled medication currently approved for reliever treatment in the US (SABA). There are no reliever treatments that carry the indication to prevent severe acute exacerbations. Furthermore, recent national and international guideline revisions (The National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Panel 4 (EPR-4) Working Group 2020; GINA Science Committee 2022) recommend the use of a concomitant PRN ICS with SABA for some patients as the preferred alternative to 'SMART' (single maintenance and reliever therapy with ICS/formoterol), which is currently not approved in the US for such an indication.

The primary efficacy analysis for MANDALA demonstrated a statistically significant improvement for both BDA 160/180 and BDA 80/180, compared to AS, on the primary endpoint of time to first severe exacerbation in adults (≥18 years of age) and in all subjects ≥12 years of age. Statistically significant improvements in key secondary endpoints, including annualized rate of severe asthma exacerbations and total SCS exposure, further support efficacy. However, in subgroup analyses of both pediatric cohorts (12 to <18 years and 4 to <12 years), point estimates for the hazard ratios using the proposed doses (160/180 for adolescents and 80/180 for children) favored AS vs BDA. Very few exacerbation events were observed in both pediatric subpopulations, leading to wide and skewed confidence intervals that lend a high degree of uncertainty that limits interpretation. This degree of uncertainty was consistent across all key secondary endpoints, including annualized rate of severe exacerbations and total annualized SCS dose, in both pediatric cohorts. Results from DENALI, which enrolled even fewer pediatric subjects and assessed FEV1, did not provide efficacy data beyond what is already known about the mono-components in this age group.

There was an adequate safety database of adults subjects to support review, in addition to the well-characterized safety profiles of the mono-components. No new safety signals were identified based on the submitted data. Given the novel use of an ICS as a reliever treatment and concerns about potential additive effects of using BDA on top of controller ICS, adverse events related to ICS class effects were a focus of review. Based on these data, there were no unexpected safety findings. Another focus of the safety review was pediatric subjects, who are more vulnerable to the known and potential toxicities of ICS. No new or unique safety signals were identified in this population, but the scope of the pediatric data—sample size, duration of exposure, and frequency of dosing—was limited. The risks of BDA for adults can be adequately addressed through labeling and routine post-marketing pharmacovigilance.

Ultimately, the development program demonstrated substantial evidence of effectiveness in adults, but was insufficient to demonstrate conclusive evidence of benefit in pediatric subjects. The Division and Applicant attempted to address the inconclusive results in pediatric subjects through *post-hoc* Bayesian analyses, which demonstrated the requirement to borrow approximately 95% of events from adults to achieve meaningful results. Thus, a central focus of the review of pediatric data was whether almost complete extrapolation of adult efficacy data to pediatric subjects was appropriate in this context. For subjects 4 to <12 years of age, there is too much residual uncertainty regarding disease similarity and response to treatment for the novel indication to support such a high degree of extrapolation. For subjects ≥12 to <18 years of age, there is likely greater disease similarity with adults; however, outstanding uncertainties remain regarding expected response to treatment, particularly given this is a novel indication for reduction of the risk of severe exacerbations. For this age group, the available evidence do not meet the standards outlined in the recent FDA Guidance, *E11A Pediatric Extrapolation*, to support such a high degree of extrapolation (FDA 2022).

Although no new or unexpected safety signals were identified in pediatric subjects, the scope of the safety database was limited in size and duration of observed exposure. The long-term potential and known toxicities of ICS are most relevant to pediatric subjects; therefore, without clear evidence of the benefit of the ICS component of BDA for PRN reliever treatment in pediatric patients, the benefit-risk assessment did not favor BDA for subjects <18 years of age.

Following a comprehensive review of benefit risk assessment for the pediatric and adults subgroups, and incorporating feedback from the Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting on November 8, 2022 (refer to Section 9), the review team's recommendation is to *approve* BDA for subjects ≥18 years of age for the indication, "as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma", (b) (4).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is a chronic, heterogenous, and potentially life-threatening disease, of which airway inflammation is a central component. • Episodic increases of airway inflammation in response to triggers, known as acute exacerbations, can occur despite appropriate controller therapy. Most asthma exacerbations may be managed in the outpatient setting with PRN SABA or with SCS, which may themselves be associated with morbidity and effects on quality of life. • Severe exacerbations may require hospitalization, higher or prolonged doses of SCS, and may result in death. All patients with asthma are vulnerable to severe exacerbations. • When appropriate, drug development programs and management guidelines (NAEPP, GINA) often group subjects ≥12 with adults. However, residual uncertaintities remain about disease differences and responses to treatment among adolescents, particularly the efficacy of ICS as reliever therapy. • Greater uncertaintities exist regarding disease similarity and response to treatment in subjects 4 to 11 years of age.	Most patients with asthma do not have severe disease, but all patients are vulnerable to severe exacerbations, which may be life-threatening. Residual uncertaintities remain regarding disease similarity and response to reliever tratment with ICS to prevent severe exacerbations between adult and pediatric patients.
Current Treatment Options	• There are many therapies approved for the controller (maintenance) treatment of asthma, but there is only one class of inhaled therapy (SABA) approved in the US as reliever treatment. • Although management guidelines recommend ICS/formoterol as a first-line reliever treatment for many paitents with asthma, it is not currently approved for this indication in the US.	There is a need for safe and effective therapies to prevent severe acute exacerbations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There are no approved reliever treatments that carry the indication to prevent severe acute exacerbations. • Historically, approval in adolescents has often been supported by concurrent enrollment of adolescents in adults trials and demonstration of efficacy and safety results consistent with those in adults, not necessarily with statistical significance. • The basis for approvals in children younger than 12 has usually been dedicated pediatric efficacy trials, and extrapolation has supported approval in a few instances. • This model for approval of inhaled products in pediatric subjects has been leveraged when approving a drug for an established indication for the drug class or drug itself, rather than a novel intended use.	
Benefit (adults)	• In MANADLA, in subjects ≥18, BDA 160/180 compared to AS resulted in a statistically significant difference in time to first severe asthma exacerbation. • In subjects ≥18, BDA 160/180 demonstrated a significant difference, compared to AS, on key secondary endpoints, including: annualized rate of severe asthma exacerbations and total annualized dose of systemic corticosteroids. BDA 160/180 compared to AS resulted in a nominally significant benefit on ACQ-5, a validated PRO measuring asthma symptom control. • Evidence of benefit, as measured by the onset of action and duration of bronchodilation, as well as fulfillment of the combination rule, comes from DENALI.	In subjects ≥18 (and in subjects ≥12, combining adolescents and adults), both pivotal trials met the FDA-agreed upon primary endpoints. In addition, BDA 160/180 demonstrated benefit in the key secondary endpoints of reducing severe asthma exacerbation rate and reducing systemic corticosteroid use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In subjects ≥18, BDA 160/180 demonstrated a statistically significant benefit on both FEV1 AUC and trough FEV1 when compared to BD alone, AS alone, and placebo.	
Benefit (12 – <18 year olds)	• In a prespecified, but not statistically powered, non-alpha controlled sub-group analysis of subjects ≥12 to <18, BDA 160/180 (high dose) did not demonstrate benefit in preventing severe acute exacerbations compared to AS (HR 1.44, CI 0.54,3.87). In *post hoc* subgroup analyses of key secondary endpoints, BDA 160/180 did not demonstrate benefit compared to AS. Study results for BDA 160/180 in subjects ≥12 to <18 are inconclusive and demonstrate a large degree of uncertainty across endpoints. The total number of exacerbation events among subjects ≥12 to <18 and the differences in event rates between arms were too small to support clear evidence of effectiveness. • In both a prespecified, but not statistically powered, non-alpha controlled sub-group analysis of the primary endpoint and in *post hoc* subgroup analyses of some secondary endpoints in subjects ≥12 to <18, BDA 80/180 (low dose), compared to AS, demonstrated numeric trends that favored BDA 80/180. These trends raise additiional uncertainty, given the proposed dose for ≥12 to <18 years is BDA 160/180. • In DENALI, in exploratory sub-group analyses of FEV1, trends suggested benefit of BDA 160/180 compared to AS for this age group, but this information does not contribute beyond what is already known about the monocomponents of BDA.	Given the limitations and uncertainty with the available data, almost complete extrapolation from adult data (>95%) would be necessary to support evidence of benefit in ≥12 to <18 years. The available evidence, including the limited data, uncertaintity around dose, inconclusive nature of the relevant literature, and discussion at PADAC do not support almost complete extrapolation from adults to adolescents for this new combination drug and novel indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Discussion at the November 8, 2022 Pulmonary-Allergy Drugs Advisory Committee did not support near complete extrapolation of adult data to this age group; the committee vote was split on the favorability of the benefit-risk assessment (8 Yes, 9 No).	
Benefit (4 – <12 year olds)	• In a prespecified, but not statistically powered, non-alpha controlled sub-group analysis of subjects ≥4 to <12, BDA 80/180 did not demonstrate benefit in preventing severe acute exacerbations compared to AS (HR 1.09, CI 0.46,2.57). • In *post hoc* subgroup analyses of key secondary endpoints, BDA 80/180 did not demonstrate benefit compared to AS. • Study results for BDA in subjects ≥4 to <12 are inconclusive and do not support evidence of benefit across endpoints. Similarly, the total number of exacerbation events among subjects ≥4 to <12 and the differences in event rates between arms were too small to support clear evidence of effectiveness. • Discussion at the November 8, 2022 Pulmonary-Allergy Drugs Advisory Committee did not support extrapolation of adult data to this age group; the committee voted against a favorable benefit-risk assessment (1 Yes, 16 No).	Given the limitations and uncertainty with the available data, almost complete extrapolation from adult data (>95%) would be necessary to support evidence of benefit. The available evidence, including the limited data, inconsistent literature, discussion at PADAC, and significant uncertainty regarding similarity of disease and response to treatment between children and adults do not support such a high degree of extrapolation of adult data to children for this new combination drug and novel indication.
Risk and Risk Management	• The program for BDA demonstrated a safety profile consistent with the known risks of both monocomponents. No new safety signals were identified.	The program did not identify new or unexpected safety signals For adults, routine pharmacovigilance and accurate labeling will constitute appropriate risk management strategies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The incidences of all AEs and SAEs in subjects ≥12 to <18 were low. The safety profile in this age group was both similar to that in adults and consistent with the known risks of both monocomponents. • The incidences of all AEs and SAEs in subjects ≥4 to <12 were low. The safety profile in this age group was both similar to that in adults and consistent with the known risks of both monocomponents. • The scope of the safety database for pediatric subjects was small, and the program was not designed to capture long term effects.	For pediatric subjects, although no new or concerning signals were identified, the data was too limited in scope to provide definitive conclusions. Furthermore, the program was not designed to capture some known or potential risks associated with ICS (e.g., irreversible growth restriction, longer-term effects on risk for infection). Finally, off-label use (e.g., for the treatment of exercise-induced bronchoconstriction) and thereby unecesssary exposure to ICS, is most likely to occur among pediatric patients, in whom excess ICS poses the greatest risk of harm.

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)	Section 8.2.1
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.2.1
		☐	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)		
	X	Other: (Please specify):		E-diary, Section 8
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	X	Input informed from participation in meetings with patient stakeholders		Advisory Committee Meeting, Nov 8, 2022, Section 9
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Asthma is a common and potentially serious chronic respiratory disease characterized by variable symptoms and airway inflammation. The management of patients with asthma is based on a stepwise treatment approach that entails a continuous cycle of assessment, treatment, and review of the patient's response to medication. Asthma is a potentially life-threatening disease that may be associated with significant morbidity and health care utilization. Exacerbations account for a large portion of the physical and financial burden of asthma. Patients of all ages with all severities of asthma are vulnerable to severe exacerbations and rely on reliever medications to manage symptoms.

Despite advances in the treatment of asthma, it remains a serious global health problem. While both adult and pediatric disease share chronic airway inflammation and hyper-responsiveness, there are significant differences in the pathogenesis and natural history that remain areas of active investigation. A variety of immunologic, anatomical, and environmental factors likely account for the differences between pediatric and adult disease. The relative difficulty of directly studying younger pediatric patients and fully assessing lung function contribute to this knowledge gap.

2.2. Analysis of Current Treatment Options

The diagnosis and management of asthma are outlined by national and international guidelines, particularly GINA and NAEPP (The National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Panel 4 (EPR-4) Working Group 2020). Two broad categories comprise the foundation of asthma treatment: controller medications and reliever medications. Historically, patients with mild or intermittent asthma were started on PRN SABA as reliever therapy, with escalation of controller therapy in a stepwise fashion to an ICS for persistent symptoms, followed by increasing doses of ICS with or without additional controllers, such as long-acting beta-agonists (LABA) or long-acting antimuscarinic antagonists (LAMA). Table 1 summarizes many of the controller and reliever medications currently approved and marketed in the US.

Table 1. Summary of Approved Asthma Medications

Class	Generic	Brand Name
Inhaled corticosteroids	Beclomethasone Dipropionate Budesonide Ciclesonide Fluticasone furoate Fluticasone propionate Mometasone	Qvar Pulmicort Alvesco Arnuity Ellipta Flovent Asmanex

Combination inhaled corticosteroids / long-acting bronchodilator(s)	Budesonide/formoterol Fluticasone/salmeterol Mometasone/formoterol Fluticasone/vilanterol Fluticasone/vilanterol/umeclidinium	Symbicort Advair Dulera Breo Ellipta Trelegy Ellipta
Anticholinergics	Tiotropium	Spiriva
Leukotriene Modifiers	Montelukast Zafirlukast Zileuton	Singulair Accolate Zyflo
Biologics	Omalizumab (anti-IgE) Mepolizumab (anti-Il5) Reslizumab (anti-Il5) Benralizumab (anti-Il5R) Dupilumab (anti-Il4R) Tezepelumab (anti-TSLP)	Xolair Nucala Cinqair Fasenra Dupixent Tezspire
Xanthines	Theophylline	Multiple
Short-acting bronchodilators (beta2-agonists)	Albuterol sulfate Levalbuterol	ProAir Proventil Ventolin Vospire ER Xopenex

As noted in Section 1, in recent years, the paradigm of asthma treatment has changed. Guidelines now recommend the initiation of SMART with an ICS/LABA relatively early in disease severity. In the absence of SMART—since no ICS/LABA is approved for reliever treatment in the US—GINA guidelines recommend use of an ICS in combination with SABA as the preferred alternative rescue treatment in patients as young as 6 years of age with mild disease (Steps 1 and 2 in Figure 1 and Figure 2). NAEPP guidelines similarly recommend an as needed ICS with SABA for patients ≥12 years of age with mild disease (Step 2 in Figure 3). Of note, MANDALA enrolled subjects approximately correlating with Steps 2-5 (Figure 1 and Figure 2) in terms of severity, and DENALI enrolled subjects approximately correlating with Steps 1-3 (Figure 3).

Figure 1. GINA 2022 Asthma Management Guidelines, Children 6-11 Years

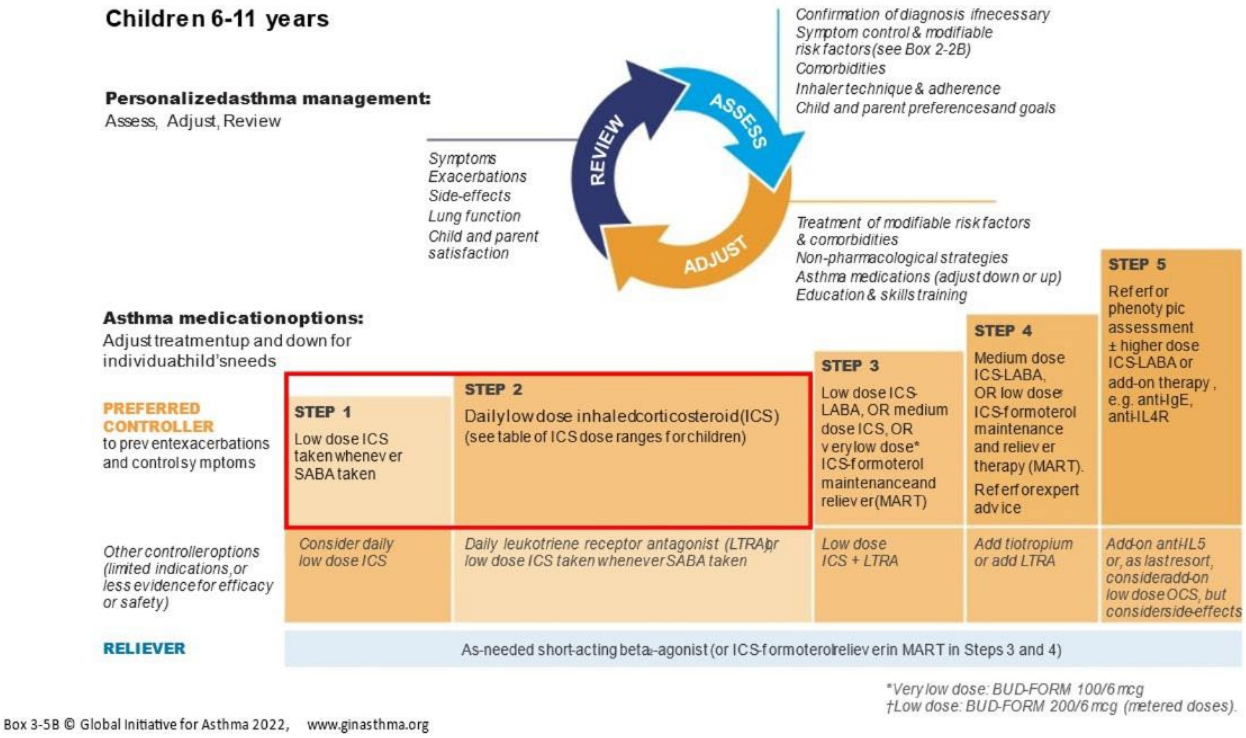


Figure 2. GINA Asthma Management Guidelines 2022 Adults and Adolescents ≥ 12 Years

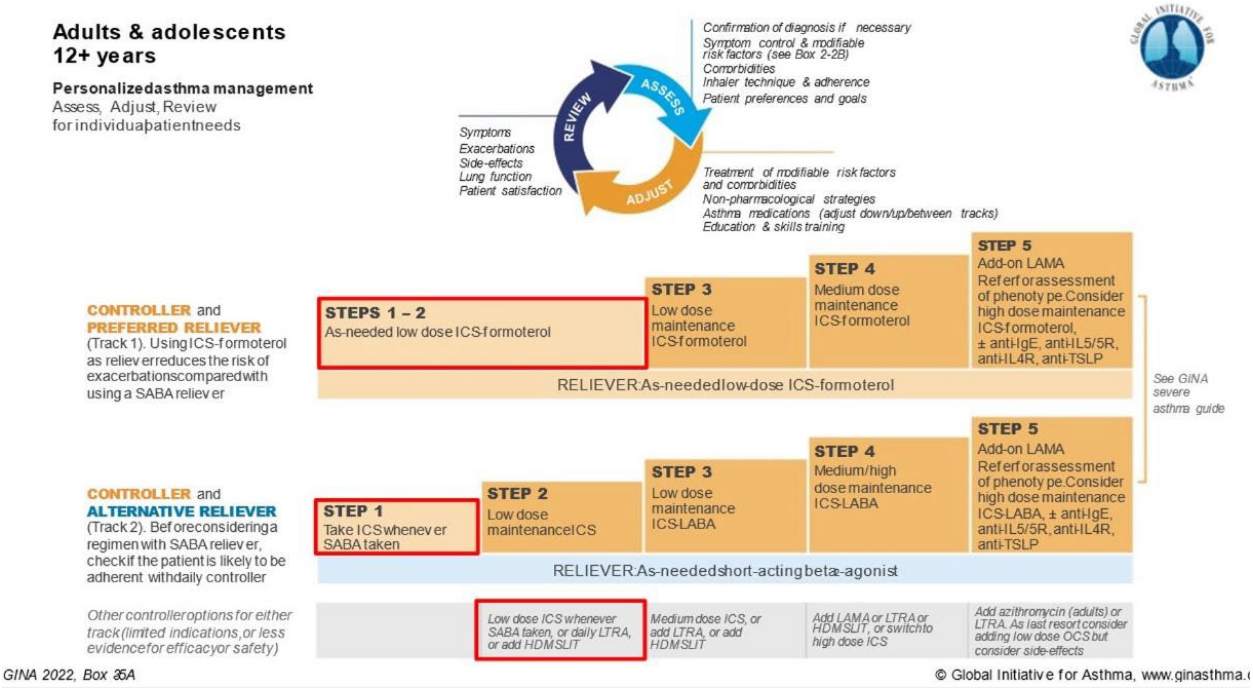


Figure 3. NAEPP Asthma Management Guidelines 2020 Ages ≥ 12 Years

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 ■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA ▲	Daily and PRN combination low-dose ICS-formoterol ▲	Daily and PRN combination medium-dose ICS-formoterol ▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA ▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA, ▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA ▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy ▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

Source: (The National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Panel 4 (EPR-4) Working Group 2020).

Approval of BDA would represent a novel indication and intended use for ICS in asthma; however, as illustrated by the above guidelines, the concept of symptom-triggered use of an ICS to abort or reduce the risk for progression of asthma exacerbations is not new. Several trials have previously evaluated the use of PRN ICS, with or without concomitant SABA or LABA, to prevent exacerbations. We provide a brief summary here, since understanding this literature provides important context, particularly when considering the issue of extrapolation of efficacy for pediatric approval.

The literature on escalating doses of ICS to reduce exacerbations is extensive, but remains inconclusive. Some early observational studies suggested that increasing ICS amongst pediatric patients was beneficial (Wilson and Silverman 1990; Connett and Lenney 1993; Volovitz et al. 2001), and more recent studies have suggested benefit in adults (Israel et al. 2022). Several trials, however, have failed to demonstrate reduction in exacerbations or improvement of asthma control in pediatric patients (Garrett et al. 1998; Harrison et al. 2004; Bisgaard et al. 2006; Guilbert et al. 2006; Lemanske et al. 2010; Yousef et al. 2012; Kew et al. 2016; O'Byrne et al. 2018; Sobieraj et al. 2018; Beasley et al. 2019; O'Byrne et al. 2021) with as much as a quintupling of ICS dose. Some of these trials even demonstrated a worsening in asthma control

with higher doses of ICS (Jackson et al. 2018), and irreversible growth restriction among pediatric patients, while small in magnitude, was consistent (Lemanske et al. 2010; Cates and Karner 2013). In spite of the uncertainties regarding escalating ICS alone, results from the published literature ((Bisgaard et al. 2006; O'Byrne et al. 2018; Sobieraj et al. 2018; Beasley et al. 2019; O'Byrne et al. 2021) have more uniformly demonstrated that PRN BD, administered concomitantly with formoterol, reduced exacerbation rates among adult and pediatric asthmatics. These data have informed recent updates to asthma treatment guidelines to include SMART recommendations, although no ICS/LABA product is currently FDA-approved for a PRN indication or for use as SMART. Similarly, there is literature that supports that ICS plus SABA reduces exacerbation rates in patients ≥12 (Boushey et al. 2005; Papi et al. 2007; Calhoun et al. 2012) and 4-to-11-years (Martinez et al. 2011). While the available literature may support some degree of efficacy extrapolation of adult data to children, near full extrapolation is not supported for use of ICS as a reliever to reduce the risk of exacerbations.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The individual components of BDA, budesonide and albuterol, have been approved and marketed under various tradenames and formulations since 1997 and 1981, respectively. The LDPs for BDA development were Pulmicort Flexhaler and Pulmicort Respules for budesonide, approved in 2007 and 2000, respectively, and Proventil HFA for albuterol, approved in 1996. A summary of the regulatory activity for BDA is provided in Table 2.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2. Key Regulatory History Related to Submission

Date	Interaction	Highlights
November 19, 2015	Type B PIND Meeting	• Agency recommended exacerbation trial to demonstrate benefit. • General agreement on factorial design trial for combination rule. • The Division suggested the sponsor consider including the full pediatric age range in its development program, rather than separate adult and pediatric programs.
August 23, 2018	Type B End-of-Phase 2 Meeting	• Applicant needs to address concern regarding safety of additive effects of ICS (BDA + background ICS). • Applicant proposed including adults, adolescents, and children down to (b) (4) years of age in the exacerbation study. • Agency encouraged enrollment of subjects down to 4 years of age in both exacerbation and lung function study since AS and BD are approved in this age group. • Agency advised to support EIB indication, study should be

		designed to demonstrate contribution of ICS to SABA since SABA effects in EIB well-established.
December 15, 2020	iPSP Agreement	• Applicant planned to enroll enough subjects ≥4 to <18 years to allow meaningful interpretation of data (projected sample size approximately 180). • No plans for data to support extrapolation given enrollment down to 4 years of age. • Waiver for <4 years based on BDA not meaningful benefit vs existing therapy.
May 26, 2021	Type C Meeting	• Consensus not to pool efficacy or safety data, given different study designs and populations.
December 20, 2021	Type B Pre-NDA Meeting	• (b) (4). TYREE did not demonstrate contribution of ICS. • Advisory Committee anticipated. • Agency recommended a treatment policy estimand in a supplementary analysis. • Agency recommended a Bayesian approach to support efficacy in pediatric subjects.

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

4.1. Office of Scientific Investigations (OSI)

Three clinical study sites were inspected by the Office of Scientific Investigations (OSI) in support of NDA 214070, covering Protocols AV003 (MANDALA) and AV004 (DENALI). The clinical sites were selected for GCP inspections using a risk-based approach that considered numbers of enrolled subjects, treatment effect, and prior inspectional history. The investigations concluded that the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of this NDA.

4.2. Product Quality

The Office of Pharmaceutical Quality reviewed drug substance, drug product, labeling, manufacturing, and microbiology and recommended that the product quality is adequate for approval. For further details, refer to the Office of Product Quality Integrated Quality Assessment Template, dated November 23, 2022.

4.3. Clinical Microbiology

A Clinical Microbiology evaluation was performed by the Office of Pharmaceutical Quality and is documented in the Office of Product Quality Integrated Quality Assessment Template, dated November 23, 2022. No deficiencies were identified and the product was determined to be adequate for approval.

4.4. Devices and Companion Diagnostic Issues

The Office of Product Quality evaluated the MDI device in their drug product review. The device constituent part of the combination product consists of an (b) (4) aluminum (b) (4) canister (b) (4) with a metering valve which is inserted into an actuator. The device constituent part also includes a dose indicator. The device is used for other approved products, (b) (4) . No deficiencies were identified and the device was determined to be adequate for approval. For further details, refer to the Office of Product Quality Integrated Quality Assessment Template, dated November 23, 2022.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant is relying upon the FDA's previous findings of safety and effectiveness from PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol for use of albuterol. The Applicant has obtained right of reference for PULMICORT RESPULES® (budesonide), Inhalation Suspension (AstraZeneca), PULMICORT FLEXHALER® (budesonide), Inhalation Powder, BEVESPI AEROSPHERE® (glycopyrrolate and formoterol fumarate), Inhalation Aerosol (Astra Zeneca), BREZTRI™ AEROSPHERE® (budesonide, glycopyrrolate, formoterol fumarate), Inhalation Aerosol (AstraZeneca), and HFA-134a safety data ((b) (4)) to support use of budesonide, the porous particle excipient, and the propellant HFA-134a.

No new nonclinical pharmacology or toxicology studies were requested or submitted. The Applicant submitted a study of extractables with the closed container system, leachable studies under accelerated and long-term storage conditions, and a foreign particulate matters study. See Nonclinical Review by Dr. Jessica A Bonzo dated November 28, 2022 in DARRTS under NDA 214070 for a detailed review of extractables and leachables.

5.2. Referenced NDAs, BLAs, DMFs

Drug Master Files

- DMF (b) (4)
- DMF
- DMF
- DMF
- DMF

New Drug Applications

- NDA 020929 PULMICORT RESPULES® (budesonide), Inhalation Suspension (AstraZeneca)- Letter of Authorization
- NDA 021949 PULMICORT FLEXHALER® (budesonide), Inhalation Powder (AstraZeneca)- Letter of Authorization
- NDA 208294 BEVESPI AEROSPHERE® (glycopyrrolate and formoterol fumarate), Inhalation Aerosol (Astra Zeneca)- Letter of Authorization

- NDA 212122 BREZTRI™ AEROSPHERE® (budesonide, glycopyrrolate, formoterol fumarate), Inhalation Aerosol (AstraZeneca)- Letter of Authorization
- NDA 020503 PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol, (Kindeva Drug Delivery)-No Right of Reference, relying upon FDA's previous finding and/or published literature to support labeling, nonclinical pharmacology and toxicology, general safety, and efficacy

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted NDA 214070 on March 10, 2022, under 505(b)(2) regulatory pathway, seeking the marketing approval for budesonide/albuterol sulfate (BDA) metered dose inhaler (MDI), a fixed-dose combination (FDC) drug-device product for oral inhalation, for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older (Table 3). The proposed BDA MDI drug product is a pressurized metered dose inhaler that delivers a combination of BD (40 µg or 80 µg) and AS 90 µg (albuterol base) per inhalation. The LDP for BDA include Pulmicort Flexhaler (NDA 021949) and Pulmicort Respules (NDA 020929) for budesonide (BD), and Proventil HFA (NDA 020503) for albuterol sulfate (AS).

The NDA 214070 clinical pharmacology program consists of six clinical studies, including three phase 1 studies and three phase 2 studies, and three phase 3 efficacy and safety trials (Table 4). In addition, one population PK analysis report was submitted to simulate BD systemic exposure following various BDA MDI dosing scenarios.

Table 3. Summary of the Proposed BDA MDI and Listed Drug Product Products

Drug Product	Indication	Age group	Dosing Regimen
Pulmicort Flexhaler (budesonide) inhalation powder	Maintenance treatment of asthma as prophylactic therapy	≥6 years of age	• ≥18 years: 360 µg BID; max dose 720 µg BID • 6 to <18 years: 180 µg BID; max dose 360 µg BID
Pulmicort Respules (budesonide) inhalation suspension	Maintenance treatment of asthma and as prophylactic therapy	12 months to 8 years of age	• Dependent upon previous therapy, from 0.25 mg to 1 mg QD

Proventil HFA (albuterol sulfate) inhalation aerosol	Treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of EIB	≥4 years of age	• 180 µg AS Q4-6H PRN, or 15 to 30 min before exercise for EIB prevention
Proposed BDA MDI for oral inhalation	As-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations	≥4 years of age	• ≥12 years: 2 inhalations of BDA MDI 80/90µg (160/180 µg) as needed • 4-11 years: 2 inhalations of BDA MDI 40/90µg (80/180 µg) as needed • Do not take >6 doses (12 inhalations) in 24 hours

EIB, exercise-induced bronchoconstriction; HFA, hydrofluoroalkane; max, maximum; BID, twice daily; QD, daily; Q4-6H, every 4-6 hours

Table 4. Summary of Clinical Pharmacology Studies in NDA 214070

Study ID	Objectives	Study design	Study treatment
LOGAN	PK interaction between BD and AS	Phase 1, R, OL, SD, 3-way CO, in healthy subjects (n=91)	2 inhalations of BDA MDI (80/90 µg) 2 inhalations of BD MDI (80 µg) 2 inhalations of AS MDI (90 µg)
ELBRUS	BD PK comparison in adults	Phase 1, R, OL, SD, 2-way CO, in healthy subjects (n=67)	2 inhalations of BDA MDI (80/90 µg) 2 inhalations of Pulmicort Flexhaler (90 µg)
BLANC	BD PK comparison in children	Phase 1, R, OL, SD, 2-way CO, in children with asthma (4-8 years, n=12)	2 inhalations of BDA MDI (80/90 µg) Pulmicort Respules (1 mg)
ASPEN	AS PK comparison	Phase 2, R, cumulative-dose, OL, 2-period CO, in adults with asthma (n=46)	1+1+2+4+8 actuations of AS MDI (90 µg) 1+1+2+4+8 actuations of Proventil (90 µg)
PT008001	BD dose-ranging	Phase 2, R, DB, 4-period, 5-treatment, incomplete block, CO, in adults with mild to moderate asthma (n=147)	BD MDI 40, 80, 160, or 320 µg BID for 28 days
ANTORA	AS dose-ranging	Phase 2, R, DB, SD, PC, 5-period, 5-treatment, CO, in adults with mild to moderate asthma (n=147)	AS MDI 90, 180 µg Proventil 90, 180µg Placebo

R: randomized; OL: open-label; SD, single dose; CO: crossover; PC: placebo-controlled

The following are the major clinical pharmacology findings of the current review:

- Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg), BD MDI (2 inhalations of 80 µg) or AS MDI (2 inhalations of 90 µg) in healthy subjects, the systemic exposure (C_{max} and AUC) of both BD and AS are comparable when administered as BDA MDI

or as each of the monotherapies, suggesting a lack of PK interaction between BD and AS in the to-be-marketed BDA MDI drug product (Table 5).

- PK bridging was demonstrated between each of the components of BDA MDI, i.e., BD and AS, and the corresponding LDP:
  - Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg), Pulmicort Flexhaler (2 inhalations of 90 µg), or Pulmicort Respules (1 mg), BD systemic exposure (C_{max} and AUC) with BDA MDI is lower than that with Pulmicort Flexhaler and Pulmicort Respules, in adults and children (4 to 8 years of age), respectively (Table 6 and Table 7).
  - Following the cumulative dose (1+1+2+4+8 actuations, a total albuterol dose of 1440 µg) administration of AS MDI (90 µg) and Proventil (90 µg) in subjects with asthma, AS systemic exposure (C_{max} and AUC) with AS MDI is lower than that with Proventil (Table 8).
- Cross-study PK comparison indicated that, following the same single dose administration of BDA MDI 160/180 µg, the BD systemic exposure (C_{max} and AUC_{0-t}) in children (4 to 8 years of age) is about half the value of that in adults. Additional simulations mimicking the 'worst-case scenario' daily use (i.e., 12 inhalations of high dose BDA MDI (6 doses of BDA 160/180 µg) plus the maximum BD controller dose) showed that the total systemic exposure ($AUC_{0-24hours}$) of BD in adolescents and children aged 4 to 11 years remained lower than that in adults (Table 11).

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the clinical pharmacology data submitted under NDA 214070 and did not identify any approvability issues.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

BD is a corticosteroid and AS is a short-acting beta2-adrenergic agonist. The applicant conducted three phase 1 studies (Studies LOGAN, ELBRUS, BLANC) and one phase 2 study (Study ASPEN) to characterize the PK of BD and AS with the proposed BDA MDI.

BD PK

- Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg) and BD MDI (2 inhalations of 80 µg) in healthy subjects (n=91), BD systemic exposure (C_{max} and AUC) is comparable between BDA MDI and BD MDI, suggesting the presence of AS in BDA MDI does not affect BD PK (Study LOGAN, Table 5).

- Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg) and Pulmicort Flexhaler (2 inhalations of 90 µg) in healthy adults (n=67), BD C_{max} and AUC for BDA MDI is 37% and 26% lower than that for Pulmicort Flexhaler, respectively (Study ELBRUS, Table 6).
- Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg) and Pulmicort Respules (1 mg) in children with asthma aged 4 to 8 years (n=12), BD C_{max} and AUC for BDA MDI is 68% and 54% lower than that for Pulmicort Respules, respectively (Study BLANC, Table 7).

AS PK

- Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg) and AS MDI (2 inhalations of 90 µg) in healthy subjects (n=91), AS systemic exposure (C_{max} and AUC) is comparable between BDA MDI and AS MDI, suggesting the presence of BD in BDA MDI does not affect AS PK (Study LOGAN, Table 5).
- Following the cumulative dose (1+1+2+4+8 actuations, a total albuterol dose of 1440 µg) administration of AS MDI (90 µg) and Proventil (90 µg) in subjects with mild to moderate asthma (n=46), AS C_{max} and AUC for AS MDI is 27% and 21% lower than that for Proventil, respectively (Study ASPEN, Table 8).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed general dosing for BDI MDI is:

- ≥12 years: 2 inhalations of BDA MDI 80/90µg (160/180 µg) as needed
- 4-11 years: 2 inhalations of BDA MDI 40/90µg (80/180 µg) as needed
- Do not take >6 doses (12 inhalations) in 24 hours

Therapeutic Individualization

Not applicable

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The proposed BDA MDI is a fixed-dose combination drug-device product for oral inhalation, in which BD is a corticosteroid and AS is a short-acting beta2-adrenergic agonist. The applicant

conducted three phase 1 studies (Studies LOGAN, ELBRUS, BLANC) and one phase 2 study (Study ASPEN) to characterize the PK of BD and AS with the proposed BDA MDI.

PK Interaction Between BD and AS (Study LOGAN)

Study LOGAN was a randomized, single-center, 3-way cross-over study in healthy male and female subjects (N=91). Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg), BD MDI (2 inhalations of 80 µg) or AS MDI (2 inhalations of 90 µg), the systemic exposure (C_{max} and AUC) of both BD and AS are comparable when administered BDA MDI (as test product) or each of the components (as reference product), i.e. BD MDI or AS MDI, suggesting the lack of PK interaction between BD and AS (Table 5).

Table 5. Comparison of Budesonide and Albuterol PK Parameters Following a Single Dose Administration of BDA MDI (160/180 µg, Test) and Each Drug Inhaled Alone (BD MDI 160 µg) or AS MDI (180 µg, Reference) in Healthy Subjects (Study LOGAN)

Compound	PK Parameters	GeoLS Mean (Test/Reference)	GMR (90% CI) (%)
Budesonide	C_{max} (pg/mL)	275/311	88.28 (81.01, 96.20)
	AUC_{0-t} (h*pg/mL)	944/1098	85.93 (80.74, 91.46)
	AUC_{0-inf} (h*pg/mL)	1014/1156	87.73 (82.43, 93.38)
Albuterol	C_{max} (pg/mL)	473/506	93.53 (87.71, 99.74)
	AUC_{0-t} (h*pg/mL)	3377/3646	92.62 (88.01, 97.48)
	AUC_{0-inf} (h*pg/mL)	3670/3951	92.89 (88.16, 97.87)

GMR: geometric mean ratio.
(Adapted from Tables 11-3 and 11-5 of Study LOGAN CSR).

BD PK Comparison Between BDA MDI and LDPs (Studies ELBRUS and BLANC)

Study ELBRUS was an open-label, single-center, randomized, 2-way cross-over study in healthy adult male and female subjects (n=67). Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg) and Pulmicort Flexhaler (2 inhalations of 90 µg), BD C_{max} and AUC for BDA MDI is 37% and 26% lower than that for Pulmicort Flexhaler, respectively (Table 6).

Table 6. Comparison of Budesonide PK Parameters Following a Single Dose Administration of BDA MDI (160/180 µg, Test) and Pulmicort Flexhaler (180 µg, Reference) in Healthy Subjects (Study ELBRUS)

Compound	PK Parameters	GeoLS Mean (Test/Reference)	GMR (90% CI) (%)
Budesonide	C_{max} (pg/mL)	263/419	62.76 (56.89, 69.23)
	AUC_{0-t} (h*pg/mL)	916/1235	74.19 (69.05, 79.71)
	AUC_{0-inf} (h*pg/mL)	972/1280	75.93 (70.88, 81.34)

(Adapted from Table 11-4 of Study ELBRUS CSR).

Study BLANC was a randomized, open-label, single-dose, 2-way crossover study to compare the systemic exposure of budesonide delivered by BDA MDI or Pulmicort Respules in 12 children with asthma, aged 4 to 8 years. Following a single dose administration of BDA MDI 160/180 µg (2 inhalations of 80/90 µg) and Pulmicort Respules (1 mg), BD C_{max} and AUC for BDA MDI is 68% and 54% lower than that for Pulmicort Respules, respectively (Table 7).

Table 7. Comparison of Budesonide PK Parameters Following a Single Dose Administration of BDA MDI (160/180 µg, Test) and Pulmicort Respules (1 mg, Reference) in Children With Asthma Aged 4 to 8 Years (Study BLANC)

Compound	PK parameters	GeoLS mean (Test/Reference)	GMR (90% CI) (%)
Budesonide	C_{max} (pg/mL)	131/404	32.4 (16.6, 63.0)
	AUC_{0-t} (h*pg/mL)	432/937	46.2 (33.4, 63.7)

(Adapted from Table 10 of Study BLANC CSR).

AS PK Comparison Between BDA MDI and LDP (Study ASPEN)

Study ASPEN was a randomized, cumulative-dose, open-label, 2-period crossover study in subjects with mild to moderate asthma (n=46). Following the cumulative dose (1+1+2+4+8 actuations, a total albuterol dose of 1440 µg) administration of AS MDI (90 µg) and Proventil (90 µg), AS C_{max} and AUC for AS MDI is 27% and 21% lower than that for Proventil, respectively (Table 8).

Table 8. Comparison of Albuterol PK Parameters Following the Cumulative Dose (1+1+2+4+8 Actuations, a Total Albuterol Dose of 1440 µg) Administration of AS MDI 90 µg (Test), and Proventil (90 µg, Reference) in Subjects With Mild to Moderate Asthma (Study ASPEN)

Compound	PK Parameters	GeoLS Mean (Test/Reference)	GMR (90% CI) (%)
Albuterol	C_{max} (pg/mL)	3706/5105	72.61 (66.48, 79.30)
	AUC_{0-t} (h*pg/mL)	21496/27269	78.83 (73.39, 84.67)

(Adapted from Table 22 of Study BLANC CSR).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant conducted two dose-ranging studies, Studies PT008001 and ANTORA for BD and AS, respectively, in the clinical development program. Based on the dose-ranging results, two dosing levels of BD (i.e., 80 and 160 µg) with fixed AS dose (i.e., 180 µg) were further evaluated in phase 3 trials MANDALA and DENALI. Of note, the same MDI device was used in these two studies. Refer to Section 8 for detailed information regarding the efficacy assessment from the phase 3 studies.

Study PT008001 was a randomized, double-blind, chronic dosing (4 weeks), 4-period, 5-treatment, incomplete block, cross-over, multi-center study in approximately 150 adult subjects with mild to moderate persistent asthma, who remained symptomatic despite treatment with Pulmicort Flexhaler 180 µg. All subjects received BD MDI at doses of 320 µg, 160 µg, 80 µg, and 40 µg twice daily or placebo MDI. Analysis of the primary efficacy endpoint, the mean change from baseline in morning pre-dose trough FEV1 at the End of the Treatment Period, showed that the estimated LS mean differences (p-values) versus placebo were 0.114 L (p<0.0001), 0.115 L (p<0.0001), 0.083 L (p=0.0039), and 0.085 L (p=0.0029) for the BD MDI 320, 160, 80, and 40 µg doses, respectively (Table 9).

Table 9. Change From Baseline in Morning Pre-Dose Trough FEV1 at the End of the Treatment Period, mITT Population (Study PT008001)

	BD MDI 320 µg (N=112)	BD MDI 160 µg (N=118)	BD MDI 80 µg (N=57)	BD MDI 40 µg (N=58)	Placebo MDI (N=118)
Change from baseline in morning pre-dose trough FEV_1 (L)					
n	109	109	56	56	111
LS mean (SE)	-0.002 (0.0175)	-0.001 (0.0174)	-0.034 (0.0242)	-0.031 (0.0242)	-0.116 (0.0173)
95% CI	-0.036, 0.033	-0.035, 0.033	-0.081, 0.014	-0.079, 0.016	-0.150, -0.082
Difference versus Placebo MDI (L)					
LS mean (SE)	0.114 (0.0229)	0.115 (0.0229)	0.083 (0.0285)	0.085 (0.0284)	NA
95% CI	0.069, 0.160	0.070, 0.161	0.027, 0.139	0.029, 0.141	
P-value	<0.0001	<0.0001	0.0039	0.0029	

Source: Section 11, Table 2.1.1

BD=budesonide; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; MDI=metered-dose inhaler; mITT=Modified Intent-to-Treat; NA=not applicable; SE=standard error.

Note: 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.

(Source: Table 7-1 of Study PT008001 CSR).

Study ANTORA was a randomized, double-blind, single-dose, placebo-controlled, 5-period, 5-treatment, crossover, multicenter study to assess the bronchodilatory effect and safety of 2 dose levels of AS MDI (90 and 180 µg) compared with placebo MDI and open-label Proventil (90 and 180 µg) in adult and adolescent subjects with mild to moderate asthma. Results showed that both doses of AS MDI were statistically superior to placebo MDI for the change from baseline in FEV1 $AUC_{0\text{-}6hours}$, with LS mean differences (p-values) of 196 mL (p<0.0001) and 134 mL (p<0.0001), respectively, and noninferior to Proventil (Table 10).

Table 10. Change From Baseline in FEV1 $AUC_{0\text{-}6hours}$ (mL[a]) (mITT Analysis Set) (Study ANTORA)

		AS MDI		Proventil	
Parameter	Placebo MDI	90 µg	180 µg	90 µg	180 µg
Change from baseline					
N	78	79	79	78	77
LS mean (SE)	70 (23.9)	203 (23.8)	266 (23.9)	240 (23.9)	282 (24.0)
Difference vs Placebo MDI					
LS mean (SE)	NA	134 (20.7)	196 (20.8)	171 (20.9)	212 (20.9)
95% CI		(93, 175)	(155, 237)	(130, 212)	(171, 253)
p-value[b]		<0.0001	<0.0001	<0.0001	<0.0001
Noninferiority vs Proventil[c]					
LS mean (SE)	NA	-37 (20.8)	-16 (20.8)	NA	NA
95% CI		(-78, 4)	(-57, 25)		

Abbreviation: NA=not applicable.
Baseline was defined as the mean of evaluable 60- and 30-minute predose values across Visits 2 through 6.
The model was a linear mixed effect model with a random subject effect for the correlation across periods and fixed effects for treatment, treatment sequence, baseline FEV_1, and period.
[a] For ease of interpretation, data were converted to mL from L by multiplying the values presented in the source table by 1000.
[b] p-values are for tests of superiority.
[c] Comparisons were made against the equivalent dose of Proventil (ie, AS MDI 180 µg vs Proventil 180 µg and AS MDI 90 µg vs Proventil 90 µg). Noninferiority was concluded when the lower CI limit for the difference between treatments was greater than -100 mL.

(Source: Table 19 of Study ANTORA CSR).

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

Yes, the proposed general dosing regimen is appropriate from a clinical pharmacology perspective.

For a locally acting drug product, such as the proposed BDA MDI, the drug's systemic exposure is correlated with its systemic safety profile, but not efficacy. In the PK studies (Studies ELBRUS, BLANC, and ASPEN) comparing the systemic exposure of BD or AS with the proposed BDA MDI and the LDPs, the systemic exposure (C_{max} and AUC) of both BD and AS with BDA MDI are lower than that with the LDPs (Table 6, Table 7, Table 8). A cross-study PK comparison indicated that, following the same single dose of BDA 160/180 µg, the BD systemic exposure (C_{max} and $AUC_{0\text{-}t}$) in children is about half the value of that in adults (Table 11).

Additional simulations were performed to mimic the 'worst-case scenario' daily use: i.e., 12 inhalations of high dose BDA (6 doses of BDA 160/180 µg) plus the maximum BD controller dose. Results showed that, in this situation, the total systemic exposure ($AUC_{0\text{-}24hours}$) of BD in adolescents and children aged 4 to 11 years is still expected to be lower than the value in adults (Table 12). Note that PK samples were not collected from children aged 9 to <18 years from the BDA clinical development program; therefore, our simulation assumed the same bioavailability of BD in subjects ≥9 years old via the inhalational route. This assumption is considered conservative, because all approved BD inhalational products (Pulmicort Flexhaler, Pulmicort Respules, and Symbicort) have demonstrated comparable or lower bioavailability and systemic exposure of BD in pediatric patients compared to adults.

Table 11. Comparison of Budesonide Systemic Exposure Between Adults (Study ELBRUS) and Children (Study BLANC) Following a Single Dose of BDA MDI

Geometric Mean (gCV%) of PK Parameters	Study ELBRUS in Adult Healthy Subjects		Study BLANC in Asthma Patients 4 to 8 Years of Age	
	BDA 160/180 µg (n=66)	Pulmicort Flexhaler 180 µg (n=66)	BDA 160/180 µg (n=11)	Pulmicort Respules 1000 µg (n=10)
C_{max} (pg/mL)	263 (49.7)	417 (40.9)	116 (46.6)	447 (156)
AUC_{0-t} (h*pg/mL)	916 (36.9)	1235 (37.3)	398 (46.3)	985 (78.7)
AUC_{0-inf} (h*pg/mL)	968 (34.8)	1279 (36.7)	NA	NA

(Adapted from Table 11-3 of Study ELBRUS CSR and Table 10 of Study BLANC CSR).

Table 12. Comparison of Total Budesonide Systemic Exposure ($AUC_{0-24hours}$) Between Adults and Children Under the Worst-Case Scenario Use (12 Inhalations BDA MDI/Daily Plus the Maximum BD DPI Maintenance Dose)

Age Groups	BDA MDI Maximum Dose[1]	Maximum BD DPI Maintenance Dose	Total BD Exposure in Children Relative to Adults Under Worst-Case Scenario Use
Adults	12 inhalations (960 µg)/day	720 µg BID[2]	1.0
Adolescents (≥12 years)[2,4]	12 inhalations (960 µg)/day	360 µg BID[2]	0.68
Children 9-11 years[2,4]	12 inhalations (480 µg)/day	360 µg BID[2]	0.48
Children 4-8 years	12 inhalations (480 µg)/day	1000 µg QD or 500 µg BID[3]	0.21

DPI : dry powdered inhaler.
1 As proposed by the Applicant.
2 Approved maximum BD dose from Pulmicort Flexhaler (6 to 17 years of age)
3 Approved maximum BD dose from Pulmicort Respules (1 to 8 years of age)
4 No observed PK data in children 9 to 18 years of age from the BDA program, the simulated results are based on adult bioavailability value

Refer to the clinical review and statistical review by Dr. Elisabeth Boulos and Dr. Dong-Hyun Ahn, respectively, for more details for the observed efficacy and safety data. Refer to the pharmacometrics review for the technical details for PK simulations.

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

BDA MDI has been developed under 505(b)(2) regulatory pathway. The proposed dosing regimen or management strategy based on intrinsic factors is consistent with the LDPs, which is reasonable.

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

There are no clinically relevant food-drug interactions for this inhalation drug product. BDA MDI has been developed under the 505(b)(2) regulatory pathway. The proposed management strategy regarding drug-drug interactions is consistent with the LDPs, which is reasonable.

The applicant also conducted a PK study (LOGAN) to evaluate the drug-drug interaction between BD and AS. Following a single dose administration of BDA MDI (2 inhalations of 80/90 µg), BD MDI (2 inhalations of 80 µg) or AS MDI (2 inhalations of 90 µg), the systemic exposure (C_{max} and AUC) of BD and AS are comparable when administered BDA MDI or each of the components, i.e. BD MDI or AS MDI, suggesting the lack of PK interaction between BD and AS (Table 5).

Question on clinically relevant specifications (TBD)?

None.

7. Sources of Clinical Data and Review Strategy

7.1. Review Strategy

The NDA submission contained three trials designed to evaluate the efficacy and safety of BDA (refer to Section 1 and Table 13): a 24-week, event-driven trial to evaluate the contribution of ICS to ICS/SABA combination as PRN treatment in preventing severe acute exacerbations of asthma (MANDALA); a 12-week trial to evaluate the contribution of each mono-component of BDA to its effect on lung function (DENALI); and a single-dose trial to evaluate the effect of BDA on lung function after exercise challenge testing (TYREE). Section 8 includes the protocol and efficacy review for each trial. Neither efficacy nor safety analyses were pooled, per previous agreement with the Agency, because of the trials' disparate populations and designs. Discussion of TYREE is limited since it did not contribute data to support the proposed indication and, the trial design did not include an AS arm to evaluate the contribution of BD.

8. Statistical and Clinical and Evaluation

8.1. Table of Clinical Studies

Table 13. Clinical Trials to Support NDA 214070

Trial Identifier	Trial Population	Trial Design	Number Treated, Regimen	Primary and Key Secondary Endpoints	Number of Patients	Number of Centers and Countries
MANDALA **AV003** **D6930C00005** **NCT03769090**	Subjects ≥ 4 years with asthma requiring maintenance treatment with medium to high ICS or low to high doses of ICS in combination with LABA +/- other controller medication	Minimum 24-week, variable duration, event driven, R, DB, PG	Number treated: 3127 AS (1057), BDA 80/180 (1055), BDA 160/180 (1015)	Primary: Time to first severe asthma exacerbation Secondary: Annualized severe exacerbation rate, total SCS exposure, ACQ-5, AQLQ+12 / PAQLQ	3132 randomized, 3127 treated	Centers: 296 Countries: 11

Trial Identifier	Trial Population	Trial Design	Number Treated, Regimen	Primary and Key Secondary Endpoints	Number of Patients	Number of Centers and Countries
DENALI **AV004** **D6930C00004** **NCT03847896**	Subjects ≥ 4 years with asthma requiring treatment with PRN SABA alone or low dose ICS + PRN SABA	12-week, R, DB, PC	Number treated: 1000 Placebo (199), AS (201), BD 160 (199), BDA 80/180 (204), BDA 160/180 (197)	Dual primary endpoints: Change from baseline in FEV1 AUC from 0-6 hours / 12 weeks; Change from baseline in trough FEV1 Secondary: Time to onset and duration of response (15% increase in FEV1) on day 1, ACQ-7, Trough FEV1 at week 1	1001 randomized, 1000 treated	Centers: 110 Countries: 7
TYREE **AV005** **D6930C00006** **NCT04234464**	Subjects ≥ 12 years with asthma and EIB treated with PRN SABA only or ICS + PRN SABA	Single dose R, DB, PC, Crossover	Number treated: 60 Placebo (31/29), BDA 160/180 (29/31)	Primary: Maximum % fall in FEV1 Secondary: % subjects with maximum % fall in FEV1 < 10%	60 randomized, 60 treated	Centers: 6 Countries: 1

8.2. Review of Relevant Individual Trials Used to Support Efficacy

8.2.1. MANDALA Trial Design

Trial Design

The primary objective of MANDALA was to assess the contribution of the ICS to the ICS/SABA combination when used as a PRN treatment for asthma symptoms. MANDALA was a phase 3, randomized, double-blind, active comparator-controlled, variable-length, event-driven trial with a treatment period of at least 24 weeks designed to evaluate the safety and efficacy of BDA on the time to first severe asthma exacerbation in pediatric and adult subjects with moderate to severe asthma. The study schema is shown below (Figure 4). Subjects administered both BDA and the active comparator, AS, PRN in response to asthma symptoms. Throughout the treatment period, all subjects remained on background maintenance therapy for asthma. Subjects ≥ 12 years were randomized 1:1:1 to the following interventions:

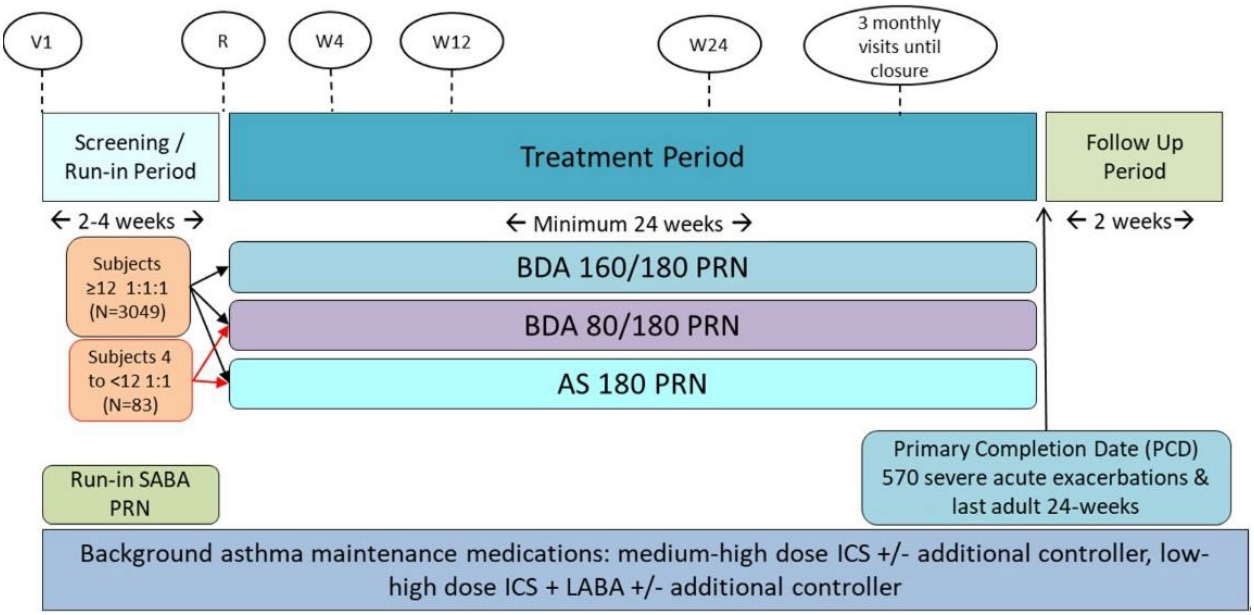
- BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg per puff) PRN
- BDA MDI 80/180 µg (given as 2 actuations of BDA MDI 40/90 µg per puff) PRN
- AS MDI 180 µg (given as 2 actuations of AS MDI 90 µg per puff) PRN
- Subjects 4-11 years were randomized 1:1 to BDA MDI 80/180 µg or AS MDI 180 µg treatment arms only.

The maximum daily dose was 12 puffs per day, and subjects were advised not to exceed 8 puffs per day and to contact the study site if their symptoms necessitated more frequent use. The Schedule of Assessments is shown below (Table 14), and the key aspects of the study visits are summarized here:

- The screening period included Visit 1 and lasted 2 to 4 weeks. If a severe asthma exacerbation occurred, the screening period could be extended for up to 9 weeks (1 week of SCS and 4 weeks of wash-out). The Applicant supplied all subjects with Ventolin to use as a PRN treatment until the morning of Visit 2.
- Randomization occurred at Visit 2. For all subjects ≥12 years, randomization was stratified by age (≥12 to 17, ≥18); region; and number of severe exacerbations (1, >1) in the prior year. For all subjects, the treatment period lasted a minimum of 24 weeks. The study period included both the treatment period and the extension phase. The primary completion date (PCD) represented the point when at least 570 first severe acute exacerbations occurred, and the last adult subject completed 24 weeks.
- The end of study visit (EOS) occurred for all currently-enrolled subjects once the PCD was met.

- Subjects who discontinued treatment early were encouraged to undergo a premature discontinuation visit (PDV).
- Following the treatment period, there was a 2-week safety follow up period.

Figure 4. MANDALA Study Schema



Source: Clinical Reviewer.

Table 14. MANDALA Schedule of Assessments

	Screening and run-in	*Double-blind Treatment Period*						*Extension Phase*	*EOS [d] (last clinic visit)*	*PDV [e] (if applicable)*	*Safety Follow-up TC (2 weeks [±4 days]after EOS or PDV)*
Visit [a]	*1/1a [b]*	*2*	*3*	*4*	*5*	*6 [c]*	*7*	*(every 12-weeks ±4 days until the PCD)*			
Week	*-4 to -2*	*0*	*4*	*8*	*12*	*24*	*36*				
Day	*-28 to -14*	*1*	*28 ±2*	*56 ±2*	*84 ±4*	*168 ±4*	*252 ±4*				
Informed consent/assent	X										
Eligibility criteria	X	X									
Clinical procedures											
Medical/surgical history	X[b]										
Demography	X										
Physical examination	X							X	X	X	
Height (cm) [f]	X					X[f]			X[f]	X[f]	
Concomitant medications	X[b]	X	X	X	X	X	X	X	X	X	X
Albuterol/salbutamol reversibility test [g]	X										
Safety measurements											
Vital signs	X[b]	X	X	X	X	X	X	X	X	X	
12-lead ECG	X[b]	X				X			X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [h]	serum	urine	urine [h]	urine [h]	urine [h]	serum	urine [h]	urine [h]	serum	serum	
Safety laboratory assessments (clinical chemistry and hematology)	X[b]					X			X	X	
Morning serum cortisol assessment	X					X			X	X	

	Screening and run-in	Double-blind Treatment Period						Extension Phase	EOS [d] (last clinic visit)	PDV [e] (if applicable)	Safety Follow-up TC (2 weeks [±4 days]after EOS or PDV)
Visit [a]	1/1a [b]	2	3	4	5	6 [c]	7	(every 12-weeks ±4 days until the PCD)			
Week	-4 to -2	0	4	8	12	24	36				
Day	-28 to -14	1	28 ±2	56 ±2	84 ±4	168 ±4	252 ±4				
Efficacy measurements											
Collection/review of exacerbations [i]	X	X	X	X	X	X	X	X	X	X	
ACQ-5 [j]		X	X	X	X	X	X	X	X	X	
ACQ-7 [k]	X										
ACT/C ACT		X	X	X	X	X	X	X	X	X	
AQLQ+12/PAQLQ		X	X	X	X	X	X	X	X	X	
Review of PEF, use of IP (reliever therapy), asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms [l]	X	X	X	X	X	X	X	X	X	X	
Spirometry (FEV_1) [m]	X	X			X	X					
eDiary	d								c	c	
Review compliance with eDiary		X	X	X	X	X	X	X	X	X	
Investigational product administration											
Randomization		X									
IP (dispense/collect)		d	c/d	c/d	c/d	c/d	c/d	c/d	c	c	
Ventolin (dispense)	d										

Abbreviations: ACQ-5/7=Asthma Control Questionnaire-5/7; ACT=Asthma Control Test; AQLQ+12=Asthma Quality of Life Questionnaire for 12 years and older; β-hCG=β-human chorionic gonadotropin; BMI=body mass index; c=collect; C ACT=Childhood Asthma Control Test; d=dispense; ECG=electrocardiogram; EOS=end-of-study; FEV_1=forced expiratory volume in 1 second; IP=investigational product; LABA=long-acting β2-agonist; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PCD=primary completion date; PDV=premature discontinuation visit; PEF=peak expiratory flow; TC=telephone call; V=visit

[a] Repeat assessments/visits, if needed, will be captured in unscheduled visits.

[b] Visit 1 will be split and used for repeated assessments, if needed (ie, Visit 1a will be needed for the repeat assessment of albuterol/salbutamol reversibility test and FEV_1, if applicable). Subjects may consent for the study in advance of Visit 1 and if required, request for medical records to support evidence of prior asthma exacerbations without triggering the 28-day screening period. Where a severe exacerbation event occurs during the screening period, this may be extended to a maximum of 9 weeks (to account for a course of systemic corticosteroids of up to 1 week duration followed by a 4-week washout period). In the event of an extension to the screening period due to a severe exacerbation event, the following will be repeated: safety laboratory assessments, ECG, vital signs, concomitant medications, and medical/surgical history.

[c] The treatment duration for the study will be at least 24 weeks for each subject to support the subject exposure data. The study treatment period will continue (extension phase) until the required 570 first severe exacerbation events, as defined per protocol, have been reached; and the last adult subject has completed 24 weeks of treatment, which will be defined as the PCD. After Visit 6, visits will be scheduled every 12 weeks with the assessments from Visit 7 to be performed in all of them.

[d] The EOS visit will be planned once the first 570 severe exacerbation events occur. If a subject's treatment lasts ≥24 weeks then the subject's EOS visit will occur at their next scheduled clinic visit. Once the PCD has been reached, any ongoing subject will return to complete an EOS visit at their next scheduled clinic visit.

[e] Subjects who prematurely withdraw from the study will undergo a PDV. In the event the PDV is performed >14 days post last IP dosing, a follow-up TC will not be required. These subjects who do not withdraw consent for follow-up will be followed for survival/death, severe exacerbations, AEs/SAEs, and concomitant medications including asthma treatment (maintenance and rescue therapies) at quarterly intervals until EOS.

[f] Additional height (cm) assessments to be collected for subjects ≤18 years of age ONLY. Assessments of height will continue in accordance with a subject's age at the time of signed informed consent/assent (where a subject changes age during the study).

[g] Demonstrate reversibility at Visit 1, with an increase in FEV_1 ≥12% (and ≥200 mL for subjects ≥18 years) relative to baseline after administration of Sponsor-provided Ventolin via central spirometry at either Visit 1 or Visit 1a (reversibility must be demonstrated at either Visit 1 or Visit 1a); Visit 1a must be used for re-testing, if needed; with only 1 reversibility re-test permitted in advance of randomization (Visit 2).

[h] A serum pregnancy test (β-hCG) will be performed at Visit 1, 6, and EOS/PDV; urine β-hCG test will be performed at all other clinic visits (for women of childbearing potential only). (In Argentina, women of childbearing potential will have additional pregnancy testing at monthly time points.)

[i] Asthma exacerbations data will be reviewed, and severe exacerbations identified as per Section 5.1.1. Subjects are to be reminded not to take any albuterol product except for the IP.

[j] Asthma Control Questionnaire-5 self-administered adult version to be used for adults and adolescents 11 years and older; the interviewer-administered version should be used for children 4 to 10 years. Subject will need to satisfy ACQ-5 (≥1.5) entry requirements at Visit 2.

[k] Subject will need to satisfy ACQ-7 (≥1.5) entry requirements at Visit 1.

[l] The AM3 device will be dispensed at screening and PEF measurements will be taken through the screening period in advance of Visit 2.

8.2.1.1. Study Endpoints

Primary Endpoint

The primary endpoint was defined as the time to first severe asthma exacerbation.

- Per protocol, an asthma exacerbation was defined as a deterioration of asthma, which included worsening signs/symptoms, increased use of PRN reliever therapy, and worsening lung function by PEF or FEV1.
- Only severe asthma exacerbations were captured as an outcome. Per protocol, a severe exacerbation was an asthma exacerbation that resulted in at least 1 of the following:
  - A temporary bolus or burst of SCS for at least 3 consecutive days to treat symptoms of asthma worsening, including a single depo-injectable dose.
  - An ED or urgent care visit (defined as evaluation and treatment for < 24 hours) for asthma that required SCS.
  - An in-patient hospitalization for asthma.
- Exacerbations of asthma that did not meet the protocol definition were not captured as efficacy or safety outcomes. Asthma signs or symptoms were recorded as AEs only when they were serious, caused the subject to discontinue IP, or inconsistent with the subject's pre-existing asthma history.
- Deteriorations of asthma (annualized rate and time to first) were captured as exploratory endpoints. Deteriorations were recorded from subject entry of symptoms in the eDiary. For the exploratory endpoint, the definition required 1 or more of the following for ≥ 2 consecutive days: decline of PEF ≥ 20%; > 4 puffs/day of IP and ≥ 2x baseline; night-time symptom score > baseline and ≥ 2 or day-time score > baseline and 3.

Secondary Endpoints

1. Severe exacerbation rate (annualized).
2. Total systemic corticosteroid (SCS) exposure over the treatment period.
3. Asthma Control Questionnaire-5 (ACQ-5) change from baseline and responder analysis at Week 24.
4. Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)/Pediatric Asthma Quality of Life Questionnaire (PAQLQ) change from baseline and responder analysis at Week 24.

The ACQ-5 is a validated patient-reported questionnaire assessing asthma symptoms. It is designed to measure both the adequacy of asthma control and any change in asthma control, which occurs either spontaneously or as a result of treatment. The ACQ-5 comprises 5 questions about asthma symptoms recalling the previous 7 days (i.e., nighttime symptoms, morning symptoms, activity limitation, shortness of breath, and wheezing) and is scored on a 7-

point scale (0=excellent control; 6=extremely poor control). The minimally clinically important difference (MCID) is a change in score of 0.5, which was set as the threshold for the responder analysis (week 24- baseline, with > -0.5 representing nonresponders and ≤ -0.5 representing responders). The ACQ-5 was self-administered as an electronic patient reported outcome (ePRO) by adults and adolescents 11 years and older. The interviewer-administered version was used for children aged 4 to 10 years. It is not validated in children younger than 6 years of age; therefore, data for subjects < 7 years was excluded from endpoint analyses. Of note, the ACQ-5 represents an abbreviated version of the ACQ-7 (excludes FEV1), and it is generally considered somewhat less accurate than the complete version.

AQLQ-12 consists of 32 questions in 4 domains and PAQLQ consists of 23 questions in 3 domains. Both are validated instruments that measure functional problems (physical, emotional, and social) related to asthma and are assessed on a 7-point Likert scale from 1 to 7, with higher values indicating better health-related quality of life. The MCID is a change in score of 0.5, which was set as the threshold for the responder analysis (week 24- baseline, with < 0.5 representing nonresponders and ≥ 0.5 representing responders). The PAQLQ is not validated in children younger than 7 years of age; therefore, data for subjects 4-6 years was excluded from endpoint analyses.

Safety Endpoints

1. Adverse events / serious adverse events.
2. Vital signs.
3. Clinical chemistry and hematology parameters.
4. Electrocardiogram.

8.2.1.2. Study Population

Key Inclusion Criteria

1. Subjects ≥ 4 years of age with asthma as defined by GINA criteria for at least 1 year.
2. Receiving 1 of the following asthma maintenance therapies for at least 3 months with stable dosing for at least 4 weeks:
    a. Medium to high dose ICS.
    b. Medium to high dose ICS + LTRA, LAMA, or theophylline.
    c. Low to high dose ICS + LABA, with or without LTRA, LAMA, or theophylline.
3. Prebronchodilator FEV1 ≥ 40 to < 90% predicted normal for adults, and ≥ 60% predicted normal for subjects aged 4 to 17 years.
4. Reversibility, as demonstrated by an increase in FEV1 ≥12% relative to baseline after administration of SABA, for subjects ≥ 12 years.

5. History of at least 1 severe asthma exacerbation within 12 months prior to Visit 1.
6. Asthma Control Questionnaire 7 (ACQ-7) and ACQ-5 scores ≥ 1.5.
7. Use of Applicant-provided Ventolin PRN for asthma systems on at least 3 days / week during the run-in period.
8. BMI < 40 kg/m2.

Key Exclusion Criteria

1. COPD or other significant lung disease, including need for supplemental O2.
2. OCS or SCS use within 6 weeks of Visit 1 or chronic use of OCS (≥3 weeks/month).
3. Receipt of any biologics, marketed or investigational, within 3 months or 5-half-lives before Visit 1, whichever is longer.
4. Current smokers or former smokers with > 10 pack-year history or with cessation < 6 months of Visit 1.
5. Asthma with previous history of intubation for hypercapnia, respiratory arrest, hypoxic seizures, or syncope.
6. Pregnant, lactating, or unable or unwilling to use appropriate contraceptive methods.

8.2.1.3. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Administration of all investigational products (IPs), as well as background asthma maintenance therapy, was recorded by subjects in an eDiary.

Permitted Concomitant Medications

Permitted therapies for asthma included ICS, LABA, LTRA, theophylline, and LAMAs. No subject was permitted > 3 maintenance therapies. Dose changes during the study period were discouraged unless clinically indicated per GINA guidelines. Allergy immunotherapy (AIT) was also permitted during the study period, as were any other medications deemed necessary for the subject's wellbeing per the discretion of investigators. Per American Thoracic Society (ATS) / European Respiratory Society (ERS) standards, medications that may have an effect on FEV1 were discontinued prior to spirometry for their respective time limits. Definition of "low", "medium," and "high" dose ICS were aligned with the GINA 2018 guidance on low, medium, and high dose ICS categorization for ICS doses in subjects ≥ 6 years of age.

Prohibited Medications

- Oral, parenteral, or rectal corticosteroids (except if required to treat severe asthma exacerbation)

- Any other asthma medication except stable doses of maintenance therapy
- Inhaled disodium cromoglycate or inhaled nedocromil sodium
- 5-lipoxygenase inhibitors (i.e., zileuton)
- Inhaled short-acting anticholinergics (or short-acting muscarinic antagonists [SAMA], i.e., Ipratropium)
- Inhaled LAMA, except those that were started before screening and continued as part of maintenance treatment
- Phosphodiesterase inhibitors (i.e., roflumilast)
- Omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab, or any other monoclonal or polyclonal antibody therapy
- Beta2-adrenergic blockers including eye-drops (specific cardio-selective beta-blockers in low daily doses, e.g., metoprolol in doses up to 100 mg/d, were allowed)

Rescue Therapy

Use of rescue IP therapy was recorded by eDiary and assessed at Visits 2-EOS. In addition, prohibited therapies could be used short-term for asthma exacerbations per investigator discretion.

8.2.1.4. Statistical Analysis Plan

Analysis Sets

- The full analysis set (FAS): FAS was defined as all subjects who were randomized to treatment and took any amount of IP. Subjects were analyzed according to the treatment they were assigned at randomization. All efficacy analyses were conducted in the FAS.
  - For primary, secondary, and exploratory efficacy analyses, a subpopulation of the FAS including patients aged 12 years and older was used to make comparisons between BDA 160/180 vs AS MDI 180.
- The safety analysis set was defined as all subjects receiving any amount of the IP. Subjects were classified on the basis of treatment they actually received. If a subject received more than 1 IP, he or she was summarized according to the treatment the subject received the most. All safety summaries were based on the safety analysis set.
- The all patients enrolled population was defined as all patients who provided informed consent. This patient population was used for descriptive summaries of disposition.

Estimands

- Efficacy estimand (primary) was defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study,

regardless of actual usage and assuming that maintenance therapy was not changed. This estimand was considered as a while-on-treatment strategy or a hypothetical strategy as defined in the draft International Conference on Harmonization (ICH) E9 (R1) Addendum.

  - All primary, secondary, and exploratory endpoints were analyzed under the efficacy estimand.

- De facto estimand was defined as the effect of a treatment policy regardless of changes in maintenance therapy or premature discontinuation of randomized treatment. This estimand was considered a treatment policy strategy as defined in the draft ICH E9 (R1) Addendum.

Sample Size Calculation

A sample size of 1000 adult and adolescent subjects per treatment group and observation of the 570 first severe exacerbation events provide this study with 87% power to observe a 25% reduction in the risk of severe exacerbation with at least 1 dose of BDA MDI versus AS MDI assuming the Hochberg procedure (Hochberg, 1988) for multiple testing and a 2-sided significance level of 5%.

In addition, up to 100 subjects in the 4-to-11-year age group with moderate to severe asthma were to be randomized with approximately 50 subjects randomized to the AS MDI group and 50 subjects randomized to the low dose BDA MDI group only.

Primary Efficacy Analysis Model

The primary variable, time to first severe asthma exacerbation, was analyzed using a Cox proportional hazards regression model to compare treatment arms. The model was adjusted for the randomization stratification factors (age group [≥4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe, and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. The summary measure to compare treatments was the estimated hazard ratio which was presented with the corresponding 95% confidence interval and p-value.

Primarily, time to first severe exacerbation was conducted under the efficacy estimand and considered severe exacerbation events occurring prior to the discontinuation of IP or a change in maintenance therapy. Subjects who did not experience a severe exacerbation prior to IP discontinuation or a change in maintenance therapy were censored at the earliest occurrence of these intercurrent events. Under the de facto estimand, all severe exacerbation events post-treatment discontinuation were considered, regardless of any changes in maintenance therapy. Therefore, subjects had not had a severe exacerbation event prior to study withdrawal were censored at the date of study discontinuation.

Secondary Efficacy Analysis Model

- Analysis of severe asthma exacerbation rate targeted the efficacy estimand in the FAS population. Annualized severe asthma exacerbation rate was analyzed using negative binomial regression to compare treatment groups. The response variable in the model was the number of severe asthma exacerbations. The model adjusted for (age group [≥4 to 11, ≥12 to 17, ≥18]); region (North America, West Europe, and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. The logarithm of the time at risk of experiencing a severe asthma exacerbation was used as an offset variable in the model. Time during a severe asthma exacerbation or in the 7 days after an exacerbation was not included in the calculation. From the negative binomial model, the annual severe asthma exacerbation rates were estimated, and the summary measure for the comparison of treatments were the estimated rate ratio which were presented with the corresponding 95% confidence interval and p-value. Analyses of the annualized severe asthma exacerbation rate was repeated under the de facto estimand and considered all severe exacerbations up to patient withdrawal from the trial.
- A comparison in total annualized SCS dose between BDA MDI 80/180 vs AS MDI 180 and BDA MDI 160/180 vs AS MDI 180 was analyzed using a Wilcoxon rank sum test and associated p-values were presented. The secondary analysis of total systemic corticosteroid exposure was analyzed under the efficacy estimand. To help describe the difference in total annualized dose of SCS between treatment groups, the predicted mean annualized dose of SCS was estimated for each treatment group from a lognormal hurdle model adjusted for randomized treatment group. The log-normal hurdle model was fit in SAS using PROC FMM with two model components: A constant distribution to describe the zero events and a log-normal distribution component to describe the patients with a non-zero annualized dose.
- The Asthma Control Questionnaire-5 (ACQ-5) overall score was calculated as the average of the non-missing 5 symptom questions. At least 4 out of the 5 symptom items were needed to provide an ACQ-5 overall score. A responder status at Week 24 [(Week 24 – baseline) ≤ -0.5] was analyzed using a logistic regression model to compare treatment groups. The model was adjusted for baseline ACQ-5 and randomization stratification factors (age group [≥4 to 11, ≥12 to 17, ≥18]); region (North America, Western Europe, and South Africa [Region 1] and rest of world [Region 2]); and number of prior severe exacerbations (1, >1) in the 12 months prior to randomization. From the logistic regression model, treatment effects were estimated by odds ratios and their corresponding 95% confidence intervals and p-values. Under the efficacy estimand, subjects who discontinued treatment for any reason or receive a change in maintenance therapy for lack of asthma control before Week 24 was classified as non-responders.
- The denominator for the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) summary was based on the number of subjects within the respective age group for whom each questionnaire was applicable; AQLQ+12 included subjects aged 12 years and over. A responder status at Week 24 was calculated as subjects achieving a change from

baseline of at least 0.5 [(Week 24- baseline) ≥ 0.5]. Subjects who discontinued treatment before Week 24 for any reason or change in maintenance therapy was classified as non-responders. The responder analysis was conducted in the same way as ACQ-5.

Multiplicity Adjustment

Comparisons of BDA MDI 80/180 µg vs AS MDI and BDA MDI 160/180 µg vs AS MDI for the primary endpoint, time to first severe exacerbation using the efficacy estimand, were conducted using Hochberg's step-up method. The type-I error was controlled for secondary endpoint treatment comparisons via a hierarchical testing procedure. The following secondary endpoints were tested under the efficacy estimand in the following sequential order, grouped by secondary endpoint:

- Annualized severe exacerbation rate
  1. BDA MDI 160/180 µg versus AS MDI 180 µg
  2. BDA MDI 80/180 µg versus AS MDI 180 µg

- Total annualized dose of systemic corticosteroid
  3. BDA MDI 160/180 µg versus AS MDI 180 µg
  4. BDA MDI 80/180 µg versus AS MDI 180 µg

- Asthma Control Questionnaire-5 (ACQ-5) change from baseline responder analysis at Week 24
  5. BDA MDI 160/180 µg versus AS MDI 180 µg
  6. BDA MDI 80/180 µg versus AS MDI 180 µg

- Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) change from baseline responder analysis at Week 24
  7. BDA MDI 160/180 µg versus AS MDI 180 µg
  8. BDA MDI 80/180 µg AS MDI 180 µg

Protocol Amendments

Between the original submission on October 11, 2018 and the final version submitted on April 8, 2021, there were three protocol amendments. The first amendment, submitted in 2019, provided clarifying language to enrollment criteria and endpoints, without resulting in substantial changes, and added the de facto estimand strategy (treatment policy) to the planned analysis procedures. The second amendment, in 2020, included additional safety measures to permit continuation of the study during the COVID-19 pandemic. The final

amendment, in 2021, included clarifying language related to the PCD and specified that the treatment period would continue for pediatric subjects who had not yet completed 24 weeks of treatment by the primary database lock.

Table 15. SAP Amendment History

Date	Brief Description of Change
30 July 2021	Added the COVID-19 estimand. Added supportive analysis to the primary endpoint where the onset of a COVID-19 related adverse event or dose interruption are considered in the censoring rule. Added supportive statistics to describe the annualized dose of systemic corticosteroids. Added subgroup summaries of compliance with maintenance therapy. Detailed methodology for handling duplicate patients. Amended the list of AEs associated with local and systemic ICS effects which were deemed not appropriate following the physician review.

Source: Statistical Analysis Plan, p.11.

8.2.1.5. Study Results

Compliance With Good Clinical Practices

All studies were conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection.

Financial Disclosure

For financial disclosure information, refer to Section 14.2.

Patient Disposition

Subjects disposition is summarized in Table 16. Among the 3132 randomized subjects, the overall early treatment discontinuation rate was 12% and the discontinuation rate was the highest in the AS arm (13%) and the lowest in the high dose BDA arm (10%). Eleven subjects (1%), 9 subjects (1%) and 9 subjects (1%) discontinued the randomized treatment due to adverse events in the low, high dose BDA and AS arms, respectively. Overall study withdrawal rate was 11%, indicating that the majority of subjects who discontinued randomized treatment

have also discontinued from the study. A major reason for treatment and study discontinuation was “subject decision” and “withdrawal by subject”, which provides limited information about the treatment discontinuation and study withdrawal.

Table 16. Subject Disposition (All Randomized Subjects)

	Number of Subjects, n (%)			
Randomized	**BDA MDI (160/180 µg) N = 1016**	**BDA MDI (80/180 µg) N = 1057**	**AS MDI (180 µg) N = 1059**	**Total N = 3132**
Subjects who discontinued randomized treatment [1]	100 (9.8)	122 (11.5)	141 (13.3)	363 (11.6)
Subject decision	52 (5.2)	62 (5.9)	74 (7.0)	188 (6.0)
Adverse event	11 (1.1)	9 (0.9)	9 (0.8)	29 (0.9)
Lack of therapeutic response	1 (0.1)	2 (0.2)	2 (0.2)	5 (0.2)
Others	36 (3.5)	49 (4.6)	56 (5.3)	141 (4.5)
Subjects withdrew from study [1]	93 (9.2)	122 (11.5)	137 (12.9)	352 (11.2)
Withdrawal by subject	48 (4.7)	56 (5.3)	68 (6.4)	172 (5.5)
Lost to follow-up	19 (1.9)	26 (2.5)	22 (2.1)	67 (2.1)
Adverse event	4 (0.4)	7 (0.7)	7 (0.7)	18 (0.6)
Others	22 (2.2)	33 (3.1)	40 (3.8)	95 (3.0)

Source: Adapted from Clinical Study Report Table 7, p.89
[1] Includes subjects who discontinued randomized treatment/study during the extension phase, post Week 24. Only includes subjects who were randomized to study treatment.

As summarized in Table 17, among the 3132 randomized subjects, 3123 subjects were qualified for the full analysis set, defined as all subjects who were randomly assigned and took any amount of IP, and these subjects were composed of adults (94.1%), adolescents (3.2%), and children (2.7%). Children aged >= 4 - <12 years were randomized only to the lower BDA dose or AS per the study design.

Table 17. Analysis Sets (All Randomized Subjects)

	Number of Subjects, n (%)			
Randomized	**BDA MDI (160/180 µg) N = 1016**	**BDA MDI (80/180 µg) N = 1057**	**AS MDI (180 µg) N = 1059**	**Total N = 3132**
Full analysis set (FAS) [1]	1013 (100)	1054 (100)	1056 (100)	3123 (100)
Adults (≥18)	979 (96.6)	981 (93.1)	980 (92.8)	2940 (94.1)
Adolescents (≥12 - < 18)	34 (3.4)	32 (3.0)	34 (3.2)	100 (3.2)
Children (≥4 - < 12)	NA	41 (3.9)	42 (4.0)	83 (2.7)

Source: Statistical Reviewer
[1] All subjects who were randomized to treatment and took any amount of IP.

Protocol Violations/Deviations

In total, 6.2% of subjects in the FAS had at least one important protocol deviation. The majority (4.5%) of these were related to entry of enrollment criteria at randomization, either resulting in subjects receiving the incorrect treatment or dose or resulting in enrollment of subjects who did not meet eligibility criteria. A handful of subjects were duplicated, and these were excluded from the FAS. Finally, a small portion of subjects (0.1%) had protocol deviations related to COVID-19. None of these deviations were considered to affect the quality of the study or the overall interpretation of results.

Table of Demographic Characteristics

The enrolled population was characterized by a mean age of 49 years, and was predominantly white (81%) and female (65%). Most subjects (68%) had a baseline FEV1 >60% predicted normal, experienced no more than 1 severe asthma exacerbation in the previous year (79%), and were managed with an ICS/LABA (75%) with a medium dose ICS (47%) at baseline. This population is appropriately representative of patients with moderate to severe but not life-threatening or unstable disease with a reasonable probability of experiencing another exacerbation in the subsequent year. The population is also appropriately representative of the general population of adult patients with asthma in the US.

Table 18. Baseline Demographic Characteristics of Full Analysis Set (FAS) Population

	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
Sex (n%)				
Female	645 (63.7)	685 (65.0)	694 (65.7)	2024 (64.8)
Male	368 (36.3)	369 (35.0)	362 (34.3)	1099 (35.2)
Age, years				
Mean (SD)	50.6 (15.06)	48.5 (16.71)	49.1 (17.23)	49.4 (16.40)
Median (Min, Max)	52.0 (12, 84)	51.0 (5, 83)	52.0 (4, 84)	52.0 (4, 84)
Age group, years (n%)				
>= 4 - <12	0	41 (3.9)	42 (4.0)	83 (2.7)
>=12 - <18	34 (3.4)	32 (3.0)	34 (3.2)	100 (3.2)
>=18 - <65	787 (77.7)	804 (76.3)	783 (74.1)	2374 (76.0)
>=65	192 (19.0)	177 (16.8)	197 (18.7)	566 (18.1)
Ethnicity (n%)				
Hispanic or Latino	233 (23.0)	260 (24.7)	315 (29.8)	808 (25.9)
Not Hispanic or Latino	780 (77.0)	794 (75.3)	741 (70.2)	2315 (74.1)
Race (N%)				
American Indian or Alaska Native	1 (0.1)	1 (0.1)	0	2 (0.1)
Asian	29 (2.9)	33 (3.1)	23 (2.2)	85 (2.7)
Black or African American	139 (13.7)	141 (13.4)	137 (13.0)	417 (13.4)
Other	26 (2.6)	32 (3.0)	28 (2.7)	86 (2.8)
White	818 (80.8)	847 (80.4)	868 (82.2)	2533 (81.1)

Table 18. Baseline Demographic Characteristics of Full Analysis Set (FAS) Population

	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
Region (n%)				
North America, Western Europe, and South Africa	536 (52.9)	556 (52.8)	563 (53.3)	1655 (53.0)
Rest of world	477 (47.1)	498 (47.2)	493 (46.7)	1468 (47.0)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: FASFL = 'Y'; Sex (n%) - Dataset: Demographics; Filter: FASFL = 'Y'; Age, years - Dataset: Demographics; Filter: None; Age group, years (n%) - Dataset: Demographics; Filter: FASFL = 'Y'; Ethnicity (n%) - Dataset: Demographics; Filter: FASFL = 'Y'; Race (n%) - Dataset: Demographics; Filter: FASFL = 'Y', Region (n%) - Dataset: Demographics; Filter: FASFL = 'Y'.
SD = Standard Deviation.

Table 19. Baseline Asthma Characteristics Full Analysis Set (FAS) Population

	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
Severe exacerbations year prior (n%)				
1 severe exacerbation	802 (79.2)	831 (78.8)	835 (79.1)	2468 (79.0)
>1 severe exacerbation	211 (20.8)	223 (21.2)	221 (20.9)	655 (21.0)
Smoking status (n%)				
Never	815 (80.5)	866 (82.2)	849 (80.4)	2530 (81.0)
Former	198 (19.5)	188 (17.8)	207 (19.6)	593 (19.0)
Baseline FEV1 (n%)				
>=60% PN	681 (67.2)	710 (67.4)	743 (70.4)	2134 (68.3)
<60% PN	332 (32.8)	344 (32.6)	313 (29.6)	989 (31.7)
Maintenance therapy (n%)				
Low-to-high-dose ICS in combination with LABA with or without an additional LTRA, LAMA, or theophylline	764 (75.4)	797 (75.6)	798 (75.6)	2359 (75.5)
Medium-to-high-dose ICS alone	157 (15.5)	165 (15.7)	173 (16.4)	495 (15.9)
Medium-to-high-dose ICS and plus either LTRA, LAMA, or theophylline	81 (8.0)	77 (7.3)	73 (6.9)	231 (7.4)
Background ICS dose (n%)				
Medium	453 (44.7)	509 (48.3)	497 (47.1)	1459 (46.7)
High	318 (31.4)	288 (27.3)	317 (30.0)	923 (29.6)
Low	235 (23.2)	257 (24.4)	238 (22.5)	730 (23.4)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: FASFL = 'Y'; Severe exacerbations year prior (n%) - Dataset: Demographics; Filter: FASFL = 'Y'; Smoking status (n%) - Dataset: Demographics; Filter: FASFL = 'Y'; Baseline FEV1 (n%) - Dataset: Demographics; Filter: FASFL = 'Y'; Maintenance therapy (n%) - Dataset: Demographics; Filter: FASFL = 'Y', GROUP03 = 'Low-to-high-dose ICS in combination with LABA with or without an additional LTRA, LAMA, or theophylline' or 'Medium-to-high-dose ICS alone' or 'Medium-to-high-dose ICS and plus either LTRA, LAMA, or theophylline'.; Background ICS dose (n%) - Dataset: Demographics; Filter: FASFL = 'Y', AVALCAT1 = 'Low' or 'Medium' or 'High'.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Since the IP was administered PRN in response to symptoms and triggers, compliance was variable and assessed via eDiary entries and investigator interview. Refer to Table 42 for more detail on IP use patterns throughout the study period. Adherence to maintenance therapy was similarly assessed via eDiary entries and investigator interviews. Adherence was balanced between treatment arms, with a reported compliance on 75% of study days.

Efficacy Results – Primary Endpoint

Table 20 shows results for the primary efficacy endpoint of time to first severe asthma exacerbation in the MANDALA study population, subjects ≥12 for the high dose BDA vs AS and subjects ≥4 for the low dose BDA vs AS. The hazard ratio estimate was 0.73 [95% CI: 0.61, 0.88; p-value <0.001] for the high dose BDA vs AS and 0.83 [95% CI: 0.70, 0.99; p-value = 0.041] for the low dose BDA vs AS, demonstrating that treatment with the high dose BDA as needed in subjects ≥12 and the low dose BDA as needed in subjects ≥4 led to statistically significant delays in time to first severe asthma exacerbations in subjects with moderate to severe asthma compared with AS alone.

Table 20. Primary Analysis of Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand[a] (Full Analysis Set)

		Number (%) of Subjects with a Severe	Comparison Vs AS MDI 180		
Treatment Group	n	Exacerbation[c]	Hazard Ratio	95% CI	P-value
≥12 years					
BDA MDI 160/180 (N=1013)	1013	207 (20)	0.73	0.61, 0.88	<0.001
AS MDI 180 (N=1014)	1014	266 (26)			
All ages					
BDA MDI 80/180 (N=1054)	1054	241 (23)	0.83	0.70, 0.99	0.041
AS MDI 180 (N=1056)	1056	276 (26)			

Source: Statistical Reviewer and Statistical Analyst using adtte.xpt.
AS, albuterol sulfate; BDA, budesonide/albuterol sulfate; MDI, Metered Dose Inhaler; N, number of subjects in treatment group; n, number of subjects in analysis.
Hazard ratios, 95% CIs for hazard ratios, and p-values are estimated using a Cox regression model with treatment group, age group, region, and number of severe exacerbations in the last 12 months prior to randomization as factors. A hazard ratio less than 1 favors BDA MDI treatment groups.
[a] Under the efficacy estimand, follow up for events was censored among subjects who did not experience a severe exacerbation prior to IP discontinuation or a change in maintenance therapy at the earliest occurrence of these intercurrent events.
[b] Full Analysis Set was defined as all randomized subjects who received at least 1 inhalation of IP, analyzed according to randomized treatment arm.
[c] Deterioration of asthma requiring use of systemic corticosteroids for at least 3 days or inpatient hospitalization, or emergency room visit, that required systemic corticosteroids.

A supportive analysis was conducted to explore an alternative estimand applying a treatment policy strategy for the intercurrent event of changes in maintenance therapy or premature discontinuation of randomized treatment. The hazard ratio estimate was 0.74 [95% CI: 0.62, 0.89; p-value = 0.001] for the high dose BDA vs AS and 0.84 [95% CI: 0.71, 1.00; p-value = 0.052] for the low dose BDA vs AS, indicating that the improvement of the low dose BDA over AS in the primary endpoint was not statistically significant (Table 21).

Table 21. Supportive Analysis - Primary Analysis of Time to First Severe Exacerbation During the Study-Period, De Facto Estimand[a] (Full Analysis Set)

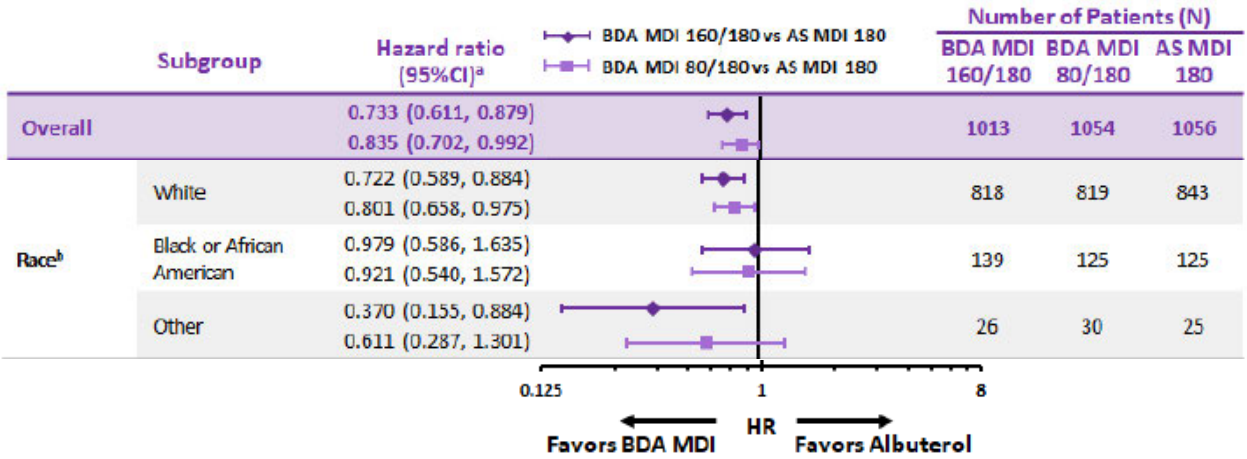
		Number (%) of Subjects with a Severe	Comparison Vs AS MDI 180		
Treatment Group	n	Exacerbation	Hazard Ratio	95% CI	P-value
≥12 years					
BDA MDI 160/180 (N=1013)	1013	212 (21)	0.74	0.62, 0.89	0.001
AS MDI 180 (N=1014)	1014	270 (27)			
All ages					
BDA MDI 80/180 (N=1054)	1054	248 (24)	0.84	0.71, 1.00	0.052
AS MDI 180 (N=1056)	1056	280 (27)			

Source: Statistical Reviewer and Statistical Analyst using adtte.xpt.
AS, albuterol sulfate; BDA, budesonide/albuterol sulfate; MDI, Metered Dose Inhaler; N, number of subjects in treatment group; n, number of subjects in analysis.
Hazard ratios, 95% CIs for hazard ratios, and p-values are estimated using a Cox regression model with treatment group, age group, region and number of severe exacerbations in the last 12 months prior to randomization as factors. A hazard ratio less than 1 favors BDA MDI treatment groups.
[a] Included all severe exacerbations, including those post randomized treatment discontinuation, or following changes in maintenance therapy.

These analyses, which conflate all age groups, support efficacy for BDA, demonstrating a larger treatment effect and more robust statistical significance for the high dose BDA relative to the low dose. However, these results include subjects ≥12 to 18 years in the analysis of high dose BDA and include subjects ≥4 years in the analysis of low dose BDA. It is important to evaluate the results in the pediatric subgroups, particularly given the small number of subjects < 18 years enrolled in MANDALA and this novel development program. Refer to Section 8.2.1.6 for more discussion regarding the results in pediatric patients.

Analyses conducted in other demographic subgroups (e.g., age, gender, race) showed that the "Black or African American" subgroup and the "Other" subgroup were generally consistent with and overalapped the results of the overall population. However, there was more uncertainty with the "Black or African American" subgroup which had wider confidence intervals that crossed 1. The smaller sample size may have contributed to the wide confidence intervals, making it difficult to draw definitive conclusions. (Figure 5).

Figure 5. Race-Based Subgroup Analysis - Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand (Full Analysis Set; All Ages)



Source: The Applicant's FDA Advisory Committee Briefing Document Figure 9 (p.39); modified by Statistical Reviewer.
[a] Comparison for BDA 160/180 vs AS MDI 180 is in patients ≥12 years of age.
[b] Note that subgroup analysis by race was not prespecified.

Data Quality and Integrity

Data quality and integrity for all pivotal trials, including both STDM and ADAM files, were assessed by OCS Clinical Services at the beginning of the review process. There were no significant issues with data integrity that prohibited review or required further action. In addition, three study sites underwent inspection by the Office of Scientific Investigations (OSI). Investigations concluded that data generated by these sites were acceptable in support of this NDA.

Efficacy Results – Secondary and Other Relevant Endpoints

All key secondary endpoints shown in Table 22 were analyzed in the FAS ≥12 years (BDA 160/180 vs AS) and sequentially in the FAS all age groups (BDA 80/180 vs AS) under hierarchical type I error control for multiple comparisons. The comparison of BDA 80/180 vs AS for total annualized dose of SCS (mg/subject) in all age groups failed to achieve statistical significance (p=0.060); therefore, results for this endpoint and results for all subsequent endpoints are considered exploratory. For the first key secondary endpoint of annualized severe exacerbation rate, both doses of BDA demonstrated a statistically significant benefit compared to AS alone; the size of the treatment effect and magnitude of statistical significance are greater for BDA 160/180 than BDA 80/180. Similarly, BDA 160/180 vs AS resulted in a statistically significant decrease in annualized total SCS dose. For the remaining exploratory endpoints of ACQ-5 and AQLQ+12, although not statistically significant, a consistent pattern emerges with nominally significant odds ratios demonstrating favorable results for the BDA 160/180 dose in the FAS ≥12 years. Pooling of subjects <12 years into the analysis for the BDA 80/180 comparison to AS appeared to dilute the magnitude of the treatment effect.

Table 22. Key Secondary Efficacy Endpoints, Efficacy Estimand (Full Analysis Set)

Secondary Endpoint	Type of Estimate	Age	Treatment Group	n	Comparison Vs AS MDI 180		
					Estimate	95% CI	P-value
Annualized severe exacerbation rate	Rate ratio	≥12 years	BDA MDI 160/180 (N=1013)	1013	0.76	0.62, 0.93	0.008*
			AS MDI 180 (N=1014)	1014			
		All ages	BDA MDI 80/180 (N=1054)	1054	0.80	0.66, 0.98	0.028*
			AS MDI 180 (N=1056)	1056			
Total annualized dose of systemic corticosteroid (mg/subject)	Difference in arithmetic means (%)	≥12 years	BDA MDI 160/180 (N=1013)	1012	-33.4	NA	0.002*
			AS MDI 180 (N=1014)	1011			
		All ages	BDA MDI 80/180 (N=1054)	1052	-24.8	NA	0.060
			AS MDI 180 (N=1056)	1052			
ACQ-5 minimal important difference [a] at Week 24, responder status	Odds ratio	≥12 years	BDA MDI 160/180 (N=1013)	1013	1.22	1.02, 1.47	0.034
			AS MDI 180 (N=1014)	1014			
		≥6 years	BDA MDI 80/180 (N=1052)	1052	1.13	0.95, 1.35	0.172
			AS MDI 180 (N=1055)	1055			
AQLQ+12 minimal important difference [b] at Week 24, responder status	Odds ratio	≥12 years	BDA MDI 160/180 (N=1013)	994	1.23	1.02, 1.48	0.028
			BDA MDI 80/180 (N=1013)	987	1.11	0.92, 1.34	0.260
			AS MDI 180 (N=1014)	993			

Source: Statistical Reviewer and Statistical Analyst using adef.xpt, adexsum.xpt and adqs.xpt.
A sequential testing strategy was used such that the hypothesis tests are listed in the table in descending order of sequence. A null hypothesis could only be rejected if all preceding null hypotheses were also rejected. Tests were each conducted at the 5% level of significance. Data up to the date of discontinuation of randomized treatment or change in maintenance therapy were included in the analysis.
* Results were statistically significant under a pre-specified hierarchical testing procedure.
[a] A responder was defined as ≥ 0.5 reduction in ACQ-5 overall score from baseline to Week 24.
[b] A responder was defined as ≥ 0.5 increase in AQLQ+12 score from baseline to Week 24.
Abbreviations: AS, albuterol sulfate; BDA, budesonide/albuterol sulfate; MDI, Metered Dose Inhaler; N, number of subjects in treatment group; n, number of subjects in analysis; NA, not applicable.

Dose/Dose Response

The Applicant evaluated two doses in MANDALA in subjects ≥12 years old, although the initial application proposed marketing only the high dose (BDA 160/180) for this population. Evidence of a dose-response relationship is apparent in Figure 6 below, where BDA 160/180 showed a greater reduction in time to first severe asthma exacerbation than BDA 80/180.

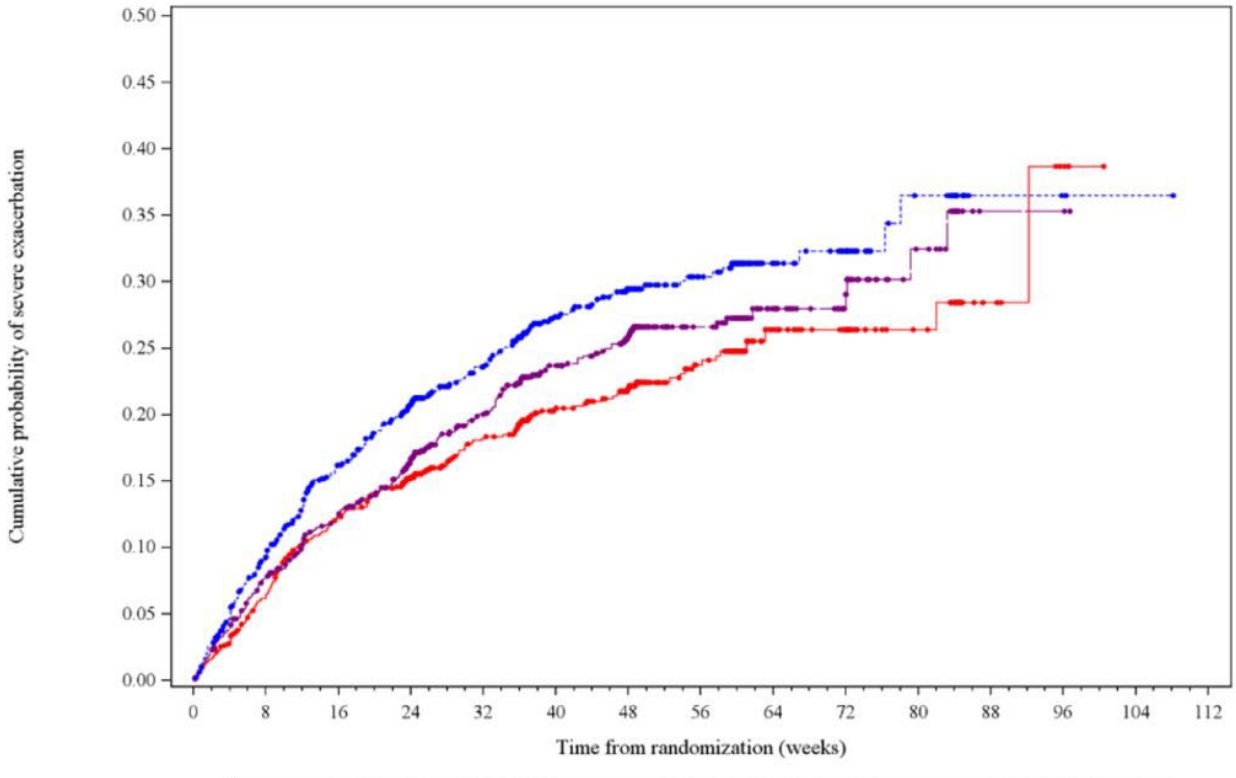
Durability of Response

Since BDA was administered PRN in MANDALA, the durability of effect was not assessed. Refer to Section 8.2.2 for relevant data from DENALI.

Persistence of Effect

The reverse Kaplan-Meier plot of time to first severe exacerbation shows an early separation of curves between the high dose BDA and AS arms and a consistently lower cumulative probability of severe exacerbation for the high dose BDA compared with AS throughout the study duration (Figure 6).

Figure 6. Time to First Severe Exacerbation During the Randomized Treatment Period, Reverse Kaplan-Meier Plot, Efficacy Estimand (Full Analysis Set; All Ages)



Number of patients at risk

BDA MDI 160/180	1013	936	863	761	551	442	389	229	79	65	37	9	4	0	0
BDA MDI 80/180	1054	958	888	777	550	433	372	228	88	69	28	2	2	0	0
AS MDI 180	1056	937	835	725	519	401	346	211	79	64	29	3	2	1	0

Source: Clinical Study Report Figure 3 , p.108.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

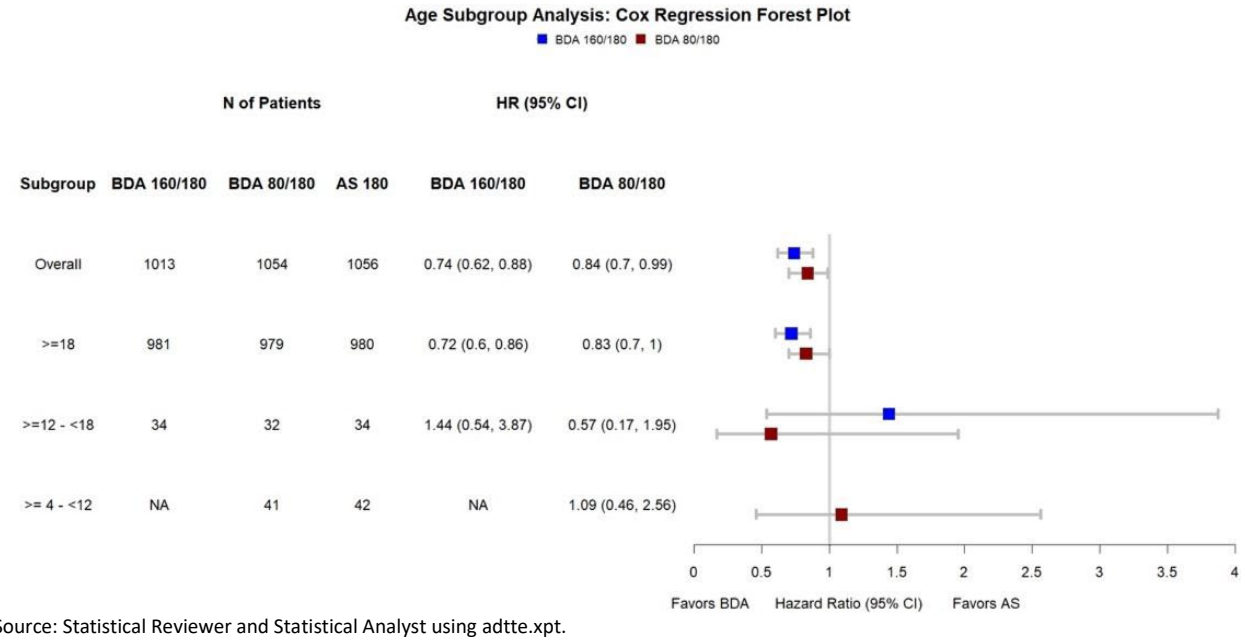
For PRO endpoints, refer to Table 22.

8.2.1.6. Additional Analyses in the Pediatric Population

As discussed above, results from MANDALA demonstrated a significant delay in time to first severe acute exacerbation in the overall population. To evaluate the efficacy across age groups, we analyzed efficacy in age cohort subgroups via a *post hoc* hierarchical approach, described in Section 14.4. Figure 7 shows results for the primary endpoint for the overall population and by age-based subgroups. Efficacy in the two pediatric subgroups (≥12 to <18 years and ≥4 to <12 years) is uncertain because the upper confidence limits for the hazard ratios exceed 1 and the confidence intervals are skewed in favor of AS.

In subjects <12 years of age, in whom only low dose BDA was studied, the results are inconclusive regarding the benefit of BDA 80/180 in preventing severe acute exacerbations [HR:1.09; 95% CI: 0.46, 2.56], as well. Among subjects ≥12 to <18 years of age, the HR for BDA 160/180 vs AS was also inconclusive, again complicated by wide confidence intervals [HR:1.44; 95% CI: 0.54, 3.87]. In both pediatric subgroups, the sample sizes, as well as the number of exacerbation events, were too small to support definitive conclusions regarding effectiveness. As shown in Table 23, in children <12 years of age, there were 10 subjects with exacerbations in the AS control arm and 11 subjects with exacerbation in the BDA arm; among adolescents, there were 7 subjects with exacerbations in the AS arm and 9 subjects with exacerbations in the BDA 160/180 arm. Further complicating interpretation of results in adolescents is the lower number of subjects with exacerbations in the BDA 80/180 arm compared to BDA 160/180 and AS; this dose is not proposed for marketing in this age group.

Figure 7. Age-Based Subgroup Analysis - Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand (Full Analysis Set; All Ages)



Source: Statistical Reviewer and Statistical Analyst using adtte.xpt.

Table 23. Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand[a], Age-based Subgroups (MANDALA, Full Analysis Set; All Ages)

Age Group Treatment Group	N	Number (%) of Subjects With a Severe Exacerbation[b]	Comparison Vs AS MDI 180 Hazard Ratio	95% CI	P-value
≥4 - <12 years					
BDA MDI 80/180	41	11 (26.8)	1.09	0.46, 2.57	0.85
AS MDI 180	42	10 (23.8)			
≥12 - <18 years					
BDA MDI 80/180	32	4 (12.5)	0.57	0.17, 1.96	0.37
BDA MDI 160/180	34	9 (26.5)	1.44	0.54, 3.87	0.47
AS MDI 180	34	7 (20.6)			
≥18 - <65 years					
BDA MDI 80/180	804	189 (23.5)	0.83	0.68, 1.01	0.07
BDA MDI 160/180	787	153 (19.4)	0.68	0.55, 0.83	<0.01
AS MDI 180	783	209 (26.7)			
≥65 years					
BDA MDI 80/180	177	37 (20.9)	0.81	0.53, 1.24	0.34
BDA MDI 160/180	192	45 (23.4)	0.89	0.59, 1.33	0.56
AS MDI 180	197	50 (25.4)			
All adults (≥18 years)					
BDA MDI 80/180	981	226 (23.0)	0.83	0.70, 0.997	0.046
BDA MDI 160/180	979	198 (20.2)	0.72	0.60, 0.86	0.0004
AS MDI 180	980	250 (26.4)			

Source: Clinical Study Report Mandala AV003 Table 14.2.8.2.1.2 (p.1556); modified by Statistical Reviewer.
Note: Hazard ratios and 95% CIs for hazard ratios are estimated using a Cox regression model with treatment group, age, region, number of severe exacerbations in the last 12 months prior to randomization, age subgroup and treatment-by-age subgroup interaction as factors. A hazard ratio less than 1 favors BDA MDI treatment groups.
[a] Under the efficacy estimand, followup for events was censored among subjects who did not experience a severe exacerbation prior to IP discontinuation or a change in maintenance therapy at the earliest occurrence of these intercurrent events.
[b] Deterioration of asthma requiring use of systemic corticosteroids for at least 3 days or inpatient hospitalization, or emergency room visit, that required systemic corticosteroids.

Given the uncertainties described above, we used a Bayesian quantitative framework to further clarify pediatric efficacy, allowing us to evaluate the degree of borrowing from adult data needed to support efficacy in adolescents and children. When such borrowing is zero, Bayesian analyses generally produce the same results as the 'frequentist' analyses we commonly employ to assess statistical significance. In the Bayesian analyses, provided directly below, we focus our attention only on the doses proposed for the label, i.e., the high dose (BDA 160/180) for adolescents (≥12 to <18 years of age) and the low dose (BDA 80/180) in children 4 to <12 years of age. Refer to Appendix 14.4 for more details on this method.

For the analysis of the high dose in adolescents (Table 24), data were borrowed from the adults treated with the high dose or AS alone. For the analysis of the low dose in children (Table 25), data were borrowed from adolescents and adults treated with the low dose or AS alone.

Table 24. Borrowing Required to Establish Efficacy of Budesonide High Dose in Adolescents[a]

Bayesian Weight on Adults in Prior	Median HR	95% CrI for HR	Number of Borrowed Adult Events	Percentage of Total Events from Adults[b]
0	1.41	(0.54, 3.68)	0	0.0%
0.25	0.98	(0.58, 3.35)	95	84.8%
0.5	0.78	(0.60, 2.95)	218	92.8%
0.75	0.75	(0.61, 2.36)	334	95.2%
0.9	0.74	(0.61, 1.62)	403	96.0%
0.95	0.74	(0.61, 0.98)	427	96.2%
1	0.73	(0.61, 0.88)	455	96.4%

HR, hazard ratio; CrI, credible interval
[a] From Bayesian robust mixture prior model described in Appendix Section 14.4
[b] Calculated as borrowed adult events ÷ (borrowed adult events + events among children + 1)

Table 25. Borrowing Required to Establish Efficacy of Budesonide Low Dose in Children[a]

Bayesian Weight on Adults in Prior	Median HR	95% CrI for HR	Number of Borrowed Adult Events	Percentage of Total Events from Adults[b]
0	1.08	(0.47, 2.50)	0	0%
0.25	0.86	(0.55, 2.13)	175	88.8%
0.5	0.84	(0.64, 1.79)	313	93.4%
0.75	0.84	(0.69, 1.34)	409	94.9%
0.9	0.83	(0.70, 1.02)	458	95.4%
0.96	0.83	(0.70, 1.00)	478	95.6%
1	0.83	(0.70, 0.99)	494	95.7%

HR, hazard ratio; CrI, credible interval
[a] From Bayesian robust mixture prior model described in Appendix Section 14.4
[b] Calculated as borrowed adult and adolescent events ÷ (borrowed adult and adolescent events + events among children + 1)

The analyses in Table 24 and Table 25, as well as additional Bayesian analyses provided by the Applicant, show that demonstration of efficacy in pediatric age groups would require inclusion of large amounts of data from adults. In particular, the upper limit of the 'credible interval' (the Bayesian version of the confidence interval) for the hazard ratio would be <1 for pediatric age cohorts only if at least 95% of the data is borrowed from adults. Whether such large amounts of borrowing from adult data is justified is therefore of critical importance, and assessment of pediatric efficacy therefore requires detailed consideration of available knowledge, and gaps in available knowledge, regarding the relationship between the adult and pediatric courses of disease and responses to treatment. As discussed in Section 1, based on a review of the available literature and discussions at the November 8, 2022 Pulmonary-Allergy Drugs Advisory Committee, there is insufficient data to support such a high degree of extrapolation for a novel combination product and indication.

We also looked to the secondary endpoint analyses in pediatric subgroups to gain any further clinical insights into differential treatment responses between age groups, although acknowledging the limitations of these *post hoc* exploratory analyses. Results of secondary endpoints are presented in order of hierarchical ranking by the Applicant.

Table 26 summarizes the secondary endpoint of annualized rate of severe exacerbations, which includes a few more events than in the primary endpoint analysis. Although confidence intervals remain wide, the point estimates are consistent with the primary endpoint in showing an unexpected more favorable trend for BDA 80/180 in subjects ≥12 to <18, unlike subjects >18, for whom BDA 160/180 was superior. In both pediatric subgroups, the number of events was small and was the same between the AS control arm and the proposed-dose BDA arm.

Table 26. Subgroup Analysis by Age—Annualized Severe Exacerbation Rate, Efficacy Estimand (MANDALA, Full Analysis Set)

Secondary Endpoint	Age Subgroup	Treatment Group	Number of Severe Exacerbations	Comparison Vs AS MDI 180		
				Rate Ratio	95% CI	P-value
Annualized severe exacerbation rate	≥4 - <12 years	BDA MDI 80/180 (N=41)	13	0.97	0.34, 2.82	0.96
		AS MDI 180 (N=42)	13			
	≥12 - <18 years	BDA MDI 160/180 (N=34)	10	0.77	0.23, 2.54	0.66
		BDA MDI 80/180 (N=32)	6	0.39	0.10, 1.44	0.16
		AS MDI 180 (N=34)	10			

Source: Summary Clinical Efficacy Tables 42 (p. 97) and 49 (p. 107); modified by Statistical Reviewer.

Table 27 presents results for the endpoint of annualized total SCS dose (mg/subject). This endpoint captured oral, IV, or IM corticosteroids and does not include inhaled corticosteroid exposure. Total SCS exposure in subjects <18 yo was a particular concern for the development program, given the potential for substantial increase in ICS, particularly if BDA is administered in addition to controller ICS. Difference in arithmetic means (%) among subjects 4 to <12 yo favors AS vs BDA; a finding which is reversed when limited to an even smaller cohort of subjects with ≥24 weeks exposure. The significance of these results is not clear.

Table 27. Subgroup Analysis by Age—Total Annualized Dose of Systemic Corticosteroid Exposure in the Randomized Treatment Period, Efficacy Estimand (MANDALA, Full Analysis Set)

			Comparison Vs AS MDI 180		
Secondary Endpoint	Age Subgroup	Treatment Group	n	Difference in Arithmetic Means (%)	P-value
Total annualized dose of systemic corticosteroid (mg/subject)	≥4 - <12 years	BDA MDI 80/180 (N=41)	41	34.3	0.52
		AS MDI 180 (N=42)	41		
	≥12 - <18 years	BDA MDI 160/180 (N=34)	34	-62.0	0.72
				-84.8	0.50
		BDA MDI 80/180 (N=32)	32		
		AD MDI 180 (N=34)	34		

Source: Summary Clinical Efficacy Tables 43 (p. 99) and 50 (p. 108); modified by Statistical Reviewer.

Table 28 and Table 29 summarize results for the two responder analyses for PROs, the ACQ-5 and AQLQ12+. Once again, the only pattern that emerges is that of a point estimate that favors the low dose BDA among adolescents (although with wide confidence intervals), inconsistent with results observed among adult subjects. Given the small sample sizes and *post hoc* nature of these analyses, the significance of this pattern is not clear.

Table 28. Subgroup Analysis by Age—Asthma Control Questionnaire 5-Item Version Minimal Important Difference at Week 24, Efficacy Estimand (MANDALA, Full Analysis Set)

			Number of	Comparison vs AS MDI 180		
Secondary Endpoint	Age Subgroup	Treatment Group	Responders (%)	Odds Ratio	95% CI	P-value
ACQ-5 Minimal important difference at Week 24	≥ 4 - <12 years	BDA MDI 80/180 (N=39)	21 (53.8)	1.27	0.53, 3.08	0.60
		AS MDI 180 (N=41)	20 (48.8)			
	≥12 - <18 years	BDA MDI 160/180 (N=34)	17 (50.0)	1.47	0.56, 3.86	0.44
		BDA MDI 80/180 (N=32)	21 (65.6)	2.90	1.06, 7.94	0.04
		AS MDI 180 (N=34)	14 (41.2)			

Source: Summary Clinical Efficacy Tables 44 (p. 100) and 51 (p. 110); modified by Statistical Reviewer.

Table 29. Subgroup Analysis by Age—Asthma Quality of Life Questionnaire 12 Years and Over at Week 24, Efficacy Estimand (MANDALA, Full Analysis Set)

Secondary Endpoint	Age Subgroup	Treatment Group	Number of Responders (%)	Comparison vs AS MDI 180		
				Odds Ratio	95% CI	P-value
AQLQ+12 Minimal important difference at Week 24	≥12 - <18 years	BDA MDI 160/180 (N=34)	12 (37.5)	1.54	0.52, 4.54	0.44
		BDA MDI 80/180 (N=32)	15 (46.9)	2.36	0.81, 6.87	0.12
		AS MDI 180 (N=34)	9 (27.3)			

Source: Summary Clinical Efficacy Tables 52 (p.111); modified by Statistical Reviewer.

In summary, MANDALA was an adequate and well-controlled trial that contributed the majority of data to support SEE. The strengths of the trial design included the exacerbation primary endpoint, clinically meaningful secondary endpoints, and administration of the IP PRN in addition to maintenance inhalers to mirror intended real-world use. Results for the primary endpoint and several key secondary endpoints in adults and in all subjects >12 combined demonstrated statistically robust differences between BDA 160/180 and AS. Subgroup analyses in pediatric subjects were inconclusive. This trial enrolled 100 adolescents and 83 children, comprising 3% and 2.6% of the randomized population, respectively. Pediatric subjects, on average, also experienced shorter duration treatment periods because of the event-driven design and very few exacerbation events overall. Further analyses demonstrated the need to extrapolate approximately 95% of data from adults to support benefit. As discussed in Section 1, there was insufficient data to support such a high degree of extrapolation for a novel combination product and indication.

8.2.2. DENALI Trial Design

Trial Design

The primary objective of DENALI was to assess the contribution of both ICS and SABA components of BDA to the effect on lung function when administered as a standing, relatively high dose (4 times daily (QID) or 8 inhalations a day). DENALI was a phase 3, randomized, double-blind, active comparator- and placebo-controlled, 12-week trial to evaluate the safety and efficacy of BDA on FEV1 in pediatric and adult subjects with moderate to severe asthma. The study schema is shown below in Figure 8. Subjects administered all IPs QID. Throughout the treatment period, subjects remained on background maintenance therapy for asthma, if taking. Subjects ≥ 12 years were randomized 1:1:1:1:1 to the following interventions:

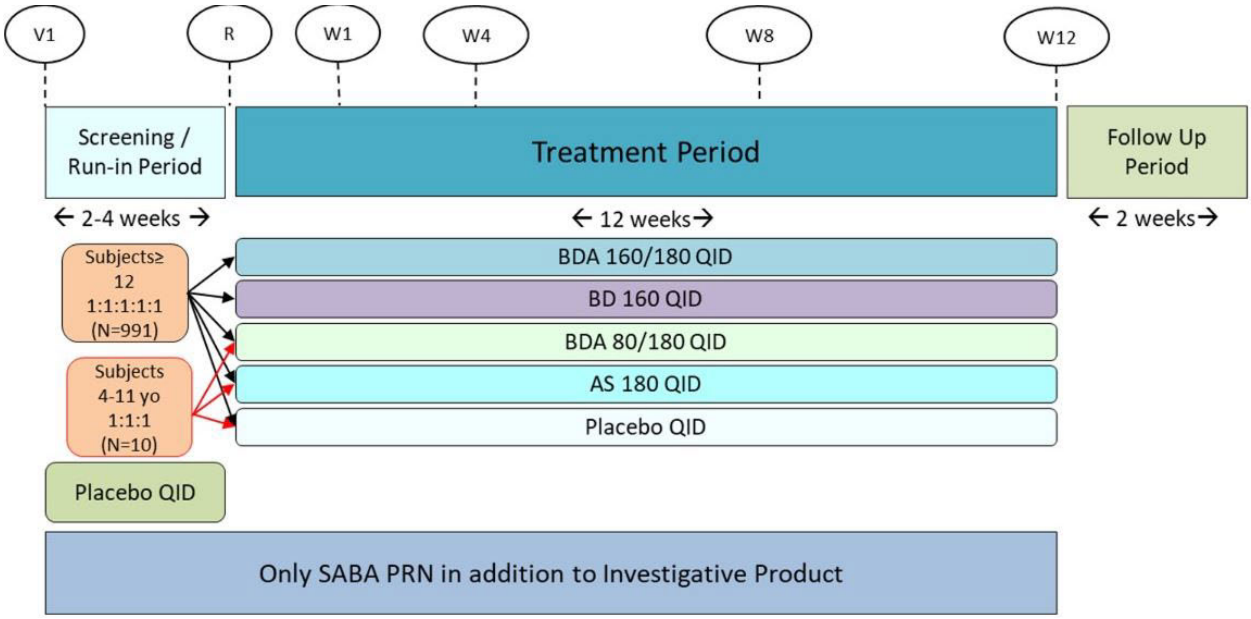
- BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg per puff) QID
- BDA MDI 80/180 µg (given as 2 actuations of BDA MDI 40/90 µg per puff) QID
- BD MDI 160 µg (given as 2 actuations of BD MDI 80 µg per puff) QID

- AS MDI 180 µg (given as 2 actuations of AS MDI 90 µg per puff) QID
- Placebo MDI (given as 2 actuations) QID

Subjects 4-11 years were randomized 1:1:1 to the following interventions only:

- BDA MDI 80/180 µg (given as 2 actuations of BDA MDI 40/90 µg per puff) QID
- AS MDI 180 µg (given as 2 actuations of AS MDI 90 µg per puff) QID
- Placebo MDI (given as 2 actuations) QID

Figure 8. DENALI Study Schema



Source: Clinical Reviewer.

The schedule of Assessments is shown below (Table 30), and key aspects of the study visits are summarized here:

- The screening / run-in period lasted 14-28 days. During this period, subjects were supplied with placebo and Ventolin HFA and instructed to use the former QID and the latter PRN, as they would use their SABA prior to enrollment. At visit 2, compliance with placebo was assessed, and qualifying subjects were randomized.
- Randomization for all subjects ≥12 years was stratified by age (≥12 to 17, ≥18); screening ACQ-7 (≤1.5, >1.5), and background therapy (ICS vs no ICS). Randomization for subjects 4-11 years was not stratified.

- The end-of-treatment (EOT) visit occurred at Visit 6 (week 12). Subjects who discontinued IP early were encouraged to undergo a premature discontinuation visit (PDV).
- Following the treatment period, there was a 2-week safety follow up period.

Table 30. DENALI Schedule of Assessments

	Screening (run-in)[b]	*Double-blind Treatment Period*					PDV[d] (if applicable)	*Safety Follow-up TC*
Visit[a]	*1 (1/1a)*	*2*	*3*	*4*	*5*	*6*[c]		*(2 weeks [±4 days] after treatment discontinuation)*
Week	*-4 to -2*	*0*	*1*	*4*	*8*	*12*		
Day	*-28 to -14*	*1*	*7±2*	*28±2*	*56±2*	*84±2*		
Informed consent	X							
Eligibility criteria	X	X						
Routine clinical procedures								
Medical/surgical history (including any on-study medical/surgical procedures)[e]	X	X	X	X	X	X	X	
Demography	X							
Physical examination[f]	X					X	X	
Concomitant medications	X	X	X	X	X	X	X	X
SABA reversibility test[g]	X							
Safety measurements								
Vital signs (HR and BP only)	X	X	X	X	X	X	X	
12-lead ECG	X	X				X	X	
Adverse events	X	X	X	X	X	X	X	X
Pregnancy test[h]	X	X	X	X	X	X	X	
Safety laboratory assessments (clinical chemistry, hematology)	X					X	X	

	Screening (run-in)[b]	Double-blind Treatment Period					PDV[d] (if applicable)	Safety Follow-up TC
Visit[a]	1 (1/1a)	2	3	4	5	6[c]		(2 weeks [±4 days] after treatment discontinuation)
Week	-4 to -2	0	1	4	8	12		
Day	-28 to -14	1	7±2	28±2	56±2	84±2		
Efficacy measurements								
Spirometry (FEV_1)[j]	X	X	X	X	X	X	X	
ACQ-5	X	X	X	X	X	X	X	
ACQ-7	X	X	X	X	X	X	X	
AQLQ+12/PAQLQ		X		X	X	X	X	
Review of PEF, use of Ventolin therapy, asthma daytime/night-time symptoms, night-time awakenings due to asthma symptoms[f]		X	X	X	X	X	X	
Dispense/collect eDiary (AM3+)	X					X	X	
Review compliance with eDiary		X	X	X	X	X	X	
Investigational product administration								
IP compliance		X	X	X	X	X	X	
Randomization		X						
IP (dispense/collect)[k]	d	c/d[k]	c/d	c/d	c/d	c/d[m]	c/d[m]	
Ventolin (collect/dispense)	d	c/d[l]	c/d[l]	c/d[l]	c/d[l]	c	c	
Ventolin administration (recorded in MasterScope)	X							
IP administration (recorded in MasterScope)[m]		X	X	X	X	X	X	

Abbreviations: ACQ-5=Asthma Control Questionnaire-5; ACQ-7=Asthma Control Questionnaire-7; AQLQ+12= Asthma Quality of Life Questionnaire for 12 years and older; β-hCG= β -human chorionic gonadotropin; BP=blood pressure; c= collect; d=dispense; eDiary=electronic diary; ECG=electrocardiogram; FEV_1= forced expiratory volume in 1 second; HR=heart rate; IP=investigational product; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PDV= premature discontinuation visit; PEF= peak expiratory flow; QID=4 times daily; SABA=short/rapid-acting β2-adrenoreceptor agonist; TC=telephone contact; V=visit

[a] Repeat assessments/visits, if needed, will be captured in unscheduled visits.

[b] Screening (run-in) Period may be 14 to 28 days. Visit 1 may be split (used for repeated assessments, if needed) for the repeat assessment of SABA reversibility test, if applicable.

[c] Planned end-of-treatment (EOT) will occur at Visit 6.

[d] Subjects who prematurely withdraw (withdraw pre-week 12) from study treatment will undergo a PDV.

[e] Details of any surgical procedures occurring during randomization and the treatment period will be also recorded.

[f] Includes evaluation of height, body mass index, and weight at Visit 1 and weight only for Visit 6 or PDV.

[g] Demonstrate reversibility at Visit 1, with an increase in FEV_1 ≥15% relative to baseline after administration of Sponsor-provided Ventolin via central spirometry at either Visit 1 (reversibility must be demonstrated at either Visit 1 or Visit 1a); Visit 1a will be used for re-testing, if needed; with only 1 reversibility re-test permitted prior to randomization (Visit 2).

[h] A serum pregnancy test (β-hCG) will be performed at Visits 1 and treatment discontinuation (EOT) or PDV; urine β-hCG test will be performed at all other visits (for women of childbearing potential only).

[i] Pre-bronchodilator (Visit 1/Visit 1a)/ Pre-dose (Visit 2 onwards) FEV_1 will be measured in the morning between 06:00 and 10:00 AM at the designated visits in Table 1, and within 1 hour of FEV_1 measured at Visit 2. Pre-bronchodilator FEV_1 of ≥50 to <85% predicted normal value for adults (≥18 years of age) and ≥50% predicted normal value for subjects aged 4 to 17 years after withholding SABA ≥6 hours (at Visit 1 or Visit 1a, if applicable). If subject took SABA within 6 hours in the morning of Visit 1, either the entire visit must be rescheduled or just PFT assessment rescheduled. At Visit 1, pre- and post- dose will be with respect to administration of Sponsor-provided bronchodilator (Ventolin). From Visit 2 onwards, pre- and post- dose measurements will be with respect to administration of IP.

[j] The eDiary (AM3+) will be dispensed at screening.

[k] All subjects will be assigned placebo during the run-in period for dosing QID. Compliance to dosing should be reviewed prior to randomization.

[l] Ventolin usage to be reviewed at each collection/dispensing visit using eDiary. Replacement kit dispensed as required. The actuator should be cleaned once per week if used in the last 7 days according to instruction summarized in Appendix J, Metered-dose Inhaler Handling and Cleaning.

[m] IP should be taken in the morning upon waking, and then distributed equally throughout the day with the final dose taken before going to sleep. The evening before clinic visits, subjects should be advised to take the last dose at 22:00 (10:00 PM) ±2 hours. For all on-treatment visits, IP should be administered before 10:00 AM in the clinic using newly dispensed IP. The actuator should be cleaned once per week if used in the last 7 days according to instruction summarized in Appendix J, Metered-dose Inhaler Handling and Cleaning.

[n] IP will be dispensed at Visit 6 and PDV for performance of FEV_1 measurements only, this will not be taken home by the subjects. IP dispensed at these visits will be retained at the site following the visit and reconciled for IP accountability.

Table 31. DENALI Timed Assessment Visits 2-6 and Premature Discontinuation Visit

Clinical Variable	Pre-Dose		IP Dose	Post-Dose									
	-60 min	-30 min	0 min	5 min	15 min	30 min	45 min	60 min	120 min	180 min	240 min	300 min	360 min
IP Collection[h]	X[a]												
IP Dispensing[i]	X[a]												
IP Dosing[j]			X										
Questionnaires ACQ-5 ACQ-7 AQLQ+12/PAQLQ	X[a,b]												
Review of Electronic Diary	X[a]												
Vital Signs[c]	X[a,d]												
12-Lead ECG	X[a,e]												
Clinical Laboratory Testing	X[a,f]												
Spirometry (FEV_1)[g]	X	X		X	X	X	X	X	X	X	X	X	X

Abbreviations: ACQ-7=Asthma Control Questionnaire 7, AQLQ+12= Asthma Quality of Life Questionnaire for 12 years and older; ECG=electrocardiogram; FEV_1= forced expiratory volume in 1 second; IP=investigational product; min=minute; PAQLQ=Pediatric Asthma Quality of Life Questionnaire; PDV= premature discontinuation visit

Note: Time point for dosing is regarded as "0 minutes". When data collection time-points are concurrent, variables should be collected in the following order: Questionnaires, vital signs, ECG, clinical laboratory assessments, and spirometry.

a. *This is not a timed assessment. Sites should plan to perform these activities to allow for collection of timed spirometry.*
b. *Questionnaires (ACQ-5, ACQ-7, AQLQ+12, and PAQLQ) are collected at all visits (except Visit 3 AQLQ+12, and PAQLQ).*
c. *Vital signs should be started (approximately 5 to 10 minutes) ahead of the specified time point to ensure spirometry will be conducted as close to the specified time points as possible.*
d. *Pre-dose vital signs (heart rate, blood pressure) will be collected twice, at least 5 minutes apart.*
e. *Pre-dose ECG will be collected at Visit 2, Visit 6, and PDV only, or as clinically indicated.*
f. *All clinical laboratory tests (hematology and chemistry) will be assessed approximately 60 minutes prior to dosing at Visit 6 in advance of first spirometry measurement. Laboratory tests may be performed at all other visits as clinically indicated.*
g. *Every effort should be made to assess subjects' trough pre-dose and post-dose FEV_1 at the same time throughout the study. Pre-dose FEV_1 will be measured in the mornings between 06:00 and 10:00 AM, and within 1 hour of FEV_1 measured at Visit 2. From Visit 2 onwards, pre- and post-dose measurements will be with respect to administration of IP (Table 3).*

8.2.2.1. Study Endpoints

Primary Endpoint

The dual primary endpoints were change from baseline in FEV1 $AUC_{0\text{-}6hours}$ over 12 weeks and change from baseline in trough FEV1 at week 12.

- All spirometry was performed using equipment from a centralized vendor and with strict adherence to American Thoracic Society (ATS) standards.

Secondary Endpoints

1. Derivation of time to onset of 15% increase in FEV1 on day 1 and duration of effect on day 1. The duration of effect for each subject was defined as the time from onset of at least a 15% increase in FEV1 to the offset of the 15% increase in FEV1 relative to baseline. If the offset was not achieved in the assessment period (up to 360 minutes), the last available time was used.
2. Number of subjects who have an ACQ-7 of ≥1.5 at baseline who achieve a clinically meaningful improvement (decrease of ≥0.5 units) at week 12.
3. Trough FEV1 at week 1.

Safety Endpoints

1. Adverse events / serious adverse events.
2. Vital signs.
3. Clinical chemistry and hematology parameters.
4. Electrocardiogram.

8.2.2.2. Study Population

Key Inclusion Criteria

1. Subjects ≥ 4 years of age with asthma as defined by GINA criteria for at least 6 months.
2. Receiving 1 of the following inhaled asthma medications with stable dosing for at least 1 month:
   a. SABA PRN
   b. Stable low-dose ICS with PRN SABA. For definition of "low" dose refer to Section 8.2.1.
3. Prebronchodilator FEV1 ≥50 to <85% predicted normal for adults, and ≥50% predicted normal for subjects aged 4 to 17 years.
4. Use of Ventolin ≥2 days out of 7 prior to visit 2.
5. BMI < 40 kg/m2.

Key Exclusion Criteria

1. COPD or other significant lung disease.
2. SCS use within 3 months before visit 1 and ≥3 weeks of SCS within 6 months prior.
3. Receipt of any biologics, marketed or investigational, within 3 months or 5-half-lives before visit 1, whichever is longer.
4. Current smokers or former smokers with > 10 pack-year history or cessation <6 months of visit 1.
5. Asthma with previous history of intubation for hypercapnia, respiratory arrest, hypoxic seizures, or syncope.
6. Use of ≥12 actuations per day of Ventoin during run-in period:
   a. ≥2 days out of 14
   b. ≥3 days out of 15-21
   c. ≥4 days out of 22 or more.
7. Pregnant, lactating, or unable or willing to use appropriate contraceptive methods.

8.2.2.3. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

IP compliance was recorded in the subject's eDiary and from dose indicator readings from returned kits.

Permitted Concomitant Medications and Prohibited Medications

During the study period, the only permitted asthma medications were the IP and Applicant-provided Ventolin to be used PRN for asthma symptoms. All other asthma medications were prohibited.

Rescue Therapy

Use of rescue Ventolin was recorded by the eDiary. Prohibited therapies could be initiated if needed for worsening asthma.

8.2.2.4. Statistical Analysis Plan

Analysis Sets

- The full analysis set (FAS) was defined as all subjects who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment. Subjects were analyzed according to the treatment they were assigned to at randomization.
- The safety analysis set was defined as all subjects receiving at least 1 puff of randomized treatment. Subjects were classified based on treatment they actually received.

Estimands

The primary estimand of interest was the efficacy estimand, defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study, regardless of actual compliance.

Sample Size Calculation

A blinded sample size re-estimation was to be performed once 44% of subjects had completed week 12. A second blinded sample size re-estimation was to be performed once approximately 65% of the revised sample size had completed 12 weeks and prior to the last subject was randomized. Final total enrolment in the study was to be confirmed following the second blinded sample size re-calculation in order to ensure 90% power.

Prior to the blinded sample size re-estimation, randomization of approximately 120 subjects to each treatment group expected provide at least 93% probability to detect a 100 mL difference

in the change from baseline in trough FEV1 at Week 12 for comparison of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation was based on a standard deviation of 210 mL obtained from the placebo MDI group of Study PT008001 and an assumed dropout rate of 10% and 15% for active and placebo treatment group, respectively, prior to Week 12.

Prior to the blinded sample size re-estimation, it was assumed that the sample size of 120 subjects per treatment group would also provide >99% probability to detect a 130 mL difference in FEV1 $AUC_{0\text{-}6hours}$ over 12 weeks for comparison of BDA MDI versus BD MDI (effect sizes for AS MDI or BDA MDI versus placebo MDI should be considerably larger). This calculation assumed a 2% dropout prior to Week 1 and an effective standard deviation of 140 mL which was derived from the following: a per visit standard deviation of 200 mL (AS MDI Dose-Ranging Study DC6930C00001), a correlation between visits of 65%, and projected subject completion of 4 out of 5 visits.

Based on the blinded estimate of variability, approximately 1000 subjects were required in order to demonstrate 85% probability to detect a 100 mL difference in the change from baseline in trough FEV1 at Week 12 for the comparison of BD MDI versus placebo MDI, BDA MDI versus placebo MDI, or BDA MDI versus AS MDI. This calculation was based on a standard deviation of 320 mL obtained from the second blinded sample size re-estimation performed after 65% of subjects completed week 12. An overall dropout rate of 7% prior to Week 12 was calculated from this data. Consequently, the total randomized adult and adolescent subjects were increased to 1000 in order to ensure sufficient power.

Primary Efficacy Analysis Model

The dual-primary endpoints, change from baseline in FEV1 $AUC_{0\text{-}6\ hours}$ over the 12-week period, and change from baseline in trough FEV1 at week 12 were each analyzed using a repeated measures (RM) linear model to compare treatment groups. The model included baseline FEV1, percentage reversibility to Ventolin, and age as continuous covariates, and visit, treatment, the treatment-by-visit interaction, and Pre-study background therapy (ICS, non-ICS) as categorical covariates. Under the efficacy estimand, only windowed data prior to treatment discontinuation were included in the primary analysis. The presentation of analysis results included the least squares mean estimates for each treatment and the least squares mean differences between the treatment groups, along with associated 95% confidence intervals and p-values. An unstructured variance-covariance matrix was implemented. Missing data were assumed to be missing at random (MAR) under the efficacy estimand.

Tipping point analysis under the missing not at random assumption (MNAR) was conducted using multiple imputation. For subjects in the BDA MDI groups, and subjects in AS MDI and BD MDI when comparing to placebo MDI, this method imputed missing values post-study discontinuation for lack of asthma control assuming they were more likely to have a worse outcome than as implied under the missing at random assumption (MAR). The tipping point analysis incrementally penalized the missing data under the missing not at random assumption

until a non-statistically significant comparison was observed in the sequential testing strategy. Upon completion of the MAR and MNAR steps, the 50 multiple imputed datasets of complete data were analyzed individually and aggregated using Rubin's rule (Rubin, 1987).

Secondary Efficacy Analysis Model

For all secondary analyses the same treatment comparisons as for the primary analysis was conducted on the FAS >=12 years.

- The median time to onset (defined as 15% increase in FEV1) over the pre-treatment value at randomization (Visit 2) was compared among treatment groups using a Wilcoxon rank sum test. Confidence intervals for the median treatment difference were calculated using the Hodges-Lehmann method. Only the patients who achieved the 15% increase in FEV1 within 30 minutes post-dose were to be included in the analysis.
  - For these secondary analyses, all efforts from the serial spirometry were used. Additionally, the proportion of patients achieving a 15% increase in FEV1 within 30 minutes post-dose on Day 1 were analyzed using a logistic regression model with treatment and prestudy background therapy (ICS, Non-ICS) as categorical covariates, and baseline FEV1 score and age as continuous covariates. The odds ratios and corresponding 95% confidence interval along with p-values were estimated from the model.
- The primary analyses of ACQ-7 were conducted in subjects that are uncontrolled at baseline (i.e., baseline ACQ-7 ≥ 1.5) as these are the subjects capable of demonstrating a clinically meaningful response with treatment. Only data from first dose up to the last dose of randomized treatment contributed to analyses of ACQ-7. The analysis of ACQ-7 in the population of patients indicating partially controlled to uncontrolled asthma at baseline (ACQ-7≥0.75) was considered as an exploratory analysis. The responder variable at Week 12 was analyzed using a logistic regression model with treatment and previous ICS use (Yes/No) as categorical covariates, and baseline ACQ-7 score, baseline post-dose percent predicted FEV1 and age as continuous covariates. From the logistic regression model treatment effects was estimated by odds ratios and corresponding 95% confidence interval along with p-values. Subjects who discontinued treatment for any reason were classified as non-responders. The frequency and percentage of responders was summarized descriptively for all study visits.
  - The treatment effect for change from baseline in ACQ-7 was estimated using a repeated measures analysis. All data up to Week 12 were included in the model, with terms for age, treatment, visit, treatment*visit, prior ICS use (Yes/No), baseline ACQ-7 score, and baseline post-dose percent predicted FEV1. Visit was fitted as a categorical variable, and the variance-covariance matrix was assumed to be unstructured. If the procedure did not converge, then a heterogeneous TOEPH was to be used instead. This model was used to give an overall assessment of the treatment effect as well as 95% confidence intervals. Data postdiscontinuation of randomized treatment did not contribute to the analyses.

Multiplicity Adjustment

The planned treatment comparisons for the primary analysis were sequentially tested in the 8-step sequence as specified below. Comparisons were stopped if a non-statistically significant result occurred (alpha = 0.05, two-sided). All comparisons were of superiority.

Change from baseline in FEV1 $AUC_{0\text{-}6hours}$ over 12 weeks:

1. AS MDI 180 µg QID vs Placebo MDI QID
2. BDA MDI 160/180 µg QID vs Placebo MDI QID
3. BDA MDI 160/180 µg QID vs BD MDI 160 µg

Change from baseline in trough FEV1 at Week 12:

1. BD MDI 160 µg QID vs Placebo MDI QID
2. BDA MDI 160/180 µg QID vs Placebo MDI QID
3. BDA MDI 160/180 µg QID vs AS MDI 180 µg QID

Statistical testing for BDA 80/180 µg proceeded in a similar manner as for BDA 160/180 µg, as shown below.

Change from baseline in trough FEV1 at Week 12:

1. BDA MDI 80/180 µg QID vs Placebo MDI QID
2. BDA MDI 80/180 µg QID vs AS MDI 180 µg QID

The comparison of BDA MDI 160/180 µg vs AS MDI 180 µg excluded the child subjects aged 4 to 11 years as they were not randomized to BDA MDI 160/180 µg. The above tests in steps 1 to 8 excluded children (age 4 to 11 years).

Protocol Amendments

Between the original submission on December 17, 2018 and the final version submitted on July 6, 2020, there were two protocol amendments. The first amendment, submitted in 2019, contained non-substantial clarifying language. The second, in 2020, modified enrollment criteria to permit easier enrollment of subjects 4-11 years old, addressed safety parameters in the context of the COVID-19 pandemic, and increased the planned sample size.

Table 32. SAP Amendment History

Date (version)	Brief description of change

16th March 2021 (V2.0)	Included text on decision following the second blinded sample size reassessment. In order to support the integrated summary of safety analyses, the total daily number of puffs of randomized treatment, grouped by actual treatment received and based on the safety analysis set will be displayed in summaries of exposure. In order to support the integrated summary of safety analyses, additional adverse events summary tables will now be reported with incidence rates/event rates, as appropriate. In order to support the integrated summary of safety, summaries of adverse events and serious adverse events will be reported within subgroups specified. Clarification added for exploratory endpoints of night-time awakenings and asthma symptom score.
28th July 2021 (V3.0)	Added the COVID-19 estimand. Added supportive analysis to the primary endpoint where the data collected following the onset of a COVID-19 related adverse event or dose interruption are excluded from the analysis. Derivation of stratification factors for patients aged 4 to 11 years added. Detailed methodology for handling duplicate patients. Clarified how the analyses populations will be used when making treatment group comparisons.

Source: Statistical Analysis Plan, p.9.

8.2.2.5. Study Results

Patient Disposition

Subjects disposition is summarized in Table 33. Among the 1001 randomized subjects, the overall early treatment discontinuation rate was 7.2% and the discontinuation rate was the highest in the placebo arm (10.6%). A major reason for treatment discontinuation was “subject decision” (3.5%) and twelve subjects (1.2%) discontinued the randomized treatment due to adverse event. Overall study withdrawal rate was 7.2%, indicating that subjects who discontinued randomized treatment have also discontinued from the study. A major reason for study discontinuation was “withdrawal by subject” (3.3%).

Table 33. Subject Disposition (Randomized)

	Number of Subjects, n (%)					
Randomized	BDA MDI (160/180 µg) N = 197	BDA MDI (80/180 µg) N = 204	BD MDI (160 µg) N = 200	AS MDI (180 µg) N = 201	Placebo MDI N = 199	Total N = 1001
Subjects who discontinued randomized treatment[1]	7 (3.6)	16 (7.8)	11 (5.5)	17 (8.5)	21 (10.6)	72 (7.2)
Subject decision	2 (1.0)	10 (4.9)	6 (3.0)	9 (4.5)	8 (4.0)	35 (3.5)
Adverse event	2 (1.0)	1 (0.5)	3 (1.5)	2 (1.0)	4 (2.0)	12 (1.2)
Severe non-compliance to protocol[2]	0	2 (1.0)	1 (0.5)	0	2 (1.0)	5 (0.5)
Condition under investigation worsened	0	0	0	1 (0.5)	1 (0.5)	2 (0.2)
Lack of therapeutic response	0	0	0	2 (1.0)	2 (1.0)	4 (0.4)
Subject lost to follow-up	0	0	0	1 (0.5)	0	1 (0.1)
A severe exacerbation event	0	0	0	0	3 (1.5)	3 (0.3)
Other	3 (1.5)	3 (1.5)	1 (0.5)	2 (1.0)	1 (0.5)	10 (1.0)
Subjects withdrawn from study[2]	7 (3.6)	16 (7.8)	11 (5.5)	17 (8.5)	21 (10.6)	72 (7.2)
Adverse event	2 (1.0)	1 (0.5)	3 (1.5)	2 (1.0)	4 (2.0)	12 (1.2)
Development of study specific discontinuation criteria	0	0	0	0	1 (0.5)	1 (0.1)
Lost to follow-up	0	0	0	2 (1.0)	0	2 (0.2)
Protocol deviation	0	2 (1.0)	1 (0.5)	1 (0.5)	2 (1.0)	6 (0.6)
Withdrawal by subject	2 (1.0)	10 (4.9)	5 (2.5)	9 (4.5)	7 (3.5)	33 (3.3)
Withdrawal by parent/guardian	0	0	1 (0.5)	0	0	1 (0.1)
Other	3 (1.5)	3 (1.5)	1 (0.5)	3 (1.5)	7 (3.5)	17 (1.7)

Source: Adapted from Clinical Study Report Table 6, p.81

[1] Patients who discontinued treatment prior to the end of the 12-week treatment period

[2] Completed the study corresponds to attending Week 12 scheduled visit and 2-week safety follow-up

Protocol Violations/Deviations

In total, 2.2% of subjects had at least 1 important protocol deviation. The majority of these (2.1%) were related to receiving the incorrect IP or dose, and 1 (0.1%) was related to development of discontinuation criteria but continuation in the trial. None of these deviations were considered to affect the quality of the study or the overall interpretation of results.

Table of Demographic Characteristics

The DENALI population was characterized by a mean age of 48 years and was also predominantly white (87%) and female (64%). Unlike MANDALA, which enrolled patients with moderate to severe disease, the DENALI population was representative of mild to moderate asthma with approximately half of subjects taking only PRN SABA prior to enrollment and half taking PRN SABA in combination with low or medium dose ICS. These characteristics were balanced across treatment arms, as was the mean reversibility to Ventolin at screening (28%).

Table 34. DENALI, Baseline Demographic Characteristics of Full Analysis Set

Characteristic	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=200)	Placebo MDI (N=199)
Sex (n%)					
F	125 (63.5)	128 (62.7)	120 (60.3)	120 (60.0)	127 (63.8)
M	72 (36.5)	76 (37.3)	79 (39.7)	80 (40.0)	72 (36.2)
Age, years					
Mean (SD)	50.0 (15.80)	48.7 (16.79)	48.3 (15.80)	47.0 (16.79)	48.6 (15.82)
Median (Min, Max)	51.0 (13, 81)	51.0 (8, 80)	49.0 (13, 90)	49.0 (10, 81)	51.0 (6, 85)
Ethnicity (n%)					
Not Hispanic or Latino	136 (69.0)	142 (69.6)	149 (74.9)	155 (77.5)	136 (68.3)
Hispanic or Latino	61 (31.0)	62 (30.4)	50 (25.1)	45 (22.5)	63 (31.7)
Race (n%)					
White	179 (90.9)	185 (90.7)	180 (90.5)	166 (83.0)	174 (87.4)
Black or African American	14 (7.1)	15 (7.4)	18 (9.0)	30 (15.0)	19 (9.5)
Other	2 (1.0)	4 (2.0)	1 (0.5)	3 (1.5)	4 (2.0)
American Indian or Alaska native	1 (0.5)	0	0	1 (0.5)	1 (0.5)
Asian	1 (0.5)	0	0	0	1 (0.5)
Region (n%)					
USA	100 (50.8)	106 (52.0)	100 (50.3)	106 (53.0)	109 (54.8)
UKR	44 (22.3)	44 (21.6)	43 (21.6)	32 (16.0)	40 (20.1)
DEU	28 (14.2)	30 (14.7)	27 (13.6)	29 (14.5)	24 (12.1)
CZE	12 (6.1)	12 (5.9)	12 (6.0)	17 (8.5)	18 (9.0)
ARG	9 (4.6)	11 (5.4)	14 (7.0)	14 (7.0)	6 (3.0)
SRB	3 (1.5)	1 (0.5)	3 (1.5)	2 (1.0)	2 (1.0)
SVK	1 (0.5)	0	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: FASFL = 'Y'. Sex (n%) - Dataset: Demographics; Filter: FASFL = 'Y'. Age, years - Dataset: Demographics; Filter: FASFL = 'Y'. Ethnicity (n%) - Dataset: Demographics; Filter: FASFL = 'Y'.Race (n%) - Dataset: Demographics; Filter: FASFL = 'Y'. Region (n%) - Dataset: Demographics; Filter: FASFL = 'Y'.
SD = Standard Deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

As in MANDALA, compliance was assessed by eDiary entry and investigator assessment. Overall compliance with randomized study treatment was high (90%) and balanced across treatment arms. Only 5 subjects experienced severe non-compliance, which counted as a protocol deviation.

Efficacy Results – Dual Primary Endpoints

Table 35 summarizes the dual primary endpoints result. Dual primary endpoints assessed the change from baseline in FEV1 area under the curve (AUC) from 0 to 6 hours post-inhalation, averaged over all treatment visits, and the change from baseline in trough FEV1 at the end of the treatment period, week 12. All subjects ≥12 are pooled in the FAS analysis; the adolescent cohort comprised 2.5% of the population (25 out of 999). Under the hierarchical testing

procedure to control type-I error for multiple comparisons, BDA demonstrated a statistically significant benefit compared to placebo, AS, and BD 160.

Table 35. FEV1 $AUC_{0\text{-}6hours}$ Over the 12-Week Period and Trough FEV1 at Week 12, Efficacy Estimand[1] (Full Analysis Set ≥12 Years)

Dual Primary Endpoints	Visit	Comparison	Least Squares (LS) Mean	Comparison Between Groups: Diff in LS Means	95% CI	P-value
Change from baseline in FEV1 $AUC_{0\text{-}6hours}$ (mL)	Treatment average over 12 weeks	AS MDI 180 (N=196) vs Placebo MDI (N=196)	157.2 vs 96.7	60.5	7.7, 113.4	0.03
		BDA MDI 160/180 (N=197) vs Placebo MDI (N=196)	258.6 vs 96.7	161.9	109.4, 214.5	<0.01
		BDA MDI 160/180 (N=197) vs BD MDI 160 (N=199)	258.6 vs178.0	80.7	28.4, 132.9	<0.01
Change from baseline in trough FEV1 (mL)	Week 12	BD MDI 160 (N=199) vs Placebo MDI (N=196)	108.9 vs 35.6	73.3	4.5, 142.1	0.04
		BDA MDI 160/180 (N=197) vs Placebo MDI (N=196)	135.5 vs 35.6	99.9	31.0, 168.7	0.01
		BDA MDI 160/180 (N=197) vs AS MDI 180 (N=196)	135.5 vs 2.7	132.8	63.8, 201.9	<0.01
		BDA MDI 80/180 (N=200) vs Placebo MDI (N=196)	123.5 vs 35.6	87.9	18.9, 156.8	0.01
		BDA MDI 80/180 (N=200) vs AS MDI 180 (N=196)	123.5 vs 2.7	120.8	51.6, 190.0	<0.01

Source: Clinical Study Report Table 14, p.110; results reproduced by Statistical Reviewer and Statistical Analyst using adre.xpt.
AS, Albuterol Sulfate; BD, Budesonide; BDA, Budesonide/Albuterol Sulfate; Diff, Difference; MDI, Metered Dose Inhaler; FEV1, forced expiratory volume in 1 second; $AUC_{0\text{-}6hours}$, area under the curve from 0 to 6 hours; CI, confidence interval; N, number of patients in treatment group
The dual-primary endpoints were modelled separately using a repeated measures model with baseline FEV1, percentage reversibility to Ventolin and age as continuous covariate, and visit, treatment, treatment-by-visit interaction, and prior inhaled corticosteroid use (Yes/No) as categorical covariates. An unstructured covariance matrix structure was used.
A sequential testing strategy was used such that the hypothesis tests are listed in the table in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance. Children (≥4 to <12 years) were excluded in the tests. Includes data from the date of first dose up to the date of last dose of randomly assigned treatment.
[1]The efficacy estimand was defined as the effect of the randomized treatment in all subjects assuming continuation of randomized treatment for the duration of the study, regardless of actual compliance.

Efficacy Results – Secondary and Other Relevant Endpoints

For the analysis of time to onset and duration of response in FEV1 on day 1, response was defined as a ≥ 15% improvement over the pre-treatment value in FEV1 within 30 minutes after the first dose on Day 1. The time to onset of response was defined as the time to a ≥ 15% improvement in FEV1 within 30 minutes over pre-treatment value following the first dose on Day 1. Duration of response was defined as the duration of this ≥ 15% improvement in FEV1. Table 36 summarizes number (percentage) of subjects achieving a response (FAS ≥ 12 years). The number of responders were similar for both BDA arms and AS arm. The percentage of subjects who responded within 30 minutes was 49.7% for the high dose BDA and 44.0% for the low dose BDA compared to 42.9% in the AS, 13.3% in the placebo, 13.6% in the BD 160 arms.

Table 36. Analysis of Subjects Achieving a 15% Increase in FEV1 Over the Pretreatment Value on Day 1, Logistic Regression (FAS ≥ 12 years)

Comparison	Number (%) of responders	Comparison Between Groups		
		Odds Ratio	95% CI	P-value
AS MDI 180 (N=196) vs Placebo MDI (N=196)	84 (42.9) vs 26 (13.3)	5.8	3.5, 9.8	<0.01
BD MDI 160 (N=199) vs Placebo MDI (N=196)	27 (13.6) vs 26 (13.3)	1.04	0.6, 1.9	0.90
BDA MDI 80/180 (N=201) vs Placebo MDI (N=196)	88 (44.0) vs 26 (13.3)	5.8	3.5, 9.8	<0.01
BDA MDI 160/180 (N=197) vs Placebo MDI (N=196)	98 (49.7) vs 26 (13.3)	7.4	4.4, 12.4	<0.01
BDA MDI 80/180 (N=201) vs AS MDI 180 (N=196)	88 (44.0) vs 84 (42.9)	1.004	0.7, 1.5	0.98
BDA MDI 160/180 (N=197) vs AS MDI 180 (N=196)	98 (49.7) vs 84 (42.9)	1.3	0.8, 1.9	0.25
BDA MDI 80/180 (N=201) vs BD MDI 160 (N=199)	88 (44.0) vs 27 (13.6)	5.6	3.4, 9.3	<0.01
BDA MDI 160/180 (N=197) vs BD MDI 160 (N=199)	98 (49.7) vs 27 (13.6)	7.1	4.3, 11.9	<0.01
BDA MDI 160/180 (N=197) vs BDA MDI 80/180 (N=201)	98 (49.7) vs 88 (44.0)	1.3	0.8, 1.9	0.25

Source: Clinical Study Report Table 15, p.115; modified by Statistical Reviewer.
AS, albuterol sulfate; BD, budesonide; BDA, budesonide/albuterol sulfate; CI, Confidence interval; FAS, full analysis set; FEV1, forced expiratory volume; MDI, metered dose inhaler; N, Number of subjects in treatment group.
Logistic regression model with baseline FEV1 (L) and age as continuous covariates, and treatment and prior inhaled corticosteroid use (Yes/No) as categorical covariates. A responder is defined as a subject with an observed increase from baseline FEV1 of at least 15% within 30 minutes post dose. Baseline is defined as the average of the 60-and 30-minute predose FEV1 measures taken at randomization. Analyses of the secondary endpoints were not included in the Type I error rate control and p values are unadjusted.

Table 37 presents the results for estimated time to onset of response. The median time to onset response for the high dose BDA and low dose BDA were 7.5 and 7 minutes, respectively, and similar to AS (9.5 minutes). The median (mean) duration of response for the high dose BDA and low dose BDA was 185.5 (186.9) and 174.0 (191.4) minutes, respectively, compared to 158.5 (168.2) minutes for AS (Table 38).

Table 37. Analysis of Time to 15% Increase in FEV1 Over the Pretreatment Value, for Subjects With a 15% Increase in FEV1 on Day 1 (FAS ≥ 12 Years)

		Comparison between groups		
Comparison	n	Median time to onset	Median difference	95% CI
AS MDI 180 (N=196) vs Placebo MDI (N=196)	84 vs 26	9.5 vs 14.0	-2.5	-6.0, 1.0
BD MDI 160 (N=199) vs Placebo MDI (N=196)	27 vs 26	17.0 vs 14.0	3.0	-3.0, 9.0
BDA MDI 80/180 (N=201) vs Placebo MDI (N=196)	88 vs 26	7.0 vs 14.0	-4.5	-9.0, 0.0
BDA MDI 160/180 (N=197) vs Placebo MDI (N=196)	98 vs 26	7.5 vs 14.0	-4.5	-9.0, 0.0
BDA MDI 80/180 (N=201) vs AS MDI 180 (N=196)	88 vs 84	7.0 vs 9.5	-1.5	-3.0, 0.0
BDA MDI 160/180 (N=197) vs AS MDI 180 (N=196)	98 vs 84	7.5 vs 9.5	-1.0	-2.0, 0.0
BDA MDI 80/180 (N=201) vs BD MDI 160 (N=199)	88 vs 27	7.0 vs 17.0	-6.5	-11.0, -2.0
BDA MDI 160/180 (N=197) vs BD MDI 160 (N=199)	98 vs 27	7.5 vs 17.0	-6.5	-11.0, -2.0
BDA MDI 160/180 (N=197) vs BDA MDI 80/180 (N=201)	98 vs 88	7.5 vs 7.0	0.0	-1.0, 1.0

Source: Clinical Study Report Table 16, p.116; modified by Statistical Reviewer.
AS, albuterol sulfate; BD, budesonide; BDA, budesonide/albuterol sulfate; CI, confidence interval; FAS, full analysis set; FEV1, Forced expiratory volume in 1 second; MDI, metered dose inhaler; N, number of subjects in treatment group; n, number of subjects in analysis.
Note: The time to onset is defined as the time (minutes) from the first inhalation of randomly assigned treatment (Day 1) to the first instance where a percentage change from baseline in FEV1 of at least 15% is observed. Subjects were only included in the analyses if a percent change from baseline of at least 15% is observed within 30 minutes post dose. Baseline FEV1 is defined as the average of the 60- and 30-minute predose spirometry measures taken at randomization. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method. Analyses of the secondary endpoints were not included in the Type I error rate control.

Table 38. Duration of 15% Increase in FEV1 Over the Pre-treatment Value on Day 1, Descriptive Statistics (FAS ≥ 12 Years)

Statistic	BDA MDI 160 (N = 197)	BDA MDI 80 (N = 201)	BD MDI 160 (N = 199)	AS MDI 180 (N = 196)	Placebo MDI (N = 196)
n	98	88	27	84	26
Mean	186.9	191.4	163.9	168.2	191.5
SD	122.5	127.3	153.0	128.0	152.8
Median	185.5	174.0	98.0	158.5	229.5
Min	4	10	14	9	8
Max	363	362	354	363	356

Source: Clinical Study Report Table 17, p.118; modified by Statistical Reviewer.
AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; FAS = full analysis set; FEV1 = Forced expiratory volume in 1 second; Max = maximum; MDI = metered dose inhaler; Min = minimum; N = number of subjects in treatment group; n = number of subjects in analysis; SD = standard deviation
Note: The duration of onset is defined as the time (minutes) of the continual period in which a percentage change from baseline in FEV1 of at least 15% is observed. Subjects will only be included in the analyses if a percent change from baseline of at least 15% is observed within 30 minutes post dose. If a subject has multiple periods of onset, only the first will contribute to the summary. Baseline FEV1 is defined as the average of the 60- and 30-minute predose spirometry taken at randomization.

Table 39 displays the responder analysis in ACQ-7 at Week 12 for uncontrolled subjects at baseline for FAS ≥ 12 years. Subjects on BDA doses had nominally higher odds of a response in ACQ-7 compared with AS. The odds ratio was 2.328 (95% CI 1.471, 3.687) for the high dose BDA vs AS and 2.297 (95% CI 1.456, 3.626) for the low dose BDA vs AS.

Analyses of the secondary endpoints were not included in the Type I error rate control and p values are unadjusted.

Table 39. Secondary Analysis of Asthma Control Questionnaire 7-item Version (ACQ-7) Minimal Important Difference at Week 12 for Uncontrolled Subjects at Baseline (FAS ≥ 12 Years)

		Comparison Between Groups		
Comparison	Number (%) of responders	Odds Ratio	95% CI	P-value
AS MDI 180 (N=163) vs Placebo MDI (N=159)	77 (47.2) vs 88 (55.3)	0.7	0.5, 1.1	0.12
BD MDI 160 (N=162) vs Placebo MDI (N=159)	100 (61.7) vs 88 (55.3)	1.4	0.9, 2.2	0.16
BDA MDI 80/180 (N=166) vs Placebo MDI (N=159)	108 (65.5) vs 88 (55.3)	1.6	1.0, 2.5	0.04
BDA MDI 160/180 (N=161) vs Placebo MDI (N=159)	107 (66.5) vs 88 (55.3)	1.6	1.0, 2.6	0.04
BDA MDI 80/180 (N=166) vs AS MDI 180 (N=163)	108 (65.5) vs 77 (47.2)	2.3	1.5, 3.6	<0.01
BDA MDI 160/180 (N=161) vs AS MDI 180 (N=163)	107 (66.5) vs 77 (47.2)	2.3	1.5, 3.7	<0.01
BDA MDI 80/180 (N=166) vs BD MDI 160 (N=162)	108 (65.5) vs 100 (61.7)	1.2	0.7, 1.8	0.53
BDA MDI 160/180 (N=161) vs BD MDI 160 (N=162)	107 (66.5) vs 100 (61.7)	1.2	0.7, 1.9	0.50
BDA MDI 160/180 (N=161) vs BDA MDI 80/180 (N=165)	107 (66.5) vs 108 (65.5)	1.0	0.6, 1.6	0.96

Source: Clinical Study Report Table 18, p.120

ACQ-7, Asthma control questionnaire (7-item); AS, a buterol sulfate; BD, budesonide; BDA, budesonide/albuterol sulfate; CI, confidence interval; FAS, full analysis set; FEV1, Forced expiratory volume; MDI, metered dose inhaler; N, umber of uncontrolled subjects in treatment group.

Logistic regression model with baseline ACQ-7, baseline predose percent predicted FEV1 and age as continuous covariates and treatment and prior inhaled corticosteroid use (Yes/No) as categorical covariates. A responder is defined as a subject with a reduction from baseline ACQ-7 score of at least 0.5. The overall ACQ-7 score is the average score across the 7 domains. All subjects who discontinue treatment prior to Week 12 are classified as non-responders. The analysis only includes subjects who are uncontrolled at baseline, that is, baseline ACQ-7 ≥ 1.5. An odds ratio greater than 1 corresponds to having a greater relative improvement in asthma control compared to the control group. Analyses of the secondary endpoints were not included in the Type I error rate control and p values are unadjusted.

DENALI was an adequate and well-controlled trial that contributed data relevant to supporting SEE. It demonstrating that 12 weeks of chronic QID treatment with BDA led to statistically significant improvements in post-dose FEV1 $AUC_{0\text{-}6hours}$ compared with BD and in trough FEV1

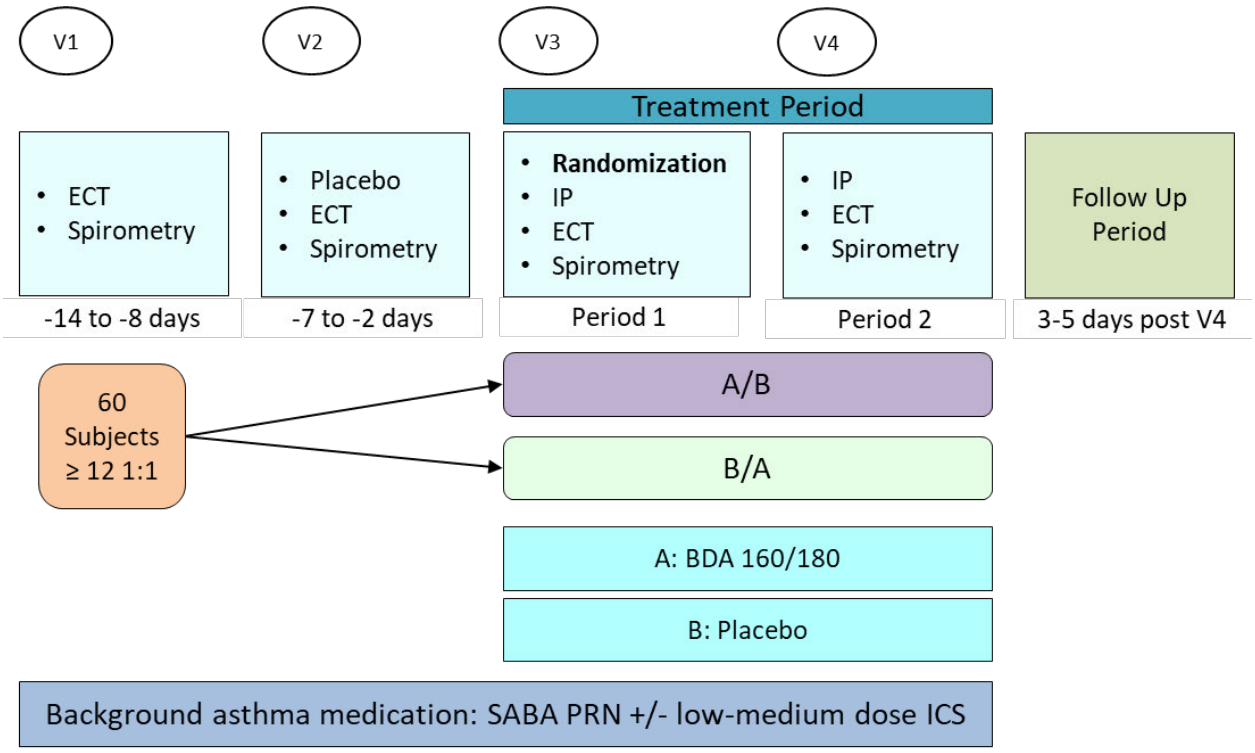
compared with AS.The factorial design comparing BDA to its monocomponents and placebo provided necessary data to satitisfy the combination rule. The 12-week QID standing dose regimen provided additional insights into the safety BDA when administered at a higher frequency than what was observed, on average, in MANDALA. Finally, the Day 1 FEV1 data support characteriziation of the onset-of-action and duration of bronchodilation, which is important for a novel PRN reliever inhaler.

8.2.3. TYREE Trial Design

Trial Design

The primary objective of TYREE was to evaluate the effect of BDA on FEV1 when administered prophylactically before exercise-challenge testing (ECT) in subjects with mild asthma and exercise-induced bronchoconstriction (EIB). TYREE was a single dose, cross-over study, and the study schema is presented in Figure 9. During development, the Division had advised the Applicant that TYREE should demonstrate the contribution of BD to BD/AS on EIB, since AS is already approved for EIB and its effects are well-described. The BDA vs placebo design would not evaluate the effect of BDA on EIB beyond what is already known about AS. (b) (4) therefore, we present only the primary endpoint result and high-level overview here.

Figure 9. TYREE Study Design



8.2.3.1. Study Endpoints

Primary Endpoint

Maximum percentage fall from post-dose, pre-exercise baseline in FEV1 observed up to 60 minutes post-exercise challenge test.

Secondary Endpoint

Proportion of subjects with a maximum percentage fall in FEV1 post-exercise challenge of <10%.

8.2.3.2. Study Population

Key Inclusion Criteria

1. Subjects ≥12 years of age with asthma as defined by GINA criteria for at least 6 months.
2. Receiving 1 of the following inhaled asthma medications with stable dosing for at least 1 month:
    a. SABA PRN
    b. Stable low-medium dose ICS with PRN SABA.
3. Each pre-ECT (and pre-dose at Visits 2 and 3) best FEV1 determination from the beginning of screening and before randomization ≥70% predicted normal.
4. EIB as defined by a ≥20% decrease from pre-ECT best FEV1 observed within 60 minutes after an exercise challenge at Visit 1 and at Visit 2.

Key Exclusion Criteria

1. COPD or other significant lung disease.
2. SCS use within 3 months before visit 1.
3. Current smokers or former smokers with > 10 pack-year history or cessation <6 months of visit 1.
4. Asthma with previous history of intubation for hypercapnia, respiratory arrest, hypoxic seizures, or syncope.
5. Pregnant, lactating, or unable or willing to use appropriate contraceptive methods.

8.2.3.3. Study Results

Table 40 summarizes the results from the primary efficacy analysis of maximum percentage fall from post-dose, pre-exercise baseline in FEV1 up to 60 minutes post-exercise challenge for the full analysis set. The high dose BDA met statistical significance for the primary endpoint for the full analysis set in the all-subjects population, non-ICS subpopulation and ICS subpopulation.

Table 40. Primary Efficacy Analysis – Maximum Percentage Fall From Postdose Pre-Exercise Baseline in FEV1 Up to 60 Minutes Postexercise Challenge (Full Analysis Set)

Background Therapy	Treatment Group	Least Squares Mean	95% CI	Comparison Versus Placebo MDI		
				Difference in LS Mean	95% CI	P-value
All subjects	BDA MDI 160/180 (N=60)	5.45	2.56, 8.35	-13.51	-16.94, -10.09	<0.01
	Placebo MDI (N=60)	18.97	16.06, 21.88			
Non-ICS	BDA MDI 160/180 (N=31)	4.27	0.16, 8.37	-15.73	-20.61, -10.84	<0.01
	Placebo MDI (N=31)	19.99	15.84, 24.14			
ICS	BDA MDI 160/180 (N=29)	6.65	2.45, 10.84	-11.35	-16.18, -6.52	<0.01
	Placebo MDI (N=29)	18.00	13.81, 22.19			

Source: Clinical Study Report Table 13, p.61
BDA, budesonide/albuterol sulfate; CI, confidence interval; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LS, least squares; MDI, metered-dose inhaler; N, number of subjects in treatment group.
Maximum percentage fall in post-dose pre-exercise FEV1 up to 60 minutes post-exercise challenge is analyzed using a mixed effects model adjusted for treatment, treatment period, treatment sequence as categorical fixed effects, period-specific pre-dose baseline FEV1 and average pre-dose baseline FEV1 as continuous covariates, and a random subject within treatment sequence effect. Background therapy estimates are calculated by additionally adjusting for background therapy and background therapy*treatment group interaction in the mixed model. A sequential testing strategy is used such that the hypothesis tests are listed in the table in descending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.

8.3. Integrated Review of Effectiveness

The Applicant submitted results from 3 pivotal clinical trials: MANDALA, DENALI, and TYREE. We considered both MANDALA and DENALI to represent adequate and well-controlled trials that contributed to SEE.

The primary source of efficacy data supporting this application is MANDALA because it evaluated the use of BDA as intended (PRN) and is the only trial to evaluate exacerbations as the primary endpoint. The MANDALA study demonstrated that treatment with the high dose BDA as needed in subjects ≥12 and the low dose BDA as needed in subjects ≥4 led to statistically significant delays in time to first severe asthma exacerbations in subjects with moderate to severe asthma compared with AS alone. This was supported by a statistically significant reduction in the annualized rate of severe asthma exacerbations for both doses. There was also a statistically significant difference in annualized total SCS exposure for the high dose BDA compared with AS. However, primary efficacy in the two pediatric subgroups (≥12 to <18 years and ≥4 to <12 years) is uncertain because the upper confidence limits for the hazard ratios exceed 1. In subjects <12, in whom only low dose BDA was studied, the results were inconclusive regarding the benefit of BDA in preventing severe acute exacerbations. Among subjects ≥12 to <18 years, the HR for BDA 160/180 vs AS was also inconclusive regarding the benefit of BDA, complicated by wide confidence intervals and a small sample size. Bayesian analyses show that demonstration of efficacy among the pediatric subgroups requires borrowing large amounts of adult data relative to the collected pediatric data.

Efficacy results from the adult subgroup in MANDALA support the indication “to reduce the risk of exacerbations” and other claims included in Section 14 of the label, such as reduction in the

annualized rate of severe exacerbations and in systemic corticosteroid use, as well as statistically significant improvements in the ACQ-5 scores.

The DENALI study provided data to support the combination rule and information on BDA use in a mild to moderate asthma severity population, demonstrating that 12 weeks of chronic QID treatment with BDA led to statistically significant improvements in post-dose FEV1 $AUC_{0\text{-}6hours}$ compared with BD and in trough FEV1 compared with AS. Furthermore, the single dose data demonstrating the effects of BDA of onset-of-action and duration of action of bronchodilation support efficacy claims in Section 14 and the "treatment and prevention of bronchoconstriction" component of the indication statement.

TYREE is an exercise-induced bronchospasm trial that does not contribute significant clinically meaningful data to support the proposed indication.

In conclusion, the Applicant has demonstrated substantial evidence of effectiveness for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 18 years of age and older based on statistically and clinically persuasive results on the time to first severe exacerbation primary endpoint, annualized severe exacerbation rate and total SCS exposure, from MANDALA. DENALI provides data to support the combination rule and confirmatory evidence of the efficacy of BDA.

8.4. Review of Safety

8.4.1. Safety Review Approach

Given the significant differences in trial design between MANDALA and DENALI, findings from each trial were analyzed and are discussed separately. This reviewer used JMP clinical and Analysis Studio to analyze independently the safety data in the safety analysis set, defined as all subjects receiving any amount of IP, classified by treatment received.

8.4.2. Review of the Safety Database

Overall Exposure

Both components of BDA are approved asthma medications with well-established safety profiles, with which there is extensive clinical experience. To support this application, the Applicant relied upon the listed drug products (LDPs) in accordance with a 505(b)(2) marketing pathway. The LDPs are: Pulmicort Flexhaler® and Pulmicort Respules® for budesonide, and Proventil® HFA for albuterol. The total safety database generated for the BDA development program is summarized below (Table 41).

Table 41. Safety Population, Size, and Denominators

Safety Database for BDA MDI[1] Individuals exposed to BDA in this development program for the indication under review N= 4,351 (N is the sum of all available numbers from the columns below)					
Fixed Dose Combination Controlled Trials					
	BDA 80/90 (n=)	BDA 40/90 (n=)	AS 90 (n=)	BD 80	Placebo (n=)
MANDALA	1015	1055	1057	N/A	N/A
DENALI	197	204	201	199	199
TYREE	60	N/A	N/A	N/A	60
Controlled Trials in Support of Asthma					
LOGAN	91	N/A	91	91	N/A
PT008001	N/A	N/A	N/A	73	74

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Adequacy of the Safety Database

The extent and duration of exposure to both doses of BDA in controlled clinical trials met International Council for Harmonization guidelines for the safety evaluation of drugs intended for chronic use. All subjects in DENALI were exposed to 8 inhalations a day for 12 weeks. Since MANDALA was an event-driven trial in which the IP was used PRN (refer to Section 8.2.1 for study design), subject exposure was variable. For adults, the mean duration of exposure was balanced between treatments arms and was approximately 305 days, with a median number of daily inhalations of 2.6, also balanced between arms. For pediatric subjects, the mean duration of exposure was shorter because of later randomization relative to primary database lock. There was more variability in usage between arms among adolescents and less usage overall among children. The clinical reasons for these differences are not clear. Ulimately, there was a paucity of safety data related to pediatric subjects, both because of the small sample size and because of the shorter duration of enrollment and more limited exposure to IP.

Table 42. MANDALA Investigative Product Use Patterns

Population	Mean Duration Treatment Period (Days)	Proportion Subjects With ≥24 Weeks Treatment Period (N, %)	Mean / Median Daily Inhalations per IP
Safety Analysis Set, All Ages (N=3,127)	305	2,744 (88%)	BDA 160/180: 2.6 / 2.3 BDA 80/180: 2.6 / 2.3 AS: 2.8 / 2.4
≥12 years to <18 years (N=100)	227	70 (70%)	BDA 160/180: 2.9 / 3.1 BDA 80/180: 2.6 / 1.7 AS: 2.3 / 2.4
≥4 years to <12 years (N=83)	235	55 (66%)	BDA 80/180: 2.1 / 1.0 AS: 1.8 / 1.2

Source: Clinical reviewer.

8.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues regarding data integrity or submission quality. Investigations were performed at several study sites and did not uncover concerns with data or study conduct integrity. See Section 4.1 for more information.

Categorization of Adverse Events

The Applicant used definitions of adverse events (AEs) and serious adverse events (SAEs) consistent with the requirements outlined in 21 Code of Federal Regulations 312.32. All AEs, regardless of investigator adjudication of relatedness, were collected from the time of informed consent / assent through the safety follow up period. AEs were analyzed during the entire study period (run-in, treatment period, and follow up). As explained in Section 8.1, signs and symptoms of asthma, the disease under study, were recorded as AEs only when they were serious, led the subject to discontinue IP, or were new to the subject or inconsistent with the subject's documented asthma history, as assessed by the investigator. Since the safety profiles of the monocomponents are well-established in the asthma population, adverse events of special interest (AESI) were not specified. The Applicant analyzed Standardized MedDRA Queries (SMQs) during their analysis and coded AEs using MedDRA dictionary version 24.0.

Routine Clinical Tests

Routine clinical tests for MANDALA and DENALI were assessed per the schedule outlined in Table 14 and Table 30, respectively. Descriptive summaries of all hematology and chemistry results were provided by the Applicant.

8.4.4. Safety Results: MANDALA

Safety Overview

Overall, **adverse events (AEs) were balanced across treatment arms in all three pivotal trials. In general, no new safety signals or concerns were identified in any age group within the BDA development program. Review of Safety Results will focus largely on data from MANDALA.**

MANDALA

In MANDALA, AEs were generally balanced between arms. Table 43 summarizes AEs of any category during the randomized treatment period in MANDALA. Any AEs during the safety follow up period or after premature discontinuation of IP were also captured and reviewed. Narratives for all SAEs, whether on or off randomized treatment, were reviewed. Although there was a slightly higher incidence of total serious adverse events (SAEs) in the BDA 160/180 arm compared to BDA 80/180 and AS arms (5.4% vs 4.1%, 4.9%), there were no findings that were unexpected given the drug classes of ICS and SABA, the patient population, and conduct of the trial during the COVID-19 pandemic.

Table 43. Number of Subjects With any Category of Adverse Event in the Randomized Treatment Period (Safety Analysis Set)

Adverse Event	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Any AE	469 (46.2)	497 (47.1)	490 (46.4)
Any AE causally related to randomized treatment	21 (2.1)	20 (1.9)	16 (1.5)
Any AE with outcome of death	4 (0.4)	2 (0.2)	1 (0.1)
Any SAE (including events with outcome of death)	55 (5.4)	43 (4.1)	52 (4.9)
Any AE leading to discontinuation of IP	10 (1.0)	9 (0.9)	9 (0.9)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Any AE - Dataset: Adverse Events; Filter: AAE001FL = 'Y', APHASE = 'Randomized Treatment'.
Any AE causally related to randomized treatment - Dataset: Adverse Events; Filter: AREL = 'Related', APHASE = 'Randomized Treatment'.
Any AE with outcome of death - Dataset: Adverse Events; Filter: AESDTH = 'Y', APHASE = 'Randomized Treatment'.
Any SAE (including events with outcome of death) - Dataset: Adverse Events; Filter: AAE003FL = 'Y'.
Any AE leading to discontinuation of IP - Dataset: Adverse Events; Filter: AAE005FL = 'Y', APHASE = 'Randomized Treatment'.

Deaths

A total of eight deaths were reported during the clinical development program, all of which occurred in MANDALA. Seven of these deaths occurred during the randomized treatment period, with one death reported in the AS arm after the two-week safety follow up period. Deaths during the randomized treatment period are summarized inTable 44. None of these deaths was attributed by investigators as causally related to IP. Narratives and case report forms (CRFs) for all subjects with an outcome of death were reviewed. There was a higher number of deaths in the BDA 160/180 arm (4), compared to BDA 80/180 (2) and AS (2) arms, but there was no clear clinical pattern that supported IP causality. One death in the BDA 160/180 arm was attributed to “blood glucose increased” in a patient with diabetes mellitus II.

The family refused to provide medical records or a death certificate; therefore, a limited narrative was available for review. It is not clear whether this death was related to IP. No deaths occurred in pediatric or adolescent subjects. Based on these data, no new safety signals were identified.

Table 44. Number of Subjects With Adverse Event of Death in the Randomized Treatment Period by System Organ Class and Preferred Term (Safety Analysis Set)

Adverse Event	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Subjects with AE with an outcome of death			
Infections and infestations	2 (0.2)	1 (0.1)	1 (0.1)
COVID-19	2 (0.2)	0	1 (0.1)
COVID-19 pneumonia	0	1 (0.1)	0
Pneumonia	0	0	1 (0.1)
Cardiac disorders	1 (0.1)	0	0
Cardiac arrest	1 (0.1)	0	0
Investigations	1 (0.1)	0	0
Blood glucose increased	1 (0.1)	0	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	1 (0.1)	0
Metastases to lung	0	1 (0.1)	0
Respiratory, thoracic, and mediastinal disorders	0	1 (0.1)	0
Pneumothorax	0	1 (0.1)	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Subjects with AE with an outcome of death - Dataset: Adverse Events; Filter:
Abbreviations: AESDTH = 'Y', APHASE = 'Randomized Treatment'.

Serious Adverse Events

Table 45 summarizes all SAEs during the randomized treatment period of MANDALA. In total, 141 subjects experienced 190 SAEs. Narratives for all SAEs were reviewed. Overall, there were no clinically significant imbalances between treatment arms. The most common SAEs by preferred term (PT) were COVID-19 (0.8% total population), pneumonia (0.4% total population), and asthma (1.1% total population). The slightly higher incidence of SAEs in BDA 160/180 was driven by more COVID-19 and pneumonia events in BDA 160/180 compared to other arms. Refer to Section 8.4.4.1 for more detail. Infection, including respiratory infection, is a known risk of ICS described in the label for all drugs in class. More asthma events occurred in AS compared to both BDA 160/180 and BDA 80/180 (1.9% vs 0.7%, 0.8%). Independent analysis of SAEs stratified by background ICS (low, medium, high), did not demonstrate any additional clinically significant imbalances. These data were not unexpected given the population, drug

class, and conduct of the trial during the COVID-19 pandemic and did not raise new safety concerns.

Table 45. Number of Subjects With a Serious Adverse Event During the Randomized Treatment Period by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Infections and infestations	17 (1.7)	17 (1.6)	17 (1.6)
COVID-19	14 (1.4)	9 (0.9)	13 (1.3)
Pneumonia	5 (0.5)	4 (0.4)	2 (0.2)
Influenza	0	3 (0.3)	0
Urinary tract infection	0	0	3 (0.3)
Diverticulitis	1 (0.1)	0	1 (0.1)
Appendicitis	0	0	1 (0.1)
Clostridium difficile colitis	0	0	1 (0.1)
Gastroenteritis	0	1 (0.1)	0
Infection	0	0	1 (0.1)
Lower respiratory tract infection	0	1 (0.1)	0
Pneumonia viral	1 (0.1)	0	0
Sepsis	0	0	1 (0.1)
Suspected COVID-19	0	0	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	8 (0.8)	9 (0.9)	20 (1.9)
Asthma	7 (0.7)	8 (0.8)	20 (1.9)
Nasal polyps	1 (0.1)	0	0
Pneumothorax	0	1 (0.1)	0
Cardiac disorders	2 (0.2)	7 (0.7)	2 (0.2)
Atrial fibrillation	0	2 (0.2)	0
Myocardial infarction	0	1 (0.1)	1 (0.1)
Acute myocardial infarction	1 (0.1)	0	0
Atrioventricular block second degree	0	0	1 (0.1)
Cardiac arrest	1 (0.1)	0	0
Coronary artery stenosis	0	1 (0.1)	0
Pericardial effusion	0	1 (0.1)	0
Supraventricular tachycardia	0	1 (0.1)	0
Tachycardia	0	1 (0.1)	0
Injury, poisoning and procedural complications	2 (0.2)	6 (0.6)	1 (0.1)
Accidental overdose	0	1 (0.1)	0
Animal bite	0	1 (0.1)	0
Concussion	0	1 (0.1)	0

System Organ Class Preferred Term	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Femur fracture	0	1 (0.1)	0
Joint dislocation	1 (0.1)	0	0
Limb injury	1 (0.1)	0	0
Lumbar vertebral fracture	0	1 (0.1)	0
Radius fracture	0	1 (0.1)	0
Tendon rupture	0	1 (0.1)	0
Urinary retention postoperative	0	0	1 (0.1)
Hepatobiliary disorders	6 (0.6)	1 (0.1)	1 (0.1)
Cholecystitis acute	3 (0.3)	0	0
Cholelithiasis	1 (0.1)	0	1 (0.1)
Cirrhosis alcoholic	0	1 (0.1)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3 (0.3)	3 (0.3)	1 (0.1)
Acute promyelocytic leukaemia	0	1 (0.1)	0
Adenocarcinoma of colon	0	1 (0.1)	0
Cholesteatoma	1 (0.1)	0	0
Haemangioma	0	1 (0.1)	0
Lung neoplasm malignant	1 (0.1)	0	0
Metastases to lung	0	1 (0.1)	0
Neoplasm skin	0	0	1 (0.1)
Rectal adenoma	1 (0.1)	0	0
Rectal cancer	1 (0.1)	0	0
Nervous system disorders	2 (0.2)	1 (0.1)	4 (0.4)
Ataxia	1 (0.1)	0	0
Cerebrovascular accident	0	0	1 (0.1)
Cervicobrachial syndrome	0	0	1 (0.1)
Headache	0	0	1 (0.1)
Intensive care unit acquired weakness	1 (0.1)	0	0
Migraine	0	1 (0.1)	0
Transient ischaemic attack	0	0	1 (0.1)
Gastrointestinal disorders	3 (0.3)	0	3 (0.3)
Duodenal ulcer	1 (0.1)	0	0
Gastritis	1 (0.1)	0	0
Intestinal obstruction	1 (0.1)	0	0
Nausea	0	0	1 (0.1)
Small intestinal obstruction	0	0	1 (0.1)
Umbilical hernia	0	0	1 (0.1)
Musculoskeletal and connective tissue disorders	2 (0.2)	2 (0.2)	2 (0.2)

System Organ Class Preferred Term	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Osteoarthritis	1 (0.1)	1 (0.1)	1 (0.1)
Foot deformity	1 (0.1)	0	0
Intervertebral disc protrusion	0	0	1 (0.1)
Polyarthritis	0	1 (0.1)	0
Vascular disorders	4 (0.4)	0	1 (0.1)
Hypertensive crisis	1 (0.1)	0	1 (0.1)
Accelerated hypertension	1 (0.1)	0	0
Deep vein thrombosis	1 (0.1)	0	0
Haematoma	1 (0.1)	0	0
Immune system disorders	2 (0.2)	1 (0.1)	1 (0.1)
Allergy to arthropod sting	1 (0.1)	0	0
Anaphylactic shock	1 (0.1)	0	0
Drug hypersensitivity	0	0	1 (0.1)
Food allergy	0	1 (0.1)	0
General disorders and administration site conditions	2 (0.2)	1 (0.1)	0
Chest pain	1 (0.1)	0	0
Non-cardiac chest pain	0	1 (0.1)	0
Pyrexia	1 (0.1)	0	0
Psychiatric disorders	2 (0.2)	0	1 (0.1)
Adjustment disorder with depressed mood	1 (0.1)	0	0
Mixed anxiety and depressive disorder	1 (0.1)	0	0
Post-traumatic stress disorder	0	0	1 (0.1)
Renal and urinary disorders	0	0	3 (0.3)
Acute kidney injury	0	0	1 (0.1)
Haematuria	0	0	1 (0.1)
Nephrolithiasis	0	0	1 (0.1)
Reproductive system and breast disorders	2 (0.2)	1 (0.1)	0
Cervical dysplasia	0	1 (0.1)	0
Colpocele	1 (0.1)	0	0
Vaginal haemorrhage	1 (0.1)	0	0
Investigations	1 (0.1)	0	1 (0.1)
Blood glucose increased	1 (0.1)	0	0
Troponin I increased	0	0	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)	0	1 (0.1)
Diabetes mellitus inadequate control	1 (0.1)	0	0
Vitamin D deficiency	0	0	1 (0.1)
Ear and labyrinth disorders	0	0	1 (0.1)

System Organ Class Preferred Term	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Vertigo	0	0	1 (0.1)
Eye disorders	1 (0.1)	0	0
Diplopia	1 (0.1)	0	0
Skin and subcutaneous tissue disorders	0	1 (0.1)	0
Dermatitis	0	1 (0.1)	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
System Organ Class, Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE003FL = 'Y'.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 46 summarizes AEs leading to treatment discontinuation or withdrawal. In total, there were 33 AEs that led to discontinuation of IP, which were balanced with 11 events across all 3 treatment arms. The most frequent etiology for discontinuation was COVID-19 pneumonia, with 5 events each in the BDA 160/180 and AS arms, and 1 in the BDA 80/180 arm. All other AEs leading to IP discontinuation were isolated events, with the exception of dysphonia (2 in the BDA 80/180 arm). These data were not unexpected given the population, drug class, and conduct of the trial during the COVID-19 pandemic. These data did not raise new safety concerns.

Table 46. Number of Subjects With an Adverse Event Leading to Dropout or Discontinuation During the Randomized Treatment Period by System Organ Class and Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
System Organ Class, Preferred Term			
Infections and infestations	5 (0.5)	1 (0.1)	5 (0.5)
COVID-19	5 (0.5)	0	5 (0.5)
COVID-19 pneumonia	0	1 (0.1)	1 (0.1)
Pneumonia	1 (0.1)	0	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	2 (0.2)	4 (0.4)	1 (0.1)
Asthma	1 (0.1)	0	1 (0.1)
Dysphonia	0	2 (0.2)	0
Chronic obstructive pulmonary disease	1 (0.1)	0	0
Cough	0	1 (0.1)	0
Oropharyngeal pain	0	1 (0.1)	0
Pneumothorax	0	1 (0.1)	0
Skin and subcutaneous tissue disorders	1 (0.1)	2 (0.2)	1 (0.1)
Rash	1 (0.1)	0	1 (0.1)
Dermatitis	0	1 (0.1)	0
Erythema multiforme	0	1 (0.1)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	2 (0.2)	0
Acute promyelocytic leukaemia	0	1 (0.1)	0

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Metastases to lung	0	1 (0.1)	0
Nervous system disorders	0	0	2 (0.2)
Cerebrovascular accident	0	0	1 (0.1)
Dysgeusia	0	0	1 (0.1)
Endocrine disorders	0	1 (0.1)	0
Secondary adrenocortical insufficiency	0	1 (0.1)	0
General disorders and administration site conditions	1 (0.1)	0	0
Oedema	1 (0.1)	0	0
Investigations	1 (0.1)	0	0
Blood glucose increased	1 (0.1)	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
System Organ Class, Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE005FL = 'Y'.

Significant Adverse Events

Table 47 summarizes all AEs rated by investigators as severe in intensity. Severity was assessed independently of seriousness and describes the intensity of signs or symptoms. The only severe AEs occurring in > 0.5% of subjects were COVID-19 and asthma. Rates of severe COVID-19 were generally balanced across arms, and rates of asthma were slightly higher in the AS arm (1.7%) compared to both BDA arms (0.4%, 0.5%). Overall, severe AEs were balanced across arms, and no new safety signals were identified from these data. x

Table 47. Number of Subjects With an Adverse Event Rated as Severe During the Randomized Treatment Period by System Organ Class and Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
System Organ Class, Preferred Term			
Infections and infestations	16 (1.6)	12 (1.1)	13 (1.2)
COVID-19	12 (1.2)	7 (0.7)	11 (1.1)
Pneumonia	4 (0.4)	3 (0.3)	1 (0.1)
Influenza	0	3 (0.3)	0
Appendicitis	1 (0.1)	0	1 (0.1)
Diverticulitis	1 (0.1)	0	1 (0.1)
Pneumonia viral	2 (0.2)	0	0
Bronchitis	0	0	1 (0.1)
Fungal infection	1 (0.1)	0	0
Gastroenteritis	0	1 (0.1)	0
Lower respiratory tract infection	0	1 (0.1)	0
Mastoiditis	1 (0.1)	0	0
Pneumonia staphylococcal	1 (0.1)	0	0
Sepsis	0	0	1 (0.1)
Sinusitis	0	0	1 (0.1)
Upper respiratory tract infection	0	1 (0.1)	0
Urinary tract infection	0	0	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	6 (0.6)	6 (0.6)	18 (1.7)

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Asthma	4 (0.4)	5 (0.5)	18 (1.7)
Dyspnoea	1 (0.1)	0	0
Nasal polyps	1 (0.1)	0	0
Pneumothorax	0	1 (0.1)	0
Pulmonary embolism	1 (0.1)	0	0
Injury, poisoning and procedural complications	4 (0.4)	5 (0.5)	1 (0.1)
Animal bite	0	1 (0.1)	0
Concussion	0	1 (0.1)	0
Femur fracture	0	1 (0.1)	0
Ligament rupture	1 (0.1)	0	0
Limb injury	1 (0.1)	0	0
Meniscus injury	1 (0.1)	0	0
Neck injury	0	0	1 (0.1)
Procedural pain	1 (0.1)	0	0
Radius fracture	0	1 (0.1)	0
Road traffic accident	0	1 (0.1)	0
Tendon rupture	0	1 (0.1)	0
Cardiac disorders	1 (0.1)	6 (0.6)	2 (0.2)
Tachycardia	0	2 (0.2)	0
Atrial fibrillation	0	1 (0.1)	0
Atrioventricular block second degree	0	0	1 (0.1)
Cardiac arrest	1 (0.1)	0	0
Coronary artery disease	0	0	1 (0.1)
Coronary artery stenosis	0	1 (0.1)	0
Pericardial effusion	0	1 (0.1)	0
Supraventricular tachycardia	0	1 (0.1)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5 (0.5)	3 (0.3)	1 (0.1)
Acute promyelocytic leukaemia	0	1 (0.1)	0
Adenocarcinoma of colon	0	1 (0.1)	0
Benign ovarian tumour	1 (0.1)	0	0
Cholesteatoma	1 (0.1)	0	0
Invasive ductal breast carcinoma	1 (0.1)	0	0
Lung neoplasm malignant	1 (0.1)	0	0
Metastases to liver	0	1 (0.1)	0
Metastases to lung	0	1 (0.1)	0
Metastases to lymph nodes	0	1 (0.1)	0
Neoplasm skin	0	0	1 (0.1)
Rectal cancer	1 (0.1)	0	0
Musculoskeletal and connective tissue disorders	3 (0.3)	3 (0.3)	2 (0.2)
Intervertebral disc protrusion	1 (0.1)	0	1 (0.1)
Osteoarthritis	0	1 (0.1)	1 (0.1)
Back pain	1 (0.1)	0	0
Foot deformity	1 (0.1)	0	0
Spinal osteoarthritis	0	1 (0.1)	0
Spinal pain	0	1 (0.1)	0
Nervous system disorders	3 (0.3)	0	5 (0.5)

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Headache	0	0	2 (0.2)
Carpal tunnel syndrome	1 (0.1)	0	0
Cerebrovascular accident	0	0	1 (0.1)
Cervicobrachial syndrome	0	0	1 (0.1)
Intensive care unit acquired weakness	1 (0.1)	0	0
Migraine	1 (0.1)	0	0
Transient ischaemic attack	0	0	1 (0.1)
Gastrointestinal disorders	1 (0.1)	0	3 (0.3)
Gastritis	1 (0.1)	0	0
Nausea	0	0	1 (0.1)
Small intestinal obstruction	0	0	1 (0.1)
Umbilical hernia	0	0	1 (0.1)
Hepatobiliary disorders	4 (0.4)	0	0
Cholecystitis acute	2 (0.2)	0	0
Cholecystitis	1 (0.1)	0	0
Cholelithiasis	1 (0.1)	0	0
Renal and urinary disorders	1 (0.1)	0	2 (0.2)
Acute kidney injury	0	0	1 (0.1)
Nephrolithiasis	0	0	1 (0.1)
Urinary retention	1 (0.1)	0	0
Eye disorders	2 (0.2)	0	0
Cataract	1 (0.1)	0	0
Diplopia	1 (0.1)	0	0
Retinal detachment	1 (0.1)	0	0
General disorders and administration site conditions	2 (0.2)	0	0
Chest pain	1 (0.1)	0	0
Pyrexia	1 (0.1)	0	0
Immune system disorders	2 (0.2)	0	0
Allergy to arthropod sting	1 (0.1)	0	0
Anaphylactic shock	1 (0.1)	0	0
Reproductive system and breast disorders	2 (0.2)	0	0
Colpocele	1 (0.1)	0	0
Vaginal haemorrhage	1 (0.1)	0	0
Skin and subcutaneous tissue disorders	0	1 (0.1)	1 (0.1)
Dermatitis	0	1 (0.1)	0
Dermatitis atopic	0	1 (0.1)	0
Pemphigoid	0	0	1 (0.1)
Vascular disorders	1 (0.1)	0	1 (0.1)
Accelerated hypertension	1 (0.1)	0	0
Hypertensive crisis	0	0	1 (0.1)
Ear and labyrinth disorders	0	0	1 (0.1)
Vertigo	0	0	1 (0.1)
Investigations	1 (0.1)	0	0
Blood glucose increased	1 (0.1)	0	0
Metabolism and nutrition disorders	0	0	1 (0.1)
Hypoglycaemia	0	0	1 (0.1)
Psychiatric disorders	1 (0.1)	0	0

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Mixed anxiety and depressive disorder	1 (0.1)	0	

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
System Organ Class, Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE001FL = 'Y', AESEV = 'SEVERE'.

Treatment Emergent Adverse Events and Adverse Reactions

Table 49 summarizes the most common (occurring in >2% of the population) adverse events during the randomized treatment period. A causal relationship between AEs and IP was adjudicated by investigators as “yes” or “no,” based on whether there was a “reasonable possibility” that an AE could have been caused by the drug. Investigators were provided with a guide to assessing “reasonable possibility” of causality, which encouraged assessment based on the following parameters: time course, consistency with known drug profile, de-challenge experience, absence or presence of alternative cause, re-challenge experience, and supportive laboratory tests. If insufficient data were available, investigators were encouraged to enter “related.” The total incidence of Adverse Reactions (ARs) was low. Overall, the most common ARs were oral candidiasis and dysphonia, with slightly more oral candidiasis in the BDA arms compared to AS (0.9% and 0.8% vs 0.4%) and balanced rates of dysphonia across arms (0.2%, 0.3%, 0.1%). These findings are not unexpected based on known class effects.

Table 48. Subjects With Adverse Reactions During the Randomized Treatment Period by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Preferred Term			
Oral candidiasis	3 (0.3)	3 (0.3)	2 (0.2)
Dysphonia	2 (0.2)	3 (0.3)	1 (0.1)
Oropharyngeal candidiasis	2 (0.2)	3 (0.3)	0
Cortisol decreased	0	2 (0.2)	2 (0.2)
Cough	1 (0.1)	3 (0.3)	0
Dry mouth	3 (0.3)	0	1 (0.1)
Dysgeusia	1 (0.1)	1 (0.1)	1 (0.1)
Palpitations	1 (0.1)	1 (0.1)	1 (0.1)
Rash	1 (0.1)	1 (0.1)	1 (0.1)
Upper respiratory tract infection	1 (0.1)	1 (0.1)	1 (0.1)
Dry throat	0	1 (0.1)	1 (0.1)
Headache	0	0	2 (0.2)
Nausea	1 (0.1)	0	1 (0.1)
Oropharyngeal pain	0	1 (0.1)	1 (0.1)
Sinusitis	1 (0.1)	0	1 (0.1)
Throat irritation	1 (0.1)	1 (0.1)	0
Asthma	1 (0.1)	0	0
Atrial fibrillation	1 (0.1)	0	0
Bronchitis	0	1 (0.1)	0
Candida infection	1 (0.1)	0	0

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Dry skin			0
Glossodynia			1 (0.1)
Glucocorticoid deficiency			0
Oedema			0
Postoperative wound infection			0
Procedural dizziness			1 (0.1)
Pruritus			0
Secondary adrenocortical insufficiency			0
Somnolence			0
Tremor			1 (0.1)
Umbilical hernia			0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Preferred Term - Dataset: Adverse Events; Filter: AAE001FL = 'Y', APHASE = 'Randomized Treatment', AREL = 'Related'.

Table 49 summarizes the most common AEs (occurring in >2% of the population) in MANDALA, which were largely balanced between treatment arms. These data are consistent with known class effects of ICS and SABA use in the asthma population. Stratification by background ICS dose confirms trends of slightly higher incidences of nasopharyngitis, COVID-19 infection, and upper respiratory infection (URI) in subjects on medium or high ICS compared to those on low dose. After Infections and infestations and Respiratory Disorders, the next most common system organ class (SOC) was Nervous system, driven by the preferred term (PT) of headache. Based on these data, no new or unexpected safety concerns were identified.

Table 49. Number of Subjects With Common (>2%) Adverse Events During the Randomized Treatment Period, Stratified by Background ICS, by System Organ Class and Preferred Term (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=235)	Medium (N=454)	High (N=318)	Low (N=257)	Medium (N=510)	High (N=288)	Low (N=238)	Medium (N=498)	High (N=317)
System Organ Class, Preferred Term									
Infections and infestations	52 (22.1)	135 (29.7)	94 (29.6)	70 (27.2)	139 (27.3)	87 (30.2)	64 (26.9)	120 (24.1)	91 (28.7)
Nasopharyngitis	13 (5.5)	38 (8.4)	25 (7.9)	13 (5.1)	28 (5.5)	20 (6.9)	13 (5.5)	20 (4.0)	21 (6.6)
COVID-19	9 (3.8)	19 (4.2)	15 (4.7)	15 (5.8)	16 (3.1)	21 (7.3)	9 (3.8)	24 (4.8)	13 (4.1)
Upper respiratory tract infection	4 (1.7)	13 (2.9)	9 (2.8)	2 (0.8)	17 (3.3)	12 (4.2)	4 (1.7)	9 (1.8)	12 (3.8)
Bronchitis	5 (2.1)	11 (2.4)	9 (2.8)	7 (2.7)	13 (2.5)	7 (2.4)	6 (2.5)	13 (2.6)	9 (2.8)
Influenza	3 (1.3)	12 (2.6)	6 (1.9)	3 (1.2)	14 (2.7)	6 (2.1)	1 (0.4)	9 (1.8)	4 (1.3)
Sinusitis	1 (0.4)	9 (2.0)	5 (1.6)	4 (1.6)	11 (2.2)	2 (0.7)	6 (2.5)	10 (2.0)	8 (2.5)
Rhinitis	1 (0.4)	6 (1.3)	4 (1.3)	1 (0.4)	4 (0.8)	6 (2.1)	3 (1.3)	5 (1.0)	3 (0.9)
Urinary tract infection	3 (1.3)	0	5 (1.6)	3 (1.2)	5 (1.0)	0	1 (0.4)	7 (1.4)	7 (2.2)
Respiratory, thoracic, and mediastinal disorders	21 (8.9)	36 (7.9)	19 (6.0)	25 (9.7)	37 (7.3)	22 (7.6)	20 (8.4)	37 (7.4)	37 (11.7)
Asthma	5 (2.1)	6 (1.3)	6 (1.9)	7 (2.7)	9 (1.8)	4 (1.4)	5 (2.1)	17 (3.4)	13 (4.1)
Rhinitis allergic	2 (0.9)	10 (2.2)		6 (2.3)	8 (1.6)			6 (1.2)	5 (1.6)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=235)	Medium (N=454)	High (N=318)	Low (N=257)	Medium (N=510)	High (N=288)	Low (N=238)	Medium (N=498)	High (N=317)
Cough	1 (0.4)	7 (1.5)	2 (0.6)	2 (0.8)	8 (1.6)	4 (1.4)	3 (1.3)	1 (0.2)	7 (2.2)
Oropharyngeal pain	6 (2.6)	2 (0.4)	1 (0.3)	2 (0.8)	4 (0.8)	1 (0.3)	2 (0.8)	3 (0.6)	8 (2.5)
Nervous system disorders	18 (7.7)	32 (7.0)	19 (6.0)	12 (4.7)	38 (7.5)	20 (6.9)	18 (7.6)	32 (6.4)	21 (6.6)
Headache	12 (5.1)	21 (4.6)	11 (3.5)	8 (3.1)	29 (5.7)	13 (4.5)	13 (5.5)	22 (4.4)	15 (4.7)
Musculoskeletal and connective tissue disorders	18 (7.7)	30 (6.6)	16 (5.0)	12 (4.7)	33 (6.5)	13 (4.5)	10 (4.2)	36 (7.2)	20 (6.3)
Back pain	7 (3.0)	11 (2.4)	9 (2.8)	3 (1.2)	15 (2.9)	5 (1.7)	3 (1.3)	11 (2.2)	6 (1.9)
Arthralgia	3 (1.3)	12 (2.6)	3 (0.9)	1 (0.4)	10 (2.0)	1 (0.3)	0	9 (1.8)	2 (0.6)
Vascular disorders	5 (2.1)	15 (3.3)	12 (3.8)	7 (2.7)	16 (3.1)	7 (2.4)	9 (3.8)	14 (2.8)	12 (3.8)
Hypertension	3 (1.3)	10 (2.2)	9 (2.8)	7 (2.7)	14 (2.7)	6 (2.1)	8 (3.4)	10 (2.0)	8 (2.5)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AVALCAT1 = 'Low' or 'Medium' or 'High'.
System Organ Class, Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment'; Percent Threshold: >= 2%.

Laboratory Findings

There were no clinically significant aberrancies in routine laboratory tests for hematology. A total of 7 subjects had an AE of cortisol decrease, none of whom were 4-11 years old. These decreases were not associated with clinical signs or symptoms. One adolescent subject experienced an asymptomatic cortisol decrease in the safety follow up period. Results are summarized in Table 50. No subjects met criteria for Hy's law.

Table 50. Number of Subjects With Adverse Event of Cortisol Decrease During Randomized Treatment Period and Safety Follow Up Period (Safety Analysis Set)

	AS MDI 180 (N=1057)	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	Total (N=3127)
Age in Years				
>=12 - <18	0	1 (0.1)	0	1 (0.0)
>=18	2 (0.2)	0	5 (0.5)	7 (0.2)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Age in Years - Dataset: Adverse Events; Filter: AEDECOD = 'Cortisol decreased'.

Vital Signs, Electrocardiograms (ECGs), and QT

Vitals signs (heart rate and blood pressure) and ECGs over time were recorded in MANDALA and DENALI. There were no clinically significant changes or AEs related to change in vital signs or ECGs, including QT intervals, and there were no significant differences between treatment and comparator arms in both trials.

Immunogenicity

Not applicable.

8.4.4.1. Analysis of Submission-Specific Safety Issues

ICS-Related Adverse Events

For the BDA development program, the Applicant did not pre-specify AESIs because the safety profiles of budesonide and albuterol, are well-defined in the asthma population. Based on prior agreement with the Agency, the Applicant did collect and analyze AEs related to ICS exposure in MANDALA, which are summarized as AEs related to local-ICS toxicity (Table 51) and AEs related to systemic-ICS toxicity (Table 52). These data are stratified by background ICS dose below. The incidence of both local and systemic ICS-related AEs was low across treatment arms. The most frequent local AE that occurred in the BDA arms more than AS was oral candidiasis (1.4%, 1.2%, and 0.8%). Among systemic ICS-related AEs, the incidences were balanced across treatment arms. The most frequent AEs were contusion (0.6%, 0.5%, 0.5%); insomnia (0.4%, 0.9%, 0.4%); depression (0.4%, 0.2%,0.3%), and diabetes mellitus (0.4%, 0.2%, 0.5%). Stratification by background ICS did not elicit any unexpected clinically significant imbalances. Based on these data, no new safety concerns related to use of BDA on top of controller ICS were identified.

Table 51. Number of Subjects With Local ICS-Related Adverse Events During the Randomized Treatment Period, Stratified by Background ICS, by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=235)	Medium (N=454)	High (N=318)	Low (N=257)	Medium (N=510)	High (N=288)	Low (N=238)	Medium (N=498)	High (N=317)
Preferred Term									
Oral candidiasis	0	7 (1.5)	3 (0.9)	3 (1.2)	4 (0.8)	2 (0.7)	0	3 (0.6)	2 (0.6)
Dysphonia	1 (0.4)	1 (0.2)	2 (0.6)	0	4 (0.8)	2 (0.7)	1 (0.4)	0	3 (0.9)
Oropharyngeal candidiasis	1 (0.4)	1 (0.2)	1 (0.3)	0	2 (0.4)	1 (0.3)	1 (0.4)	0	0
Dysgeusia	0	0	1 (0.3)	0	1 (0.2)	0	0	2 (0.4)	0
Candida infection	0	1 (0.2)	0	1 (0.4)	0	0	0	0	0
Aphonia	0	0	1 (0.3)	0	0	0	0	0	0
Infection	0	0	0	0	0	0	1 (0.4)	0	0
Oesophageal candidiasis	0	0	0	0	0	0	1 (0.4)	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AVALCAT1 = 'Low' or 'High' or 'Medium'.
Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AEICSCAT = 'Local'.

Table 52. Number of Subjects With Systemic ICS-Related Adverse Events During the Randomized Treatment Period, Stratified by Background ICS, by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=235)	Medium (N=454)	High (N=318)	Low (N=257)	Medium (N=510)	High (N=288)	Low (N=238)	Medium (N=498)	High (N=317)
Preferred Term									
Insomnia	1 (0.4)	3 (0.7)	0	2 (0.8)	4 (0.8)	3 (1.0)	1 (0.4)	2 (0.4)	1 (0.3)
Contusion	1 (0.4)	3 (0.7)	2 (0.6)	2 (0.8)	3 (0.6)	0	0	5 (1.0)	0
Diabetes mellitus	0	1 (0.2)	3 (0.9)	1 (0.4)	0	1 (0.3)	2 (0.8)	1 (0.2)	2 (0.6)
Depression	1 (0.4)	3 (0.7)			0			1 (0.2)	2 (0.6)

Table 52. Number of Subjects With Systemic ICS-Related Adverse Events During the Randomized Treatment Period, Stratified by Background ICS, by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=235)	Medium (N=454)	High (N=318)	Low (N=257)	Medium (N=510)	High (N=288)	Low (N=238)	Medium (N=498)	High (N=317)
Cortisol decreased	0	0	0	1 (0.4)	4 (0.8)	0	0	1 (0.2)	1 (0.3)
Hyperglycaemia	0	2 (0.4)	0	0	0	1 (0.3)	0	2 (0.4)	0
Rib fracture	0	0	0	1 (0.4)	0	1 (0.3)	0	1 (0.2)	2 (0.6)
Type 2 diabetes mellitus	2 (0.9)	1 (0.2)	0	0	0	0	0	1 (0.2)	0
Wrist fracture	0	0	0	1 (0.4)	0	0	1 (0.4)	1 (0.2)	1 (0.3)
Blood glucose increased	1 (0.4)	0	0	0	0	1 (0.3)	0	1 (0.2)	0
Cataract	1 (0.4)	0	1 (0.3)	0	0	0	0	1 (0.2)	0
Foot fracture	0	1 (0.2)	0	0	1 (0.2)	0	0	0	1 (0.3)
Radius fracture	0	1 (0.2)	0	0	0	1 (0.3)	0	0	1 (0.3)
Adjustment disorder with depressed mood	1 (0.4)	0	0	0	0	0	0	1 (0.2)	0
Diabetes mellitus inadequate control	0	1 (0.2)	0	0	1 (0.2)	0	0	0	0
Diabetic metabolic decompensation	0	0	0	0	0	0	0	0	2 (0.6)
Stress fracture	0	0	0	0	0	0	0	1 (0.2)	1 (0.3)
Adrenocortical insufficiency acute	0	0	0	0	1 (0.2)	0	0	0	0
Ankle fracture	0	0	1 (0.3)	0	0	0	0	0	0
Femur fracture	0	0	0	1 (0.4)	0	0	0	0	0
Fibula fracture	0	0	0	0	1 (0.2)	0	0	0	0
Glaucoma	0	0	0	0	0	0	0	1 (0.2)	0
Grief reaction	0	0	0	0	0	0	0	1 (0.2)	0
Lumbar vertebral fracture	0	0	0	0	1 (0.2)	0	0	0	0
Mixed anxiety and depressive disorder	0	0	1 (0.3)	0	0	0	0	0	0
Osteopenia	0	0	1 (0.3)	0	0	0	0	0	0
Scapula fracture	0	0	0	0	0	0	0	1 (0.2)	0
Secondary adrenocortical insufficiency	0	0	0	0	1 (0.2)	0	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AVALCAT1 = 'Low' or 'High' or 'Medium'.
Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AEICSCAT = 'Systemic'.

SABA-Related Adverse Events

In MANDALA, AEs associated with SABA were also collected and analyzed by the Applicant and independently by this reviewer. The MedDRA SOCs captured as most relevant to SABA exposure were Metabolism and nutrition disorders, Psychiatric disorders, Nervous system disorders, Cardiac disorders, and Vascular disorders. The overall incidence rate was balanced across treatment arms for BDA 160/180, BDA 80/180, and AS (46.2%, 47.1%, 46.4%). The most frequent PTs and percent of subjects across arms were headache (4.3%, 4.7%, 4.7%); hypertension (2.2%, 2.6%, 2.5%), and hypercholesterolemia (0.6%, 0.7%, 1.2%). Based on these data, no new safety concerns or signals were identified.

Pneumonia and COVID-19

Given concerns about the potential additive effects of ICS, the MANDALA SAP prespecified that pneumonia-related AEs would be captured and analyzed. A high-level summary is presented in Table 53. In total, 50 subjects in MANDALA experienced an AE of pneumonia, 33 of which were associated with COVID-19 infection. Detailed narratives for all patients with pneumonia were provided and reviewed. Of the 50 pneumonia AEs, 24 were SAEs. No pediatric subjects experienced pneumonia (ages 4-11), and 2 adolescents (1 receiving BDA 160/180 arm and 1 receiving AS) experienced non-serious pneumonia AEs. Among the pneumonia events associated with COVID-19, 3 required intubation, 1 in each treatment arm; 4 were fatal, 2 in the BDA 160/180 arm and 1 in BDA 80/180 and AS, each. The incidence of SAEs associated with non-COVID-19 pneumonia was low and was 2, 2, 0 subjects in BDA 160/180, BDA 80/180, and AS, respectively. All subjects who experienced pneumonia used the IP < 6 times daily leading up to the pneumonia AE, and there was not a clear pattern of increased usage prior to pneumonia identification, per Applicant analysis. Overall, there were higher rates of pneumonia in the BDA 160/180 group compared to BDA 80/180 and AS (2.3%, 1.3%, 1.2%). Subgroup analyses stratified by low, medium, and high-dose background ICS supported this pattern, with the highest incidence occurring in the BDA 160/180 arm in those on high-dose background ICS (2.8% compared to 1.8% and 2.6% on medium and low, respectively). These data are consistent with known class effects of ICS, for which the risk of respiratory infection is included in Section 5 of the label.

Table 53. Number of Subjects With Pneumonia Adverse Events During the Randomized Treatment Period (Safety Analysis Set)

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Subjects with any Pneumonia	23 (2.3)	14 (1.3)	13 (1.2)
Subjects with Pneumonia SAE (including severe AE)	9 (0.9)	8 (0.8)	7 (0.7)
Subjects with Severe Pneumonia	8 (0.8)	6 (0.6)	5 (0.5)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Subjects with any Pneumonia - Dataset: Adverse Events; Filter: AEDECOD = 'Pneumonia' or 'Pneumonia viral' or 'Pneumonia bacterial' or 'COVID-19 pneumonia' or 'Pneumonia staphylococcal' or 'Atypical pneumonia', APHASE = 'Randomized Treatment'.
Subjects with Pneumonia SAE (including severe AE) - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE003FL = 'Y', AEDECOD = 'Pneumonia' or 'Pneumonia viral' or 'Pneumonia bacterial' or 'COVID-19 pneumonia'.
Subjects with Severe Pneumonia - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AESEV = 'SEVERE', AEDECOD = 'Pneumonia' or 'Pneumonia bacterial' or 'Pneumonia viral' or 'COVID-19 pneumonia' or 'Atypical pneumonia'.

8.4.4.2. Safety Analyses by Demographic Subgroups

Per the Applicant analysis and an independent analysis conducted by this reviewer, there were no clinically significant differences in AEs when assessed by race, region, adult age group (≥18 to < 65 and ≥ 65), and sex. The focus of this section will be the review of AEs in pediatric (≥4 to < 12) and adolescent (≥12 to < 18) subjects. The overall incidence of AEs among pediatric and adolescent subjects was low and largely balanced across treatment arms.

Table 54 provides a summary of any category of AE in subjects ≥4 to <18. The overall incidence of AEs, including SAEs, and AEs leading to IP discontinuation was low and balanced across arms. Data is presented stratified by ICS background, given the concern for potential additive effects of ICS in the pediatric population. When stratified by age (≥ 4 to < 12, ≥ 12 to < 18), the rate of AEs was balanced between age groups. In the total population in this age group, the overall incidence of AEs was higher in high dose background ICS compared to medium and low doses (56.1% vs 35.8% and 33.3%). Given the small pediatric sample size and lack of consistent pattern across randomized treatment arms, the significance is not clear and may represent a sicker baseline asthma population in the high dose ICS subgroup.

Table 54. Number of Subjects ≥ 4 to < 18 With any Category of Adverse Event in the Randomized Treatment Period, Stratified by Background ICS (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=8)	Medium (N=20)	High (N=6)	Low (N=14)	Medium (N=44)	High (N=15)	Low (N=14)	Medium (N=42)	High (N=20)
Any AE	4 (50.0)	6 (30.0)	3 (50.0)	3 (21.4)	16 (36.4)	9 (60.0)	5 (35.7)	16 (38.1)	11 (55.0)
Any AE causally related to randomized treatment	0	0	0	0	1 (2.3)	1 (6.7)	0	0	0
Any SAE	0	0	1 (16.7)	0	1 (2.3)	0	0	1 (2.4)	2 (10.0)
Any AE leading to discontinuation of IP	0	0	0	0	0	1 (6.7)	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AVALCAT1 = 'Low' or 'Medium' or 'High', AGEGR1 = '>= 4 - <12' or '>=12 - <18'; Any AE - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE001FL = 'Y'; Any AE causally related to randomized treatment - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AREL = 'Related'; Any SAE - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE003FL = 'Y'; Any AE leading to discontinuation of IP - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE005FL = 'Y'.

Table 55 summarizes SAEs in subjects ≥ 4 to < 18, stratified by background ICS. In subjects 4-11, there was one SAE of COVID-19 infection in the BDA 80/180 group. The two asthma SAEs in the AS arm and the anxiety / depressive disorder SAE in the 160/180 were in subjects 12-17. Narratives were provided for all pediatric SAEs, and all were resolved without discontinuation of IP. Based on this small sample size and small number of events, no new safety signals were identified.

Table 55. Number of Subjects >= 4 to < 18 With a Serious Adverse Event in the Randomized Treatment Period, Stratified by Background ICS (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=8)	Medium (N=20)	High (N=6)	Low (N=14)	Medium (N=44)	High (N=15)	Low (N=14)	Medium (N=42)	High (N=20)
Any AE									
Asthma	0	0	0	0	0	0	0	1 (2.4)	2 (10.0)
COVID-19	0	0	0	0	1 (2.3)	0	0	0	0
Mixed anxiety and depressive disorder	0	0	1 (16.7)	0	0	0	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AGEGR1 = '>= 4 - <12' or '>=12 - <18', AVALCAT1 = 'Low' or 'Medium' or 'High'.
Any AE - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE003FL = 'Y'.

Table 56 summarizes the most common AEs in subjects ≥4 to <18, stratified by background ICS dose. When stratified by age (≥4 to <12, ≥12 to <18), there were no significant imbalances between groups. Among all subjects ≥4 to <18, the most common AEs were similar to those in the adult population, with rates of influenza and cough being slightly higher. The overall incidence of AEs was low and was largely balanced between treatment arms. As shown in Table 56, the incidence of AEs in the SOC of Infections and infestations was slightly higher in subjects on high dose background ICS compared to medium or low, across all treatment arms, (41.5% of the total population vs 19.8% and 22.2%). Given the known class effects of ICS, these data do not represent new safety signals or concerns.

Table 56. Most Common (>2%) Adverse Events in Subjects >=4 to < 18 During the Randomized Treatment Period, Stratified by Background ICS (Safety Analysis Set)

System Organ Class, Preferred Term	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=8)	Medium (N=20)	High (N=6)	Low (N=14)	Medium (N=44)	High (N=15)	Low (N=14)	Medium (N=42)	High (N=20)
Infections and infestations	2 (25.0)	3 (15.0)	2 (33.3)	3 (21.4)	11 (25.0)	6 (40.0)	3 (21.4)	7 (16.7)	9 (45.0)
Influenza	1 (12.5)	1 (5.0)	0	0	0	3 (20.0)	0	2 (4.8)	2 (10.0)
Bronchitis	1 (12.5)	0	0	0	3 (6.8)	0	0	0	1 (5.0)
Suspected COVID-19	0	1 (5.0)	0	0	2 (4.5)	1 (6.7)	1 (7.1)	0	0
Nasopharyngitis	0	1 (5.0)	1 (16.7)	0	1 (2.3)	0	0	1 (2.4)	0
Otitis media	0	0	0	0	1 (2.3)	0	0	3 (7.1)	0
Sinusitis	0	0	0	1 (7.1)	1 (2.3)	1 (6.7)	0	0	1 (5.0)
Upper respiratory tract infection	0	0	0	0	0	2 (13.3)	1 (7.1)	0	1 (5.0)
Acute sinusitis	0	0	0	0	1 (2.3)	0	0	0	1 (5.0)
COVID-19	0	0	0	0	1 (2.3)	0	1 (7.1)	0	0
Pharyngitis streptococcal	1 (12.5)	1 (5.0)	0	0	0	0	0	0	0
Pneumonia	1 (12.5)	0	0	0	0	0	1 (7.1)	0	0
Respiratory tract infection viral	0	0	0	0	1 (2.3)	1 (6.7)	0	0	0
Tinea capitis	0	0	0	0	0	0	0	1 (2.4)	1 (5.0)
Tonsillitis	0	0	0	0	0	0	1 (7.1)	0	1 (5.0)
Viral pharyngitis	0	0	1 (16.7)	0	0	0	0	0	1 (5.0)
Viral upper respiratory tract infection	0	0	0	0	0	0	0	0	2 (10.0)
Asymptomatic COVID-19	0	0	0	0	0	0	0	0	1 (5.0)
Body tinea	0	0	0	0	0	1 (6.7)	0	0	0
Conjunctivitis	0	0	0	0	1 (2.3)	0	0	0	0
Gastroenteritis	0	0	0	0	0	0	0	0	1 (5.0)
Helminthic infection	0	0	0	0	0	0	0	0	1 (5.0)
Lower respiratory tract infection	0	0		1 (7.1)	0			0	0

System Organ Class, Preferred Term	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=8)	Medium (N=20)	High (N=6)	Low (N=14)	Medium (N=44)	High (N=15)	Low (N=14)	Medium (N=42)	High (N=20)
Oral candidiasis	0	0	0	0	0	0	0	0	1 (5.0)
Otitis externa	0	0	0	1 (7.1)	0	0	0	0	0
Pharyngitis	0	0	0	0	0	0	0	1 (2.4)	0
Viral infection	0	0	0	0	1 (2.3)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	3 (15.0)	1 (16.7)	0	2 (4.5)	3 (20.0)	1 (7.1)	5 (11.9)	4 (20.0)
Rhinitis allergic	0	1 (5.0)	1 (16.7)	0	1 (2.3)	1 (6.7)	1 (7.1)	1 (2.4)	0
Cough	0	0	1 (16.7)	0	1 (2.3)	1 (6.7)	1 (7.1)	1 (2.4)	0
Asthma	0	0	0	0	0	0	0	2 (4.8)	2 (10.0)
Oropharyngeal pain	0	0	0	0	0	1 (6.7)	1 (7.1)	0	1 (5.0)
Rhinorrhoea	0	1 (5.0)	0	0	0	0	0	0	1 (5.0)
Bronchospasm	0	1 (5.0)	0	0	0	0	0	0	0
Catarrh	0	0	0	0	0	1 (6.7)	0	0	0
Dysphonia	0	0	1 (16.7)	0	0	0	0	0	0
Nasal congestion	0	0	1 (16.7)	0	0	0	0	0	0
Sinus congestion	0	0	0	0	0	0	0	1 (2.4)	0
Sneezing	0	0	0	0	0	0	1 (7.1)	0	0
Throat irritation	0	0	1 (16.7)	0	0	0	0	0	0
Vocal cord dysfunction	0	0	0	0	0	0	0	0	1 (5.0)
Injury, poisoning and procedural complications	1 (12.5)	0	0	2 (14.3)	1 (2.3)	1 (6.7)	0	3 (7.1)	1 (5.0)
Ligament sprain	1 (12.5)	0	0	1 (7.1)	0	0	0	1 (2.4)	0
Concussion	0	0	0	0	0	0	0	0	1 (5.0)
Contusion	0	0	0	1 (7.1)	0	0	0	0	0
Craniocerebral injury	0	0	0	1 (7.1)	0	0	0	0	0
Limb injury	0	0	0	0	0	1 (6.7)	0	0	0
Procedural pain	0	0		0	0			1 (2.4)	0

System Organ Class, Preferred Term	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=8)	Medium (N=20)	High (N=6)	Low (N=14)	Medium (N=44)	High (N=15)	Low (N=14)	Medium (N=42)	High (N=20)
Sunburn	0	0	0	0	1 (2.3)	0	0	0	0
Wrist fracture	0	0	0	0	0	0	0	1 (2.4)	0
Gastrointestinal disorders	0	2 (10.0)	0	0	2 (4.5)	0	0	3 (7.1)	0
Toothache	0	0	0	0	2 (4.5)	0	0	1 (2.4)	0
Abdominal pain	0	1 (5.0)	0	0	0	0	0	0	0
Aphthous ulcer	0	0	0	0	0	0	0	1 (2.4)	0
Diarrhoea	0	1 (5.0)	0	0	0	0	0	0	0
Enteritis	0	0	0	0	0	0	0	1 (2.4)	0
Malpositioned teeth	0	0	0	0	0	0	0	1 (2.4)	0
Skin and subcutaneous tissue disorders	0	0	0	1 (7.1)	1 (2.3)	1 (6.7)	0	1 (2.4)	1 (5.0)
Urticaria	0	0	0	0	0	1 (6.7)	0	1 (2.4)	0
Dermatitis atopic	0	0	0	1 (7.1)	0	0	0	0	0
Dermatitis contact	0	0	0	0	1 (2.3)	0	0	0	0
Rash	0	0	0	0	0	0	0	0	1 (5.0)
Nervous system disorders	0	2 (10.0)	0	0	0	0	2 (14.3)	0	0
Headache	0	2 (10.0)	0	0	0	0	2 (14.3)	0	0
Blood and lymphatic system disorders	1 (12.5)	0	0	0	1 (2.3)	0	0	1 (2.4)	0
Anaemia	1 (12.5)	0	0	0	0	0	0	0	0
Hypochromic anaemia	0	0	0	0	1 (2.3)	0	0	0	0
Lymphadenopathy	0	0	0	0	0	0	0	1 (2.4)	0
General disorders and administration site conditions	0	0	0	0	0	0	2 (14.3)	0	0
Chest pain	0	0	0	0	0	0	1 (7.1)	0	0
Non-cardiac chest pain	0	0	0	0	0	0	1 (7.1)	0	0
Immune system disorders	0	0	0	0	0	1 (6.7)	0	1 (2.4)	0
Hypersensitivity	0	0		0	0			0	0

System Organ Class, Preferred Term	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=8)	Medium (N=20)	High (N=6)	Low (N=14)	Medium (N=44)	High (N=15)	Low (N=14)	Medium (N=42)	High (N=20)
Seasonal allergy	0	0	0	0	0	0	0	1 (2.4)	0
Musculoskeletal and connective tissue disorders	0	0	1 (16.7)	0	0	0	1 (7.1)	0	0
Back pain	0	0	1 (16.7)	0	0	0	0	0	0
Myalgia	0	0	0	0	0	0	1 (7.1)	0	0
Psychiatric disorders	0	0	1 (16.7)	0	0	0	0	1 (2.4)	0
Adjustment disorder with depressed mood	0	0	0	0	0	0	0	1 (2.4)	0
Anxiety disorder	0	0	1 (16.7)	0	0	0	0	0	0
Mixed anxiety and depressive disorder	0	0	1 (16.7)	0	0	0	0	0	0
Cardiac disorders	0	0	0	0	0	0	0	1 (2.4)	0
Tachycardia	0	0	0	0	0	0	0	1 (2.4)	0
Investigations	0	0	0	0	0	0	1 (7.1)	0	0
Blood creatine phosphokinase increased	0	0	0	0	0	0	1 (7.1)	0	0
Reproductive system and breast disorders	0	0	0	0	1 (2.3)	0	0	0	0
Dysmenorrhoea	0	0	0	0	1 (2.3)	0	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AVALCAT1 = 'Low' or 'Medium' or 'High', AGEGR1 = '>= 4 - <12' or '>=12 - <18'.
System Organ Class, Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment'; Percent Threshold: >= 2%.

Table 57 summarizes AEs in subjects ≥4 to <18 related to both local and systemic effects of ICS. The overall incidence of ICS-related AEs was low in this age group, and it was balanced between groups when stratified by age (≥4 to <12, ≥12 to <18). Based on these data, no new safety signals were identified.

Table 57. Local and Systemic ICS-Related Adverse Events in Subjects >=4 to <18 During the Randomized Treatment Period, Stratified by ICS (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
	Low (N=8)	Medium (N=20)	High (N=6)	Low (N=14)	Medium (N=44)	High (N=15)	Low (N=14)	Medium (N=42)	High (N=20)
System Organ Class, Preferred Term									
Injury, poisoning and procedural complications	0	0	0	1 (7.1)	0	0	0	1 (2.4)	0
Contusion	0	0	0	1 (7.1)	0	0	0	0	0
Wrist fracture	0	0	0	0	0	0	0	1 (2.4)	0
Psychiatric disorders	0	0	1 (16.7)	0	0	0	0	1 (2.4)	0
Adjustment disorder with depressed mood	0	0	0	0	0	0	0	1 (2.4)	0
Mixed anxiety and depressive disorder	0	0	1 (16.7)	0	0	0	0	0	0
Infections and infestations	0	0	0	0	0	0	0	0	1 (5.0)
Oral candidiasis	0	0	0	0	0	0	0	0	1 (5.0)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (16.7)	0	0	0	0	0	0
Dysphonia	0	0	1 (16.7)	0	0	0	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AVALCAT1 = 'Low' or 'Medium' or 'High', AGEGR1 = '>= 4 - <12' or '>=12 - <18'.
System Organ Class, Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AEICSCAT = 'Systemic' or 'Local'.

8.4.5. Safety Results: DENALI

An abbreviated summary of safety results from DENALI is provided since MANDALA was the focus of our review. Table 58 summarizes AEs of any category in DENALI. The overall incidence was low, given the shorter duration and smaller sample size. AEs leading to IP discontinuation were rare and balanced across arms. The only terms associated with more than one subject were asthma (2 subjects in AS and placebo arms, each) and COVID-19 (1 subject in BD 160 and placebo arms, each). There was a slightly higher incidence of AEs related to study IP in the BDA 160/180 arm, which was driven by 4 cases (2%) of dysphonia and 2 (1%) of oral candidiasis.

Table 58. DENALI, Number of Subjects With Any Category of Adverse Event in the Randomized Treatment Period (Safety Analysis Set)

AE	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=201)	Placebo MDI (N=199)
Any AE	66 (33.5%)	72 (35.3%)	67 (33.7%)	62 (30.8%)	69 (34.7%)
Any AE causally related to randomized treatment	10 (5.1%)	6 (2.9%)	7 (3.5%)	2 (1.0%)	3 (1.5%)
Any SAE	2 (1.0%)	4 (2.0%)	3 (1.5%)	1 (0.5%)	3 (1.5%)
Any AE leading to discontinuation of IP	2 (1.0%)	1 (0.5%)	3 (1.5%)	2 (1.0%)	4 (2.0%)

Source: Clinical Reviewer. OCS Analysis Studio, Custom Table Tool, adae.xpt, adsl.xpt.

Deaths

There were no deaths during the DENALI randomized treatment period or safety follow up period.

Serious Adverse Events

SAEs in DENALI were rare. Preferred terms are summarized in Table 59. The only events occurring in more than 1 subject were asthma and COVID-19. All other events were isolated, with no clear pattern to suggest relatedness to IP.

Table 59. DENALI Serious Adverse Events During the Randomized Treatment Period, by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=201)	Placebo MDI (N=199)	Total (N=1000)
Preferred Term						
Asthma	0	1 (0.5)	0	0	1 (0.5)	2 (0.2)
COVID-19	0	0	1 (0.5)	0	1 (0.5)	2 (0.2)
Angina unstable	0	0	1 (0.5)	0	0	1 (0.1)
Aortic dissection	0	0	0	1 (0.5)	0	1 (0.1)
Chest pain	1 (0.5)	0	0	0	0	1 (0.1)
COVID-19 pneumonia	0	1 (0.5)	0	0	0	1 (0.1)
Foot deformity	0	0	1 (0.5)	0	0	1 (0.1)
Influenza A virus test positive	0	0	0	0	1 (0.5)	1 (0.1)
Metatarsalgia	0	0	1 (0.5)	0	0	1 (0.1)
Myocardial infarction	0	1 (0.5)	0	0	0	1 (0.1)
Pancreatitis	1 (0.5)	0	0	0	0	1 (0.1)
Sepsis	0	0	0	1 (0.5)	0	1 (0.1)
Subdural haematoma	0	1 (0.5)	0	0	0	1 (0.1)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section 1 - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE003FL = 'Y'.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 60 summarizes AES associated with IP discontinuation during DENALI. As expected, given the relatively short duration of the study, rates of IP discontinuation were low. Once again, the most common reasons reported were asthma and COVID-19, consistent with the population and timing of the trial.

Table 60. DENALI Adverse Events Leading to Discontinuation of IP During Randomized Treatment Period (Safety Analysis Set)

Preferred Term	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=201)	Placebo MDI (N=199)	Total (N=1000)
Asthma	0	0	0	2 (1.0)	2 (1.0)	4 (0.4)
COVID-19	0	0	1 (0.5)	0	1 (0.5)	2 (0.2)
Anxiety	0	0	1 (0.5)	0	0	1 (0.1)
Chest discomfort	0	0	1 (0.5)	0	0	1 (0.1)
Dysphonia	1 (0.5)	0	0	0	0	1 (0.1)
Erythema	0	0	1 (0.5)	0	0	1 (0.1)
Fluid retention	0	0	1 (0.5)	0	0	1 (0.1)
Insomnia	0	0	1 (0.5)	0	0	1 (0.1)
Mental impairment	1 (0.5)	0	0	0	0	1 (0.1)
Myocardial infarction	0	1 (0.5)	0	0	0	1 (0.1)
Oropharyngeal candidiasis	1 (0.5)	0	0	0	0	1 (0.1)
Palpitations	0	0	0	0	1 (0.5)	1 (0.1)
Restlessness	0	0	1 (0.5)	0	0	1 (0.1)
Wheezing	0	0	1 (0.5)	0	0	1 (0.1)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section 1 - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE005FL = 'Y'.

Significant Adverse Events

Table 61 summarizes AEs rated as “severe” during the randomized treatment period. Severity was assessed independently of seriousness and describes the intensity of signs or symptoms. The only severe AE occurring in more than one subject was asthma in BDA 80/180 and placebo arms. No unexpected patterns suggesting relationship to study IP emerged.

Table 61. Number of Subjects With an Adverse Event Rated as Severe During the Randomized Treatment Period by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=201)	Placebo MDI (N=199)
Preferred Term					
Asthma	0	1 (0.5)	0	0	1 (0.5)
Aortic dissection	0	0	0	1 (0.5)	0
Cough	0	1 (0.5)	0	0	0

	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=201)	Placebo MDI (N=199)
COVID-19 pneumonia	0	1 (0.5)	0	0	0
Myocardial infarction	0	1 (0.5)	0	0	0
Sepsis	0	0	0	1 (0.5)	0
Toothache	0	0	0	1 (0.5)	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AESEV = 'SEVERE'.

Treatment Emergent Adverse Events and Adverse Reactions

Table 62 summarized the most common (>2%) AEs in DENALI. The nature and distribution of AEs were similar to results from MANDALA, with nasopharyngitis and headache representing some of the most common terms. Rates of nasopharyngitis were slightly higher in the BDA arms compared to comparators. Generally, AES were balanced amongst treatment arms. Based on these data, no unexpected safety signals were identified.

Table 62. DENALI, Most Common (>2%) Adverse Events During the Randomized Treatment Period, by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=201)	Placebo MDI (N=199)
Preferred Term					
Nasopharyngitis	15 (7.6)	13 (6.4)	10 (5.0)	9 (4.5)	11 (5.5)
Headache	10 (5.1)	10 (4.9)	7 (3.5)	11 (5.5)	14 (7.0)
Diarrhoea	2 (1.0)	2 (1.0)	2 (1.0)	4 (2.0)	4 (2.0)
Nausea	1 (0.5)	2 (1.0)	5 (2.5)	0	5 (2.5)
Upper respiratory tract infection	2 (1.0)	3 (1.5)	4 (2.0)	1 (0.5)	2 (1.0)
Asthma	0	3 (1.5)	0	3 (1.5)	5 (2.5)
Oropharyngeal pain	2 (1.0)	2 (1.0)	5 (2.5)	2 (1.0)	0
Hypertension	4 (2.0)	2 (1.0)	0	2 (1.0)	2 (1.0)
COVID-19	2 (1.0)	1 (0.5)	2 (1.0)	0	4 (2.0)
Dysphonia	4 (2.0)	1 (0.5)	2 (1.0)	0	0

Source: Clinical Reviewer. OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section 1 - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment'; Percent Threshold: >= 2%.

8.4.5.1. Safety Analyses by Demographic Subgroups

Pediatric Subjects

Table 63 summarizes AEs among pediatric subjects in DENALI. The overall incidence of AEs was very low, with most rated mild or moderate in severity. The only AE attributed by investigators to randomized treatment was the same SAE of asthma in an adolescent subjects randomized to BDA 80/180. Based on these limited data, no new signals were identified.

Table 63. DENALI, Number of Subjects ≥4 to <18 With any Category of Adverse Event in the Randomized Treatment Period, Safety Analysis Set

	BDA MDI 160/180	BDA MDI 80/180		BD MDI 160	AS MDI 180		Placebo MDI	
Adverse Event	>=12 - <18 (N=4)	>= 4 - <12 (N=3)	>=12 - <18 (N=7)	>=12 - <18 (N=5)	>= 4 - <12 (N=4)	>=12 - <18 (N=5)	>= 4 - <12 (N=3)	>=12 - <18 (N=4)
Any AE	0	0	2 (28.6)	2 (40.0)	2 (50.0)	1 (20.0)	1 (33.3)	0
Any AE causally related to randomized treatment	0	0	1 (14.3)	0	0	0	0	0
Any SAE	0	0	1 (14.3)	0	0	0	0	0

8.4.6. Safety Results: TYREE

Since TYREE was a single-dose study in patients with mild asthma and / or EIB, AEs were rare with only three terms reported, as shown in Table 64. The AEs of dyspnea and neck pain were both mild in severity and self-limited. The report of anxiety was rated as moderate but was also self-limited.

Table 64. TYREE, Number of Subjects With any Adverse Event During the Randomized Treatment Period, by Preferred Term (Safety Analysis Set)

Preferred Term	BDA MDI 160/180 (N=29)	Placebo MDI (N=31)
Anxiety	0	1 (3.2)
Dyspnoea	1 (3.4)	0
Neck Pain	0	1 (3.2)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Preferred Term - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment'.

8.4.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Pregnant and lactating subjects were excluded based on enrollment criteria. After randomization, 6 subjects reported an AE of pregnancy: in the BDA 160/180 treatment group, 1 pregnancy was reported resulting in a healthy baby; in the BDA 80/180 group, 1 pregnancy was reported, which resulted in an elective termination; in the AS group, 4 pregnancies were reported, with 2 resulting in healthy babies, 1 in elective termination, and 1 with unknown outcome because of withdrawn consent. Based on these data, no new safety signals were identified.

Pediatrics and Assessment of Effects on Growth

The Applicant collected height measurements on all subjects < 18 at screening and 24 weeks. Two subjects from the ≥ 4 to < 12 group were excluded because of unreliable measurements. In a post-hoc analysis in subjects ≥ 4 to < 12 that excluded those two subjects, the Applicant reports that the mean change in height in centimeters (cm) was +1.6 cm (SD = 1.94) in the BDA 80/180 arm and +2.4 cm (SD = 2.14) in the AS arm. For subjects ≥ 12 to < 18, the Applicant reports the mean changes in height were: +0.8 cm (SD = 1.00) in the BDA 160/180 arm, +1.3 cm (SD = 2.40) in the BDA 80/180 arm, and +0.9 cm (SD = 1.60) in the AS arm. Based on the relatively short duration of the growth interval and the small sample, no new conclusions about the effects of BD on growth could be drawn. The potential for growth restriction in pediatric subjects is a known class effect of ICS, and the risk of reduction in growth velocity is included in the label in Section 5.13.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdose or drug abuse potential is anticipated with the use of BDA MDI.

8.4.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant submitted a 120-day safety update report on July 8, 2022, which covered the period from the primary database lock, which occurred on August 23, 2021. This report included safety follow up data on 38 subjects 4 to 17 years of age, who were still ongoing in the study at the time of the primary database lock. During this period, three new AEs were reported of mild to moderate intensity. There were no clinically important differences in the safety data from what was presented with the original NDA submission.

Expectations on Safety in the Postmarket Setting

Post-marketing experience is unlikely to vary significantly from clinical experience to date with the mono-components or from the safety profile observed during the MANDALA trial.

8.4.9. Integrated Assessment of Safety

The safety data submitted with this application were sufficient to support a new indication for asthma in adult subjects ≥18 years of age. The primary source of safety data was MANDALA. DENALI provided supportive safety data related to standing rather than PRN administration and more frequent dosing than observed, on average, in MANDALA. Overall, the safety assessment, which included an evaluation of deaths, SAEs, all AEs, dropouts, pneumonia events, laboratory findings, vital signs, and ECGs, was consistent with other products containing SABA and ICS. No new safety signals were revealed in this application. There were no large imbalances identified between the treatment arms. Safety data among pediatric subjects was largely consistent with that in adults and did not raise new safety concerns; however, the scope of the safety database

for pediatric subjects was limited, both in size and duration, to support a definitive benefit-risk assessment in this population, in the absence of clear evidence of benefit.

8.5. Statistical Issues

Statistical issues that will be discussed in more detail include the efficacy data in pediatric patients and the robustness of the efficacy data.

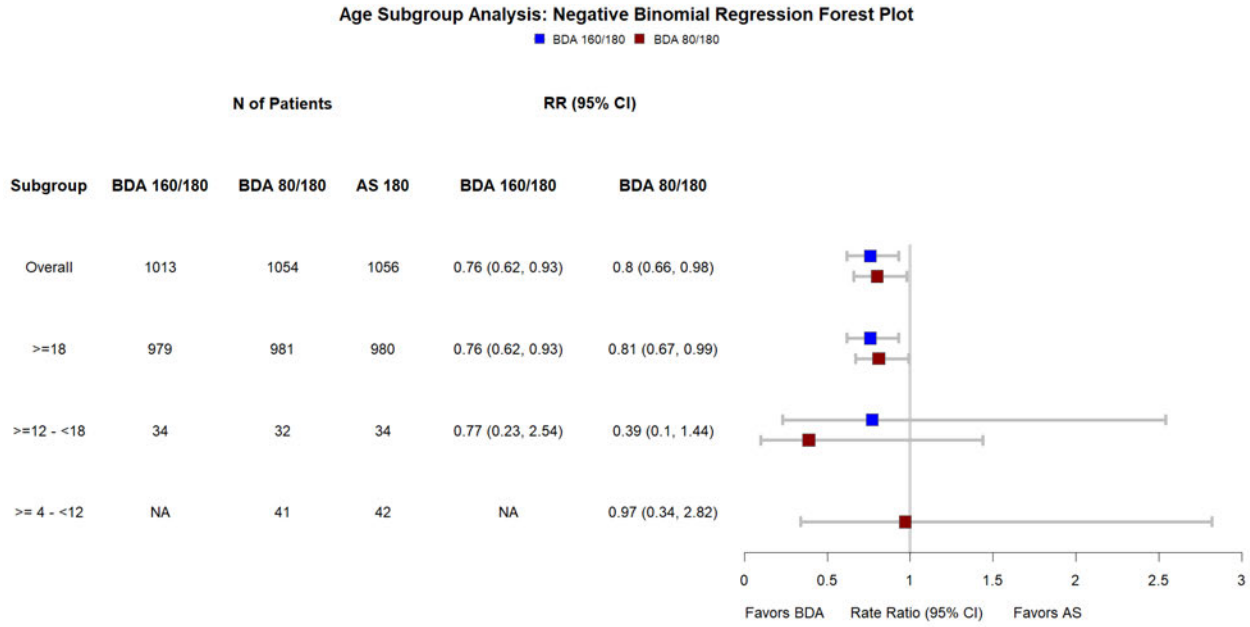
Pediatric Efficacy

MANDALA was powered for primary efficacy comparisons in subjects ≥12 years, and subjects ≥4 to <12 years were included for exploratory analyses and to collect safety data, based on the rationale that both components of BDA are already approved—although for a different indication and intended use—in younger children. This trial enrolled 100 adolescents (≥12 to <18 years) and 83 children (≥4 to <12 years), comprising 3% and 2.6% of the randomized population, respectively. The upper confidence limits for the hazard ratios exceed 1 and the confidence intervals are wide in the two pediatric subgroups for the primary endpoint (Figure 7). We hypothesize the wide confidence intervals and high degree of uncertainty that limits interpretation may be a function of small sample sizes. Furthermore, 37 of the pediatric subjects were in their early treatment duration (had not yet completed 24 weeks of randomized treatment) when the study was completed, and they were censored in the primary efficacy analysis, which made the pediatric analysis results even less statistically reliable.

Also, the trends of the efficacy results among subjects ≥4 to <12 years were generally inconsistent with those observed in adults across the key efficacy endpoints (Figure 7, Figure 10, Figure 11, Figure 12) with a high degree of uncertainty rendering it difficult to support definitive conclusions about their efficacy. Although the trends of the key secondary efficacy results for the high dose BDA in subjects ≥12 to <18 were consistent with those in adults, there was a more favorable trend for the low dose BDA in subjects ≥12 to <18.

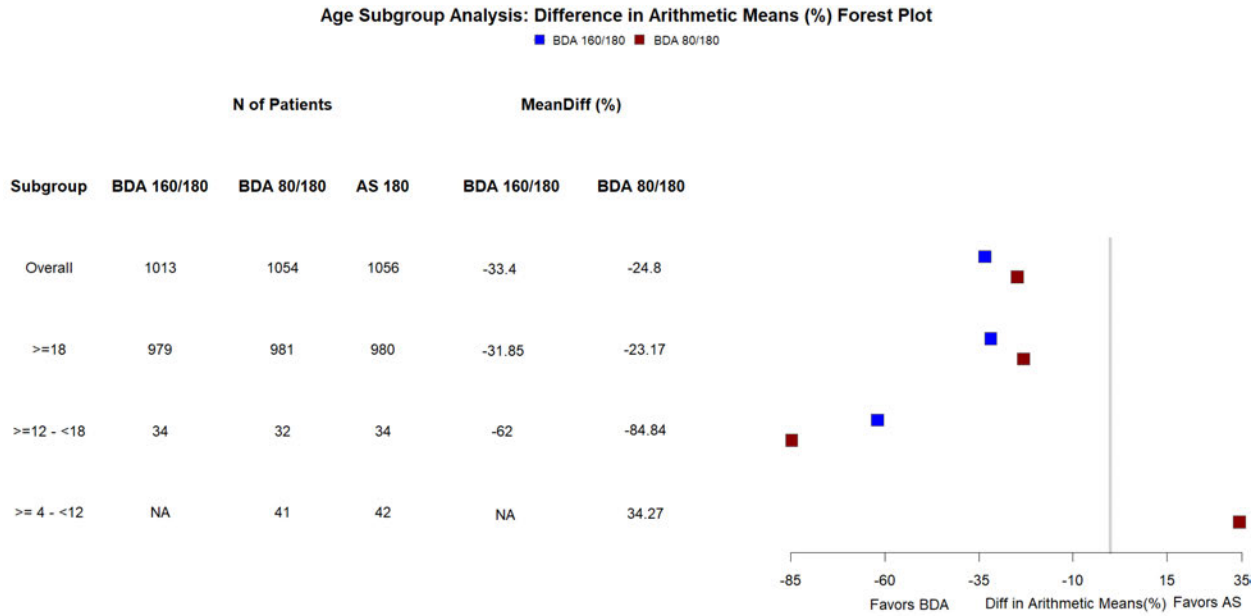
Overall, we conclude that efficacy in the two pediatric subgroups is inconclusive.

Figure 10. Forest Plot for Annualized Severe Exacerbation Rate, Efficacy Estimand, Age-Based Subgroups (FAS; All Ages)



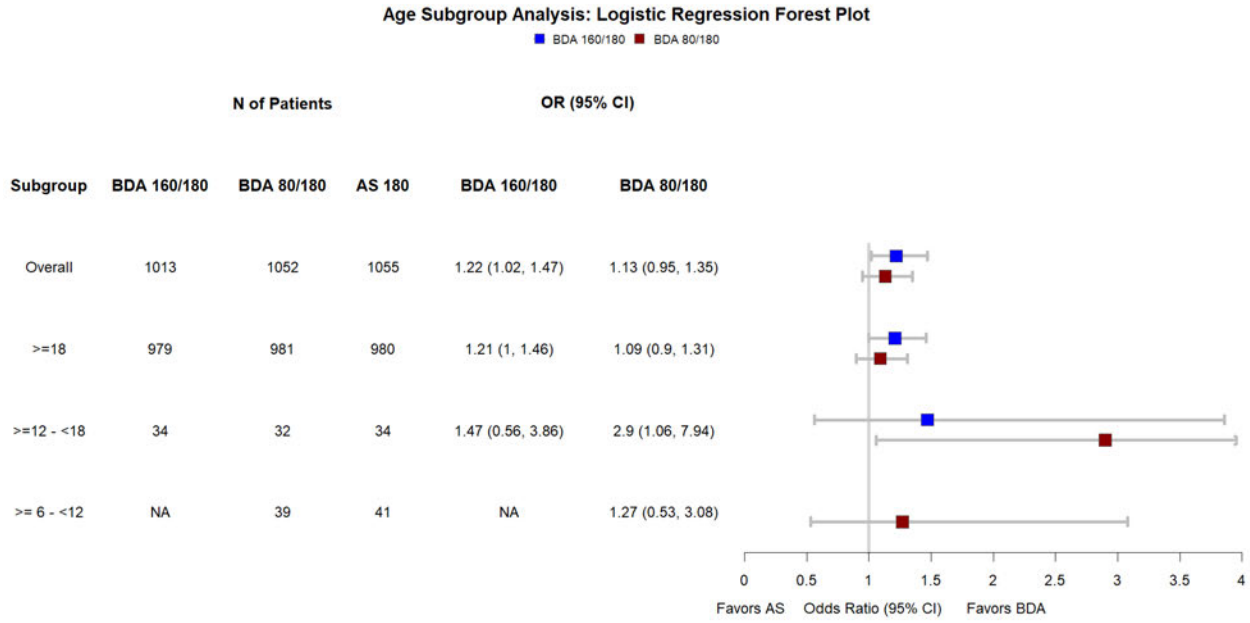
Source: Statistical Reviewer.

Figure 11. Forest Plot for Annualized Total Systemic Corticosteroid Use (mg), Efficacy Estimand, Age-Based Subgroups (FAS; All Ages)



Source: Statistical Reviewer.
Note: Estimates are % difference in arithmetic means in annualized total SCS dose. 95% CIs were not calculated.

Figure 12. Forest Plot for ACQ5 Responder, Efficacy Estimand, Age-Based Subgroups (FAS; All Ages)



Source: Statistical Reviewer.

Robustness of Efficacy Data

In MANDALA, among the 3132 randomized subjects, 363 subjects (9.8% 160/180 BDA, 11.5% 80/180 BDA, 13.3% AS) discontinued randomized treatment (see Table 16). To examine the robustness of the primary analysis results to missing data from patients discontinuing IP or changing maintenance therapy because of loss of asthma control, bi-dimensional tipping point analyses were conducted by the Applicant. In both BDA and AS arms, the event times following censoring because of discontinuation of IP or a change in maintenance therapy for loss of asthma control were imputed using multiple imputation methods. The imputation used the model predicted hazard function with a penalty δ applied, corresponding to an increased log-hazard of a severe asthma exacerbation. Delta values for each treatment arm were independently varied from δ=0.0 (corresponding to a standard censoring at random (CAR) based multiple imputation analyses) to δ=10.0 (corresponding to imputing event times immediately after the observed censoring date) as depicted in Table 65.

In the tipping point analyses for the BDA 160/180 vs AS comparison, no delta values between 0.0 and 10.0 produced a tipping point. The largest p-value observed was 0.009. This is likely an implausible scenario in which the hazard for subjects discontinuing treatment or with a change in therapy is greater than 22,000-fold that of the observed data. This result suggests that the assumptions under which the conclusion of efficacy for BDA 160/180 no longer holds are clinically implausible and, therefore, support the main conclusion of the primary analysis.

The primary analysis for BDA 80/180 vs AS, however, was less robust. The tipping point is found when the log-hazard is increased by 1.1 on the BDA arm and there is no penalty for the AS treatment group (see Table 66). This is likely a plausible scenario in which the hazard for subjects discontinuing treatment or with a change in maintenance therapy is greater than 3-fold that of the observed data. This finding suggests that the results for comparison between the low dose BDA and AS are not robust to the model assumption.

Note that these analyses imputed missing data from subjects discontinuing IP or changing maintenance therapy because of loss of asthma control (17 from 160/180 BDA, 17 from 80/180 BDA, 9 from AS), which comprise a small portion of overall missing data (79 from 160/180 BDA, 100 from 80/180 BDA, 101 from AS). Therefore, the conducted tipping point analyses examining robustness of the primary efficacy results are limited to the missing data due to lack of asthma control and does not explore the impact of CNAR assumption on overall missing data.

Table 65. Tipping Point Analysis p-Values for BDA 160/180 MDI Severe Asthma Exacerbations

AS MDI 180 Penalty	BDA MDI 160/180 Penalty													
	0	1	1.1	1.2	1.4	1.6	1.8	2	2.2	2.4	2.6	2.8	3	10
0	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.003	0.004	0.004	0.009
1	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.003	0.007
1.1	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.003	0.007
1.2	<.001	<.001	<.001	<.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.003	0.007
1.4	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.006
1.6	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.006
1.8	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.006
2	<.001	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.005
2.2	<.001	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.005
2.4	<.001	<.001	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.004
2.6	<.001	<.001	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.002	0.004
2.8	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.004
3	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.002	0.002	0.004
10	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	0.001	0.001	0.001	0.003

Source: The Applicant's response to Information Request, dated September 9, 2022 (Table 14.13.2.2.1).

Table 66. Tipping Point Analysis p-Values for BDA 80/180 MDI Severe Asthma Exacerbations

AS MDI 180 penalty	BDA MDI 80/180 penalty													
	0	1	1.1	1.2	1.4	1.6	1.8	2	2.2	2.4	2.6	2.8	3	10
0	0.0351	0.0491	**0.0518**	0.0546	0.0595	0.0655	0.0718	0.0804	0.0879	0.0975	0.1087	0.1159	0.1230	0.1665
1	0.0289	0.0407	0.0430	0.0455	0.0497	**0.0549**	0.0602	0.0677	0.0742	0.0827	0.0926	0.0990	0.1052	0.1440
1.1	0.0282	0.0399	0.0421	0.0445	0.0486	**0.0537**	0.0589	0.0663	0.0728	0.0811	0.0907	0.0970	0.1032	0.1413
1.2	0.0278	0.0393	0.0415	0.0439	0.0479	**0.0530**	0.0581	0.0654	0.0717	0.0800	0.0895	0.0957	0.1018	0.1396
1.4	0.0264	0.0375	0.0396	0.0419	0.0458	**0.0506**	0.0556	0.0626	0.0687	0.0767	0.0859	0.0919	0.0977	0.1344
1.6	0.0248	0.0352	0.0373	0.0394	0.0431	0.0477	**0.0524**	0.0590	0.0649	0.0725	0.0811	0.0869	0.0926	0.1279
1.8	0.0232	0.0331	0.0350	0.0371	0.0405	0.0449	0.0494	**0.0558**	0.0614	0.0686	0.0769	0.0824	0.0878	0.1217
2	0.0218	0.0312	0.0330	0.0349	0.0382	0.0423	0.0466	**0.0528**	0.0581	0.0650	0.0730	0.0782	0.0834	0.1161
2.2	0.0206	0.0295	0.0312	0.0330	0.0362	0.0401	0.0443	**0.0501**	0.0552	0.0618	0.0695	0.0745	0.0795	0.1111
2.4	0.0194	0.0279	0.0295	0.0313	0.0343	0.0381	0.0420	0.0476	**0.0525**	0.0588	0.0662	0.0710	0.0758	0.1061
2.6	0.0184	0.0266	0.0282	0.0299	0.0328	0.0365	0.0402	0.0456	**0.0503**	0.0565	0.0636	0.0683	0.0729	0.1022
2.8	0.0177	0.0256	0.0272	0.0289	0.0317	0.0352	0.0389	0.0442	0.0488	**0.0547**	0.0617	0.0662	0.0708	0.0994
3	0.0169	0.0245	0.0260	0.0276	0.0303	0.0337	0.0373	0.0424	0.0468	**0.0525**	0.0593	0.0637	0.0680	0.0958
10	0.0137	0.0200	0.0213	0.0226	0.0249	0.0278	0.0308	0.0351	0.0389	0.0439	0.0497	**0.0535**	0.0573	0.0817

Source: The Applicant's response to Information Request, dated September 9, 2022 (Clinical Information Amendment, Table 1.11 3-1). Gray background and bold text represent the p-value for the penalties at which the tipping point occurs.

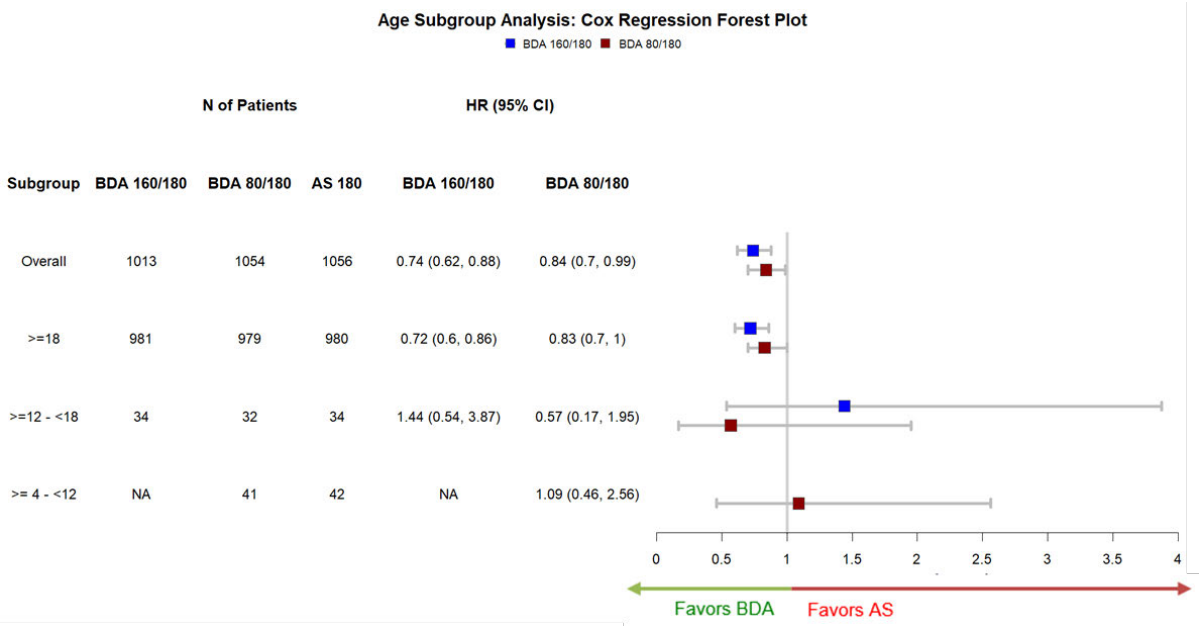
8.6. Conclusions and Recommendations

The data submitted by the Applicant demonstrated substantial evidence of effectiveness and safety for BDA 160/180 for the treatment of asthma in patients ≥18 years of age. The recommended regulatory action for this population and proposed dose is approval. (b) (4) .

MANDALA, the large, variable-duration exacerbation trial, was the primary source of data to assess substantial evidence of effectiveness. This trial enrolled 100 adolescents and 83 children, comprising 3% and 2.6% of the randomized population, respectively. Pediatric subjects, on average, also experienced shorter duration treatment periods because of the event-driven design, with only 70 adolescents and 55 children accruing 24 weeks of data by the primary completion date. Among pediatric subjects, a small number of exacerbation events occurred in each arm (<20 in BDA 80/180 and AS, <10 in BDA 160/180). In light of these limitations, the data failed to demonstrate benefit of BDA compared to AS among pediatric subjects.

This review team analyzed results in a hierarchical ranking of subgroups, as shown again in Figure 13. The analysis grouping together all subjects enrolled in the study (≥4 years of age for the low dose BDA, ≥12 years of age for the high dose BDA) supported efficacy. Similarly, the next analysis in the hierarchy, for the adult subgroup (≥18), also supported efficacy. Efficacy in the two pediatric subgroups is inconclusive, with point estimates favoring AS for the comparison of BDA 160/180 among adolescents and BDA 80/180 among children. Wide confidence intervals both exceed 1 and skew in favor of AS. This high degree of uncertainty and limitations to the data were consistent across secondary efficacy endpoints.

Figure 13. Forest Plot for Time to First Severe Asthma Exacerbation, Efficacy Estimand, Age-Based Subgroups, Full Analysis Set



Further efforts to mitigate this uncertainty through Bayesian analyses demonstrated the need to borrow approximately 95% of events from adults to achieve meaningful results in adolescents and children, i.e. nearly complete extrapolation. Given the novel combination, indication, and intended use of BDA, we determined there was too much uncertainty in disease similarity and response to therapy to support such a high degree of extrapolation. Although safety data was reassuring among pediatric subjects, its scope was too limited to support a definitive benefit-risk assessment for this age group in the context of insufficient evidence of benefit. We also weigh that pediatric patients would be the most vulnerable to the long-term risks of increased ICS exposure (e.g., growth restriction), which this program was not designed to assess, and possibly the most likely to engage in off-label use of this product (e.g., exercise-induce bronchoconstriction among adolescents).

9. Advisory Committee Meeting and Other External Consultations

This application was discussed at a virtual meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on November 8th, 2022. While factors for discussing this application with the advisory committee included the novelty as the first ICS/SABA combination product, the first use of an ICS as a reliever treatment to reduce the risk of progression to severe exacerbations, and the anticipated impact on asthma management as a replacement for albuterol for many patients, the primary goal of the meeting was to discuss the evidence supporting pediatric approval. The Agency sought the advisory committee's feedback on the efficacy, safety, and benefit-risk assessment of BDA for adults (≥18 years of age), adolescents (≥12 to <18 years of age), and children (≥4 to <12 years of age). Given the limited size of the pediatric populations studied and the need for near complete extrapolation of efficacy data from adults, the Agency specifically sought the committee's input on the appropriateness of extensive efficacy extrapolation from adults to younger children (4 to <12 years of age) and adolescents (12 to <18 years of age) to support approval.

After discussion of the available data from the BDA development program as presented by the Agency and Applicant (briefing documents, pre-recorded presentations, and live presentations), including clarifying questions to the Agency and Applicant, the committee voted in favor of the benefit-risk assessment of BDA for adults ≥18 years (16 yes, 1 no).

The committee was largely split on the vote for the benefit-risk assessment of BDA for adolescents 12 to <18 years of age (8 yes, 9 no). Of note, several committee members who voted "yes" for a favorable benefit-risk assessment in adolescents cited deferral to precedent, rather than compelling evidence from the development program; some who voted "no" also left room for Agency discretion given the potential for some adolescents to benefit from approval of BDA. The risk of use by adolescents to treat EIB with BDA, since it would functionally replace albuterol, was a topic of concern, and the limited information provided by the small pediatric safety database for a new intended use was also raised as a concern. Several committee members noted that there was considerable uncertainty not only in the data itself, mainly the wide confidence intervals and unexpected dose response, but also in the available literature to support extrapolation. The committee did not express that the totality of the literature was robust enough to bridge the gap between the available data and extensive extrapolation of efficacy data from adults.

Finally, the committee voted that the benefit-risk assessment of BDA for younger children 4 to <12 years of age was not favorable (1 yes, 16 no) , citing the lack of evidence of benefit and unaddressed long-term safety concerns with pairing an ICS with a short-acting reliever medication.

The committee expressed interest in having the Agency and Applicant work together to generate additional data to determine whether children could benefit from BDA.

10. Pediatrics

This application triggered PREA as a new active ingredient (novel combination). Both pivotal trials supporting SEE, MANDALA and DENALI, enrolled children 4 years of age and older to support approval in the pediatric population, as outlined in the Agreed initial Pediatric Study Plan (iPSP). In accordance with 21 CFR 314.55(c)(3)(i) and 314.55(a) and Sections 505B(a)(4)(B)(iii) of the Federal Food, Drug, and Cosmetic Act, the Applicant requested a partial waiver for children <4 years of age in this NDA submission based on the product not representing a meaningful therapeutic benefit over existing therapies in patients less than 4 years of age and not likely to be used in a substantial number of pediatric patients in this age group. The request was reviewed by the Pediatric Review Committee (PeRC) on November 15, 2022, and PeRC agreed to grant the partial waiver as requested. (b) (4)

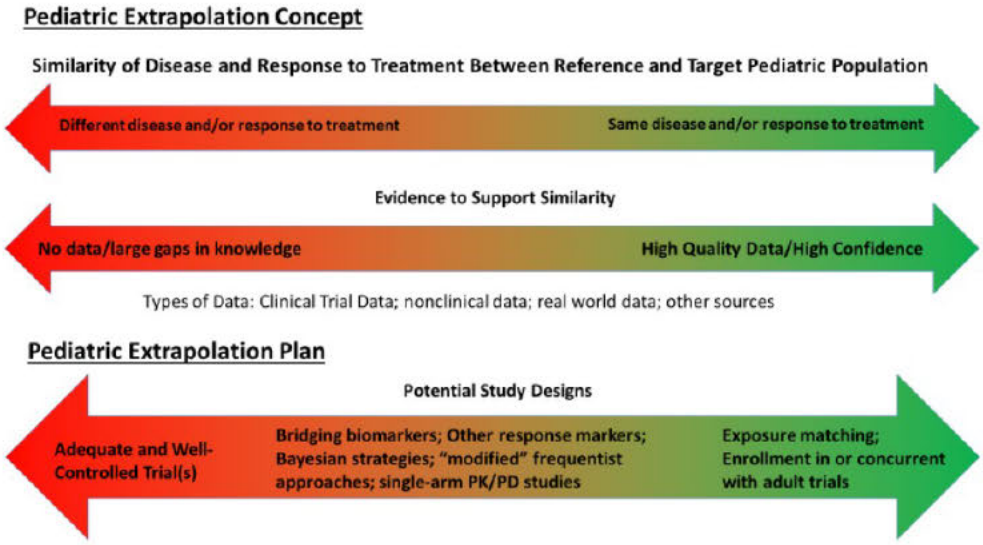
The Applicant provided an assessment of efficacy and safety in patients 4 years of age and older in the MANDALA and DENALI trials in this application:

- MANDALA included 100 adolescent subjects 12 to <18 years of age and 83 subjects 4 to <12 years of age; the trial fell slightly short of its pediatric enrollment goal due to challenges with recruitment during the COVID-19 pandemic, as previously discussed with the Agency. The analysis of the primary endpoint (time to first severe exacerbation) and key secondary endpoints (annualized rate of severe exacerbations and annualized total systemic corticosteroid dose) demonstrated benefit of BDA vs AS in subjects ≥18 and in all subjects ≥12, when grouped together. However, in *post hoc* subgroup analyses of both pediatric subgroups (4 to <12 years of age and 12 to <18 years of age), point estimates for the hazard ratios using the proposed doses favored AS vs BDA, with very wide confidence intervals. The inconclusive results were consistent across all key secondary endpoints, including annualized rate of severe exacerbations and total annualized systemic corticosteroid dose. Details of the MANDALA efficacy results and pediatric subgroup analyses are discussed in Section 8.2.1. No new safety concerns were identified, but the pediatric data was limited by the small sample size and paucity of data from pediatric subjects who had received 24 weeks of treatment by the time of the primary analysis. The adverse events AEs were balanced across treatment arms, and very few AEs led to treatment discontinuation or were attributed by investigators to randomized treatment. Serious adverse events were rare, with the greatest number occurring in the AS comparator arm and attributed to loss of asthma control.
- DENALI enrolled 25 adolescent subjects 12 to <18 years of age and 10 subjects 4 to <12 years of age. Dual primary endpoints assessed FEV1 (AUC0-6 hours over 12 weeks and change from baseline in trough FEV1 at week 12). In the adult population and full analysis set including subjects ≥12 years of age, both doses of BDA demonstrated benefit compared to AS and fulfilled the combination rule. Numeric trends in pediatric subgroups

demonstrated no benefit for BDA 80/180 in subjects 4 to <12 years of age and some benefit for both doses in adolescents 12 to <18 years of age. Details of the DENALI efficacy results and pediatric subgroup analyses are discussed in Section 8.2.2. Given the limitations of the sample sizes and pharmacodynamic endpoints, these data do not add information beyond what is already known from the approved mono-component drug products in pediatric subjects. Safety data from DENALI, while very limited in scope, was reassuring, and no unexpected signals were identified in any age cohort.

Inhalation products for asthma are locally acting, and extrapolation based upon pharmacokinetic results is not applicable for these products. Clinical data are required in pediatric patients. Asthma programs have frequently enrolled adolescents in adult efficacy and safety trials when there is sufficient safety data available and preliminary evidence for prospect of benefit to support initiation of a pediatric study. Although statistical significance in pediatric subgroups has not always been a requirement, we have generally expected trends in efficacy and safety data consistent with adults, both in terms of treatment effect and dose response. Approval in the adolescent subgroup for inhaled asthma products have typically leveraged some degree of efficacy extrapolation from adult data, but usually when there has been prior experience with the drug class or active pharmaceutical ingredient (e.g. ICS for controller treatment) or there is sufficient data to support extensive efficacy extrapolation from adults. In the case of BDA, the degree of appropriate efficacy extrapolation from adults was complicated by the novelty of the combination product, the new intended use of PRN ICS to reduce the risk of severe exacerbations, and conflicting support from available literature, in addition to the lack of evidence of benefit from the pivotal trials, uncertainty around dosing, and small scope of safety data for the new intended use. The standards and principles outlined in the FDA Draft Guidance for Industry: *E11A Pediatric Extrapolation*,as discussed in Section 1.2, helped frame our assessment of the quality of evidence available to overcome these barriers. Figure 14 below provide a visualization of key considerations for pediatric extrapolation.

Figure 14. Pediatric Extrapolation in Drug Trials



Source: FDA Draft Guidance for Industry: E11A Pediatric Extrapolation

As discussed in Section 8.2.1.6, extrapolation of efficacy in the MANDALA trial using a Bayesian approach would require around 95% borrowing of adult data to achieve significance. Based on a literature review and discussion at the November 8, 2022 PADAC meeting regarding support for near complete extrapolation of efficacy data from adults to support pediatric approval, the available evidence did not meet the standards required to support extrapolation for BDA for this proposed indication.

(b) (4)

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Table 67. Prescription Drug Labeling

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 INDICATIONS AND USAGE	AIRSUPRA is indicated for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older. *The indication was revised to adult patients from patients 4 years and older because the efficacy data did not provide conclusive evidence for use of AIRSUPRA in pediatric patients.*
2 DOSAGE AND ADMINISTRATION	The recommended dosage is AIRSUPRA 180 mcg/160 mcg (administered as 2 actuations of albuterol/budesonide 90 mcg/80 mcg) by oral inhalation as needed for asthma symptoms. Do not take more than 6 doses (12 inhalations) in a 24-hour period. *Recommended dosage and dosage form for the lower dose of AIRSUPRA (albuterol/budesonide 90 µg/40 µg) intended for pediatric patients was removed from labeling because the indication is for adults.*
4 CONTRAINDICATIONS	None.
5 WARNINGS AND PRECAUTIONS	(b) (4) was modified for 'Effects on Growth in Pediatric Patients.' *This warning and precaution title and text was modified to specify the effect in pediatric patients and text was modified to convey that AIRSUPRA is not indicated for use in the pediatric population. Otherwise, this section was class labeling and ordered by clinical importance.*
6 ADVERSE REACTIONS	• Included common adverse reactions from MANDALA study. • Adverse reactions from DENALI were provided in text. • Added Postmarketing Experience subsection to include adverse reactions from individual components (albuterol and budesonide) of AIRSUPRA.
7 DRUG INTERACTIONS	• Drug interactions reflect class labeling.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	• Updated PLLR language. • A summary of the clinical study and the inconclusive results in the pediatric population is described in Pediatric Use subsection.
12 CLINICAL PHARMACOLOGY	Removed language that was not from LDPs.
13 NONCLINICAL TOXICOLOGY	Information for this section are from LDPs.
14 CLINICAL STUDIES	• The efficacy from adult patients with moderate to severe asthma in the MANDALA study was evaluated and its' results are described to support the indication and use. Efficacy results are limited to adults ≥18 years of age

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
	and have been confirmed. • DENALI is also included to convey data on the onset of action of action and duration of action of bronchodilation for BDA, which is relevant for understanding the effects of a novel reliever inhaler.
17 PATIENT COUNSELING INFORMATION	Included information that a healthcare provider should convey to a patient focusing on risks of the drug.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Removed the lower dose (albuterol/budesonide 90 µg/40 µg) and aligned with the Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products--Quality Considerations https://www.fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations

12. Postmarketing Requirements and Commitment

There are no postmarketing requirements or commitments for this NDA.

APPEARS THIS WAY ON ORIGINAL

13. Division Director (Clinical) Comments

Product Information and Background

AstraZeneca in conjunction with Bond Avillion submitted this 505(b)(2) NDA for a new FDC of budesonide and albuterol sulfate (BDA) for the proposed indication of "as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older." The proposed tradename is Airsupra. The Applicant proposed two dose strengths of BDA:

1. High dose – 80 µg budesonide and 90 µg albuterol (equivalent to 108 albuterol sulfate).
2. Low dose – 40 µg budesonide/90 µg albuterol (equivalent to 108 albuterol sulfate).

The Applicant's proposed dosing regimen is BDA 160/180 (2 actuations of the high dose product) for patients ≥12 years of age and BDA 80/180 (2 actuations of the low dose product) for patients ≥4 to <12 years of age. The maximum dose is not to exceed 12 inhalations in 24 hours.

Budesonide and albuterol are well-established therapeutics approved for use in the management of asthma. There are numerous approved MDIs and DPIs that contain albuterol or budesonide; however, BDA represents a new combination, and it would be the first ICS/SABA combination product in the US. There are a number of ICS/LABA combination products approved for the treatment of asthma, but these products are currently approved as maintenance or long-term control medications. Thus, the proposed use of BDA as a reliever therapy to be used on an as needed basis is also a new proposed use for this combination product.

BDA was developed to provide rapid symptom relief through bronchodilation with albuterol and to treat inflammation with budesonide in order to prevent or reduce the severity of exacerbations. The concept of an ICS combined with a beta agonist for reliver therapy is not new. Single maintenance and reliever therapy (SMART) with ICS/formoterol is recommended by international guidelines for asthma, i.e., the Global Initiative for Asthma (GINA). However, ICS/formoterol is not approved in the US for as needed use. Updated US NAEPP guidelines recommend the use of a concomitant PRN ICS with SABA for some patients as the preferred alternative to SMART. BDA would provide an ICS and SABA in a fixed dose combination that would align with NAEPP guideline recommendations.

This 505(b)(2) application relies upon the FDA's previous findings of safety and effectiveness of Proventil (albuterol sulfate) HFA Inhalation Aerosol. The scientific bridge between BDA and Proventil HFA was established in a pharmacokinetic study comparing systemic exposure between the products. The Applicant also references other AstraZeneca products, including Pulmicort Respules Inhalation Suspension and Pulmicort Flexhaler Inhalation Powder. The

scientific bridge between BDA and the Pulmicort products was established in a pharmacokinetic study comparing systemic exposure between the products.

Regulatory History

Since there is no regulatory precedent for an ICS/SABA product with PRN administration, the Applicant and FDA discussed a development program that could establish the efficacy and safety of BDA for the proposed indication and satisfy the 'combination rule (*21CFR300.50a*). The Agency agreed that a large trial comparing BDA to AS, administered PRN, with asthma exacerbations as the primary endpoint would provide the primary data to support the efficacy of BDA. This design would provide information on the contribution of the ICS and also provide data to evaluate the effect on asthma exacerbations. Since AS is already approved as a reliever therapy, the benefit of the ICS component was the greater concern; therefore, an ICS comparator arm was not necessary. The Agency agreed that a separate factorial design trial with scheduled administration of treatments could fulfill the combination rule and provide additional safety information. Given what is known about AS and BD, the Agency encouraged the Applicant not only to include adolescents, but also younger children early in the BDA development program.

There was an agreed upon iPSP with the Applicant. The Applicant planned to enroll pediatric patients down to 4 years of age in the clinical program, specifically the MANDALA and DENALI trials. A waiver for children < 4 years was planned based upon the rationale that that BDA would not represent a meaningful therapeutic benefit over existing therapies and not likely to be used in a substantial number of pediatric patients in this age group. In the original iPSP, approximately 100 pediatric patients 12 to 17 years and 50 pediatric patients 4 to 11 years would be enrolled in MANDALA. In DENALI, approximately 50 patients 12 to 17 years and 30 patients 4 to 11 years would be enrolled. The iPSP states this would provide a sufficient number of pediatric patients to allow meaningful interpretation of the data. An amended iPSP was submitted that decreased the number of pediatric patients in DENALI from 50 adolescents and 30 children to 10 adolescents and 3 children due to recruitment issues and challenges related to the COVID-19 pandemic.

Chemistry Manufacturing Controls

BDA is an MDI with an integrated dose counter that uses HFA-134a as the propellant. There are no novel excipients and there are many similarities in the formulation, device, and manufacturing process to the approved Bevespi and Breztri Aerosphere products. The Applicant plans to market a 120-inhalation product. Submitted stability data support the 24-month shelf life. The OPQ team recommendation is the NDA is adequate for approval.

Nonclinical

No new nonclinical pharmacology or toxicology studies were required for this NDA. Using the 505(b)(2) pathway, the nonclinical toxicology data to support BDA is based upon the available

safety information from other listed products. See Section 5 for more information on the referenced nonclinical information.

Clinical Pharmacology

The Applicant submitted a clinical pharmacology program that demonstrated the following: 1) a lack of pharmacokinetic interaction between BD and AS in the BDA drug product; 2) the systemic exposure of albuterol sulfate in BDA was less than Proventil HFA, providing a scientific bridge to support the 505(b)(2) application; 3) the systemic exposure of budesonide in BDA was less than Pulmicort Flexhaler in adults and Pulmicort Respules in children 4 to 8 year; and 4) the budesonide exposure in children 4 to 8 years is about half the exposure in adults. Simulations were also provided to assess the budesonide exposure from the maximum potential daily use of BDA on top of BD controller therapy in pediatric patients. These simulations showed that the systemic exposure of BD in pediatric patients was lower than adults. See Section 6 for more details. There are no outstanding clinical pharmacology issues.

Clinical Program

The Applicant submitted a clinical program that included 3 efficacy trials: MANDALA, DENALI, and TYREE. Each of these clinical trials will be briefly summarized.

MANDALA

MANDALA was an event-driven, randomized, double-blind, comparator-controlled trial in 3132 patients 4 years of age and older with moderate to severe asthma. Patients were randomized to BDA (160/180 or 80/180 in patients 12 years of age and older or 80/180 in patients 4 to 11 years of age) or albuterol to be used as needed, similar to how they would use their pre-enrollment SABA. Patients were allowed to use the randomized treatment prior to exercise. The primary endpoint of MANDALA was time to first severe acute asthma exacerbation (defined as loss of symptom control and worsening lung function (by peak expiratory flow (PEF) or FEV1), requiring a burst of systemic corticosteroids for at least 3 days, with or without urgent care or ED visit or hospital admission).

Of the 3,132 subjects randomized in MANDALA, 100 subjects were 12 to <18 years of age and 83 subjects were 4 to <12 years of age. Subjects <12 years of age were not randomized to high dose BDA treatment. The primary and key secondary analysis were performed in the subgroup of patients 12 years and older. Results from MANDALA showed a significant delay in time to first exacerbation in patients 12 years and older, HR 0.74 [95% CI: 0.62, 0.89]. Subgroup analysis based upon age were performed. Table 23 shows results for the primary endpoint in age-based subgroups. A few key points are worth noting. First, the number of pediatric patients is quite small (32-42 per arm). Second, MANDALA was an event driven trial and there were few patients with events in pediatric subgroups (4 to 11). Given the few number of patients with events events, wide confidence intervals make the results difficult to interpret – see Figure 7.

Secondary endpoints (systemic corticosteroid use, severe exacerbation rate, ACQ-5 responders), were supportive of efficacy in the overall population of patients 12 years and older. Subgroup analyses of patients 12 to < 18 years and 4 to 11 years were noted to have wide confidence intervals with significant uncertainty as to interpretation.

DENALI

DENALI was a 12-week, randomized, double-blind, placebo-controlled trial in 1001 patients with mild to moderate asthma 4 years and older. Patients were randomized to one of the following treatment groups: BDA 160/180, BDA 80/180, budesonide 160, albuterol or placebo. Study medications were administered scheduled 2 inhalations QID. The dual primary endpoints were change from baseline in FEV1 $AUC_{0\text{-}6hours}$ over 12 weeks and change from baseline in trough FEV1 at week 12. The primary efficacy assessment was in patients 12 years and older. DENALI provides data to evaluate the contribution of each component of BDA to satisfy the combination rule (21CFR300.50), safety data, and efficacy data regarding the bronchodilator effect of BDA. Results from DENALI showed a significant increase in change from baseline FEV1 $AUC_{0\text{-}6hours}$ at week 12 for BDA compared to BD and placebo; and a significant increase in change from baseline trough FEV1 at week 12 for BDA both high and low dose compared to AS and placebo. These results provided evidence to demonstrate the contribution of each component of BDA on bronchodilation. Results from DENALI also provide data for the bronchodilator onset of action and duration of bronchodilation for BDA.

TYREE

TYREE was a single dose, cross-over study that evaluated the effect of BDA on exercise induced bronchoconstriction (EIB). The primary endpoint was the maximum percentage fall from post-dose, pre-exercise baseline in FEV1 up to 60 minutes post-exercise challenge. The treatment arms were BDA 160/180 and placebo. Since albuterol is already known to be effective for EIB, the Division recommended the Applicant evaluate the contribution of BD in the treatment of EIB, which would require inclusion of an albuterol treatment arm. The Applicant did not include an albuterol treatment arm in TYREE. Results from TYREE showed that BDA significantly decreases the maximum percentage fall in FEV1 post-exercise, which is consistent with the known efficacy of albuterol for EIB.

Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for BDA is based upon 2 adequate and well-controlled trials – MANDALA and DENALI. Both contribute to the body of evidence to support the effectiveness of BDA. MANDALA provides data to support the reduction in exacerbation benefit and DENALI provides data to support the bronchodilation benefit, as well as satisfaction of the combination rule.

Safety

The clinical team reviewed the safety data from the clinical program and focused the review on the additive effects of ICS (i.e., BDA in addition to controller ICS), as well as results in pediatric subjects. Overall, the review did not identify new safety signals for BDA; the data were consistent with the known safety profiles of AS and BD. There were no significant differences between age cohorts or evidence of increased risk from PRN ICS use in pediatric patients; however, there are limitations to the safety data including the small number of pediatric patients enrolled and the inability to assess potential long-term effects of ICS given the study duration.

Pediatrics

Although pediatric patients were enrolled concurrently with adults in MANDALA, the number of pediatric subjects enrolled was small and there are considerable uncertainties with respect to the efficacy results in the pediatric subgroups. The FDA and the Applicant utilized Bayesian methods to evaluate the utility of borrowing adult data to support efficacy in pediatric subpopulations. Results of our analyses show that demonstration of efficacy in the pediatric subgroups in MANDALA requires borrowing large amounts (>95%) of adult data relative to the collected pediatric data. The high degree of Bayesian borrowing required to achieve meaningful results in pediatric subgroups suggests that almost complete extrapolation from adult data would be necessary to demonstrate efficacy.

Pediatric extrapolation can extend what is known about the adult population (e.g., efficacy) to pediatric subjects based upon an assessment of the relevant similarities of disease and response to therapy within the two populations. Extrapolation is a tool that can reduce the pediatric data requirements for pediatric development programs. Pediatric extrapolation should be based on careful clinical and pharmacological evaluations to determine how similar children are to adults in the course of disease and in response to treatment. Such evaluations should include the quality of available data, as well as important knowledge gaps and uncertainties as described in the recent *FDA Draft Guidance for Industry: E11A Pediatric Extrapolation*(FDA 2022).

Inhalation products for asthma are locally acting, and extrapolation based upon pharmacokinetic results is not applicable for these products. Clinical data are required in pediatric patients. We have not always required statistical significance in the adolescent subgroup to approve a product for this age group. For a dedicated trial in younger children, however, we generally expect statistical significance to be demonstrated. There have been exceptions to this approach, when safety data has been reassuring and efficacy is consistent with adolescents and adults. In these cases, we have leveraged some degree of extrapolation. However, most inhalation products approved for pediatrics have been for an established indication for the drug class (e.g., ICS as controller therapy) or even an established indication for the drug itself (e.g., reformulation of an ICS). BDA would represent a novel combination, indication, and intended use.

Advisory Committee Meeting

We convened an FDA Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting on November 8, 2022, to discuss the BDA NDA. A main focus of the discussion was the pediatric data and the role of extrapolation for this program. The panel discussion acknowledged the uncertainty of the data in pediatric patients and there was not clear feedback on how much extrapolation was appropriate. We asked the panel to vote on whether the benefit-risk assessment for BDA for the proposed indication is favorable in the following age groups and results are as follows:

- Adults 18 years and older – 16 Yes, 1 No
- Adolescents ≥ 12 to < 18 years – 8 Yes, 9 No
- Children ≥ 4 to 12 years - 1 Yes, 16 No

Feedback from the panel was clear that the benefit risk assessment for BDA was favorable for adults and not favorable for pediatric patients < 12 years of age. The panel was split on the benefit risk assessment for the ≥ 12 to < 18 age group. With regards to pediatric patients, the panel raised concern regarding uncertainty of benefit, given the limited pediatric data. The panel also raised some safety concerns, including limited safety data particularly in the youngest age group and the potential use for EIB that may unnecessarily expose pediatric patients to ICS. Overall, the panel did not provide a strong endorsement of the use of full extrapolation in pediatric patients for BDA for the proposed indication.

After considering the feedback from the AC panel, literature, and the available data, we have concluded that the available data in pediatric patients < 18 years are not adequate to establish substantial evidence of effectiveness. Instead, we would have to rely on a high degree of extrapolation from adult efficacy, and for a novel product with a novel indication, it isn't clear that the response to treatment will be the same in adults and pediatric patients. Despite agreement on enrollment of pediatric patients in the pivotal trials, the results provide too few patients with events to make any determination regarding efficacy. (b) (4) PREA studies will be waived in patients < 4 years of age consistent with the agreed upon iPSP.

(b) (4)

(b) (4)

Benefit Risk Assessment

Overall, the benefit risk assessment for BDA for adults is favorable. Results from MANDALA provide clear data to show that BDA delays the time to first severe exacerbation, reduces rate of severe exacerbation and dose of SCS. DENALI provides data to satisfy the combination rule, assess the onset of action and duration of bronchodilation. No new safety signals for BDA were identified as the data were consistent with the known safety profiles of AS and BD.

As discussed above, the available data in pediatric patients < 18 years are not adequate to establish substantial evidence of effectiveness. There are too few exacerbation events to make a determination regarding efficacy. While no safety signals were identified in pediatric patients, without confidence in the benefit of BDA in patients < 18 years, the benefit risk assessment is not favorable.

Labeling

The main labeling issue for this application pertained to the wording of the indication, primarily the indication only in adults and wording of prevention of exacerbations vs. reduce the risk of exacerbations. The Draft FDA Guidance for Industry on Indication and Usage Section of Labeling recommends the use of "reduce the risk" as "prevention" can imply a guarantee of success. Ultimately, the final agreed upon indication is "for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older".

Action

The action will be approval of Airsupra 160/180 for the the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older. There are no PMRs or PMCs (b) (4).

(b) (4)

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14. Appendices

14.1. References

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14.2. Financial Disclosure

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1280		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 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 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 509		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 63		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 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)

14.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.3.1. OCP Appendix I: Summary of the Bioanalytical Method

The concentrations of budesonide and albuterol in human plasma were measured by solid-phase extraction followed by high performance liquid chromatography followed by tandem mass spectrometric detection (LC/MS/MS). The bioanalytical methods are fully validated, and all human plasma samples were analyzed within the duration with stability demonstrated.

14.3.1.1. Budesonide

Table 68. Budesonide Validation Results Summary (Validation Report (b) (4) 13-225)

Budesonide Validation Results	
Internal Standard:	Budesonide-d_8
LLOQ and ULOQ:	3.00 pg/mL and 500 pg/mL
Calibration Standard Concentrations:	3.00, 6.00, 12.5, 50.0, 100, 250, 450 and 500 pg/mL
Inter-Assay Accuracy (%Bias): Inter-Assay Precision (%CV):	-2.0% to 4.0% 3.1% to 9.0%
Regression and Weighting:	Linear $1/x^2$
Quality Control Levels:	3.00, 9.00, 40.0, 200 and 400 pg/mL
	LLOQ QC
Intra-Assay Accuracy (%Bias): Intra-Assay Precision (%CV): Inter-Assay Accuracy (%Bias): Inter-Assay Precision (%CV): Intra-Assay results are reported as ranges from the A/P runs. Inter-Assay results are reported as the result from the ANOVA calculations.	-13.3% to 4.0% 8.2% to 12.0% -5.0% 8.1%
	Low, Low-Medium, Medium and High QC
Intra-Assay Accuracy (%Bias): Intra-Assay Precision (%CV): Inter-Assay Accuracy (%Bias): Inter-Assay Precision (%CV): Intra-Assay results are reported as ranges from the A/P runs. Inter-Assay results are reported as ranges from the ANOVA calculations.	-10.3% to 6.6% 1.5% to 9.9% -3.5% to -0.4% 5.1% to 8.0%
Ability to Dilute:	4,000 pg/mL (DF=10)
Dilution Linearity:	50,000 pg/mL (DF=200)
Carryover of Analyte:	No carryover detected
Carryover of Internal Standard:	No carryover detected
Method Selectivity:	Evaluated using 6 Lots of blank matrix
Selectivity Blanks:	No interference greater than acceptable limits detected at the retention times of interest.

Matrix Effects	
LLOQ Reproducibility in Matrix:	Accuracy (%Bias): -12.7% Precision (%CV): 6.4%
Matrix Factor Test:	Matrix Factor (Low) Analyte = 0.688 Internal Standard = 0.691 Matrix Factor (High) Analyte = 0.736 Internal Standard = 0.744 A matrix factor greater than 1 indicates ionization enhancement. A matrix factor less than 1 indicates ionization suppression.
IS-Normalized Matrix Factor Test:	IS-Normalized MF (Low) = 1.00 IS-Normalized MF (High) = 0.991
Interference	
Analyte Only:	No significant interference found at the retention time of interest for Analyte Only samples.
Internal Standard Only:	No significant interference found at the retention time of interest for IS Only samples.
Additional Compounds:	Formoterol fumarate (100 pg/mL), Glycopyrrolate (100 pg/mL) Quantitation of budesonide is not impacted by the co-administered compounds when present at the concentrations described above.
IS Recovery:	23.8%
Analyte Recovery:	28.6% (Low) 23.4% (Medium) 21.3% (High)
Solution Stability	
IS Solution Stability	
Bench-Top:	7 Hours in water: acetonitrile (50:50 v/v) at room temperature and protected from light. Originally reported in (b) (4) 09-055 [11.1]
Analyte Solution Stability	
Bench-Top:	7 Hours in DMF at room temperature and protected from light. Originally reported in (b) (4) 09-055 [11.1]

Long-Term Stock:	Analyte stock solution concentration (0.600 mg/mL): 136 Days in DMF stored in a polypropylene container at 5 °C. Originally reported in (b) (4) 09-055TRA2 [11.1] Any additional stability conducted for this study will be added either as an addendum or appendix to that report.
Long-Term Working:	Analyte working solution concentration (0.240 ng/mL): 29 Days in DMF stored in a polypropylene container at 5 °C. Originally reported in (b) (4) 09-055TRA2 [11.1] Any additional stability conducted for this study will be added either as an addendum or appendix to that report.
Stability in Matrix	
Freeze-Thaw:	4 Cycles; stored at -70 °C and thawed at 5 °C
Bench-Top:	6 Hours at 5 °C
Intermediate-Term:	22 Days at -70 °C demonstrated by on-going analysis of QC samples against freshly prepared standards
Long-Term:	34 Days at -20 °C and -70 °C
Reinjection Reproducibility:	147 Hours at room temperature
Extract Stability:	47 Hours at room temperature
Whole Blood Stability:	2 Hours at room temperature and 5 °C
Hemolysis:	No significant impact in samples with up to 2.0% hemolysis
Hyperlipidemia:	No significant impact in samples with hyperlipidemia (Triglycerides >300 mg/dL; Total Cholesterol >250 mg/dL)
Batch Size Evaluation:	Sample analysis runs may include up to 192 samples (including Standards, QCs, Blanks, Unknowns, etc.)

*Per Report Addendum No. 3 (September 2019), the presence of albuterol up to 20,000 pg/mL in plasma has no effect on the assay performance. The bench-top stability was demonstrated to be 24 hours at room temperature for budesonide at 600,000 ng/mL prepared in DMF, budesonide-d_8 at 5.00 ng/mL prepared in H20:MeCN (50:50 v/v), and budesonide intermediate solutions at 0.240 ng/mL prepared in DMF. The matrix bench-top stability was demonstrated to be 25 hours at room temperature. The matrix freeze-thaw stability was demonstrated to be 8 cycles at -70°C. The matrix frozen stability (in the presence of albuterol) was demonstrated to be 91 days at -20°C. (Source: Page 13 of (b) (4) Report No. (b) (4) 13-225)

14.3.1.2. Albuterol

Table 69. Albuterol Validation Results Summary (Validation Report (b) (4) I 0-221)

Albuterol Validation Results Summary	
Internal Standard:	Albuterol-d_3
LLOQ and ULOQ:	1.00 pg/mL and 1,000 pg/mL
Albuterol Calibration Curve Range:	1.00, 2.00, 10.0, 50.0, 250, 500, 900 and 1,000 pg/mL
Regression and Weighting:	Linear $1/x^2$
Quality Control Levels:	1.00, 3.00, 400 and 800 pg/mL
LLOQ	
Intra-Assay Accuracy (%Bias):	-10.6% to 5.0%
Intra-Assay Precision (%CV):	3.7% to 11.6%
Inter-Assay Accuracy (%Bias):	-5.1%
Inter-Assay Precision (%CV):	8.4%
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, Medium and High	
Intra-Assay Accuracy (%Bias):	-4.0% to 3.7%
Intra-Assay Precision (%CV):	0.6% to 3.9%
Inter-Assay Accuracy (%Bias):	-2.4% to 0.3%
Inter-Assay Precision (%CV):	2.2% to 3.8%
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:	4,000 pg/mL (DF=10)
Dilution Linearity:	40,000 pg/mL (DF=100)
Carryover of Analyte and Internal Standard:	No carryover of analyte and IS detected.
Method Selectivity:	6 Lots of Blank Matrix
Selectivity Blanks:	No significant interference found at the retention times of interest.
Selectivity (Low Level):	Accuracy (%Theoretical): 97.7% Precision (%CV): 6.1%
Matrix Factor Test:	Analyte: MF=1.1 Internal Standard: MF=1.1

Interference	
Analyte and Internal Standard Only	No significant interference found at the retention time of interest for Analyte and IS Only samples.
Additional Compounds	Acetaminophen, Ibuprofen, Caffeine, Chorpheniramine maleate, Naproxen and R,R(-)-Pseudoephedrine (2,000 ng/mL) Quantitation of albuterol is not impacted by the co-administered compounds when present at the concentrations described above.
IS Recovery:	73.7%
Albuterol Recovery:	78.6 to 84.3%
Solution Stability	
IS Solution Stability	
Bench-Top:	7 Hours in DMF at room temperature and protected from light
Albuterol Solution Stability	
Bench-Top:	7 Hours in DMF at room temperature and protected from light
Long-Term:	48 Days in DMF at 1 to 8 °C and protected from light Any additional stability conducted for this study will be added either as an addendum or appendix to this report
Stability in Matrix	
Freeze-Thaw:	4 Cycles; stored at -20 °C and thawed at room temperature
Bench-Top:	6 Hours at room temperature
Intermediate-Term:	21 Days at -20 °C demonstrated by on-going analysis of QC samples against freshly prepared curves
Long-Term:	See footnote at end of table
Reinjection Reproducibility:	99 Hours at room temperature
Extract Stability:	97 Hours at room temperature
Whole Blood Stability:	Up to 1 Hour at 1 to 8 °C
Hemolysis:	No significant impact in samples evaluated with up to 2.0% hemolysis
Batch Size Evaluation:	Sample analysis runs may include up to 220 samples (including Standards, QCs, Blanks, Unknowns, etc.)

*In Amended Report No 3 (April 2020), additional freeze-thaw stability (6 cycles) and long-term matrix stability was demonstrated to be 189 days at -20 °C and 124 days at -70 °C. Stock solution stability was demonstrated to be 6 hours room temperature for 1.00 mg/mL albuterol and 0.5 ng/mL albuterol-d3, and 171 days 5 °C for albuterol. In addition, a method modification to capture truncated calibration range (50.0

to 1000 pg/mL) was established.
(Source: Page 13 of (b) (4) Report No. (b) (4) 10-221).

14.3.2. OCP Appendix II: Individual Study Review

14.3.2.1. Study LOGAN (D6930C00003)

Title

A Phase 1, Randomized, Open-label, Single-dose, 3-way Cross-over Study to Compare the Pharmacokinetics of Budesonide and Albuterol Delivered by PT027 Compared with PT007 and PT008 Administered Separately (LOGAN)

Study Period

21 Jan 2019 – 20 May 2019

Objective

Primary

- To compare the systemic exposure after single-dose administration BD/AS delivered via BDA MDI with BD MDI monotherapy and AS MDI monotherapy

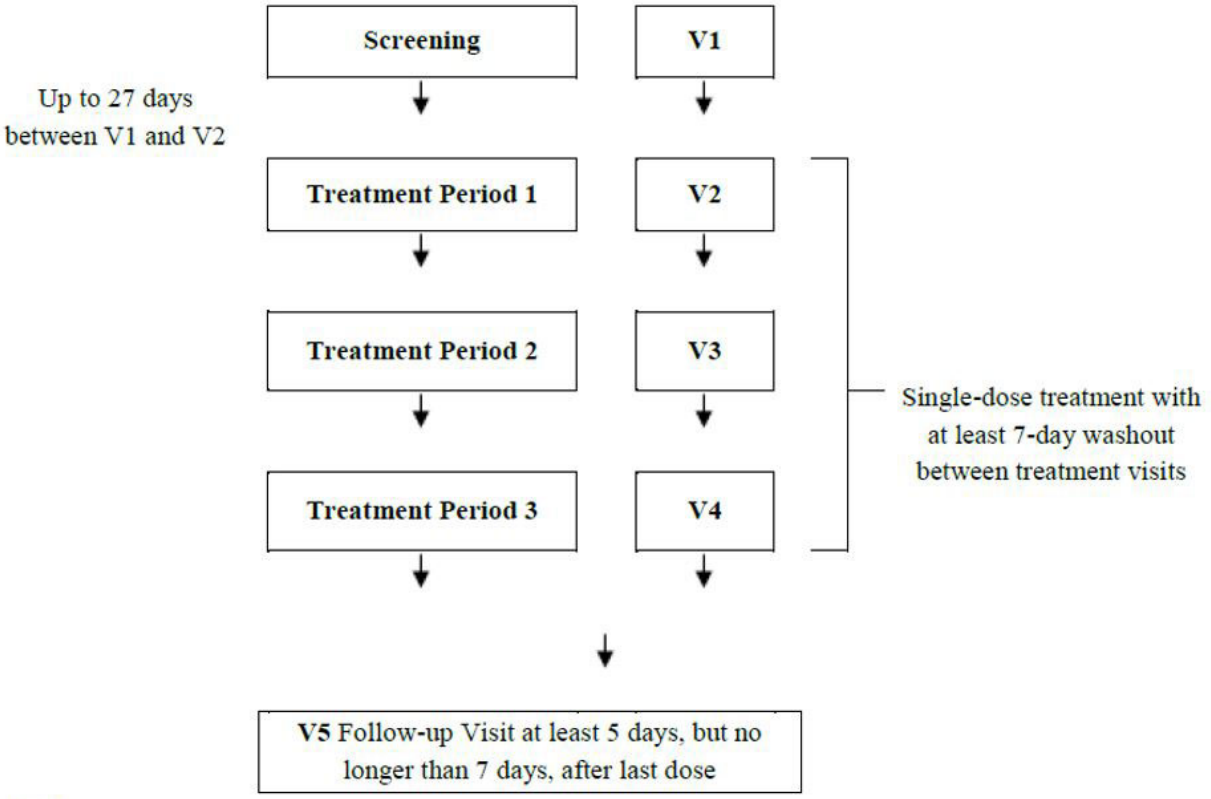
Secondary

- PK, safety, tolerability

Study Design

This study was a randomized, single-center, 3-way cross-over study in healthy male and female subjects. A total of 90 healthy male or female subjects were planned to be randomized in this study to ensure at least 81 evaluable subjects. The study comprised of a screening period, three treatment periods, and a follow-up visit. Three treatment periods included: BDA MDI (Test drug, 80/90 µg), BD MDI (Reference, 80 µg), and AS MDI (Reference, 90 µg) in randomized order per subject allocation scheme. Subjects were randomized to 1 of 6 treatment sequences in the ratio of 1:1:1:1:1:1. Subjects received a single dose (2 inhalations) of study treatment on Day 1 of each treatment period, under fasted condition, and were discharged on the morning of Day 2. There was a minimum washout period of 7 days between each dose administration.

Figure 15. Design of Study LOGAN



V = visit
(Source: Figure 9-1 of Study LOGAN CSR).

Table 70. Test Drug and Dose

	Investigational Medicinal Products		
	Treatment A (test product)	Treatment B (reference product)	Treatment C (reference product)
Study treatment name	BDA MDI – PT027	BD MDI – PT008	AS MDI – PT007
Supplier:	AstraZeneca	AstraZeneca	AstraZeneca
Formulation:	BDA MDI	BD MDI	AS MDI
Strength/concentration:	80 µg/90 µg	80 µg	90 µg
Dose:	2 inhalations	2 inhalations	2 inhalations
Route of administration:	Oral inhalation	Oral inhalation	Oral inhalation
Regimen:	Single-dose	Single-dose	Single-dose
Batch/Manufacturing Lot Number:	BDA1	BD1	AS1

PK Samples

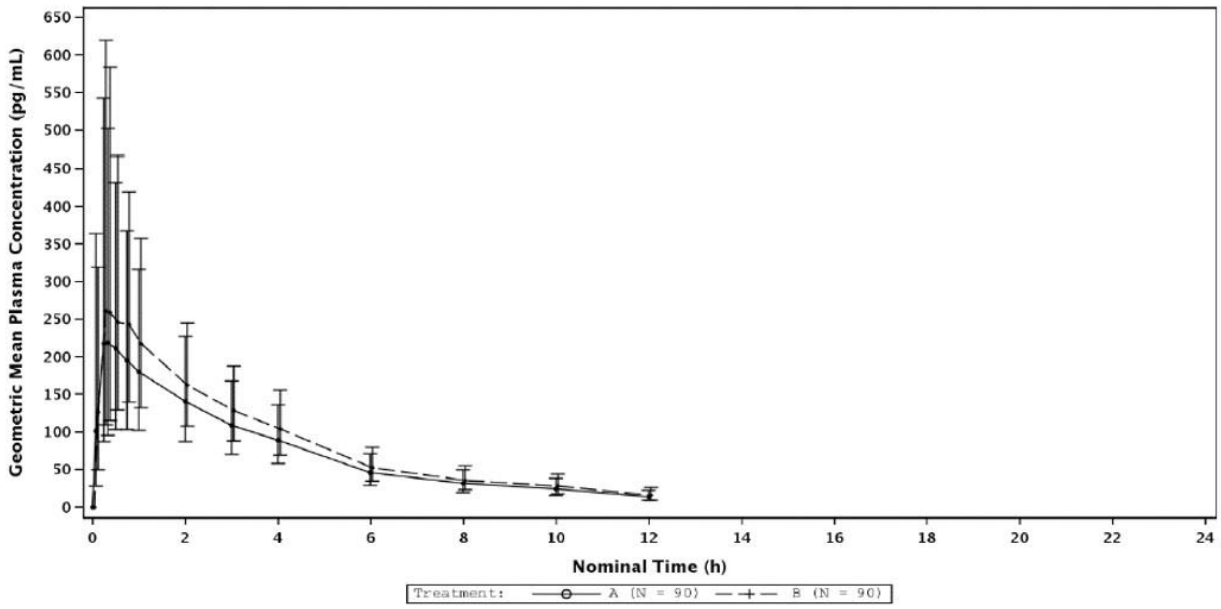
In each treatment period, plasma samples were collected pre-dose, 5, 15, 20, 30 and 45 minutes and 1, 2, 3, 4, 6, 8, 10, 12 hours post-dose on Day 1, and 24 hours post-dose on Day 2.

Results

BD PK Results

Following a single dose of BDA MDI (2× 80/90 µg) and BD MDI (2× 80 µg), the plasma PK profiles and PK parameters of BD are shown as below.

Figure 16. Geometric Mean (+/-Error) Plasma Concentration (pg/mL) of Budesonide Versus Time by Treatment (Linear Scale) (Study LOGAN)



A: Budesonide/Albuterol Sulfate metered dose inhaler (BDA MDI) - PT027 (Test); B: Budesonide metered dose inhaler (BD MDI) - PT008(Reference).
LLOQ: lower limit of quantification for plasma budesonide (3.00 pg/mL); N: Number of subjects.
Vertical lines represent the gmean±error.
Gmean+error: exp(mean(log(PK Conc))+SD(log(PK Conc))).
Gmean-error: exp(mean(log(PK Conc))-SD(log(PK Conc))).
(Source: Figure 11-1 of Study LOGAN CSR).

Table 71. Summary of Plasma PK Parameters of Budesonide (Study LOGAN)

PK Parameter (Units)	Summary Statistic	Treatment A (BDA MDI) (N=90)	Treatment B (BD MDI) (N=90)
C_{max}	Gmean (gCV%)	272.8 (70.36)	316.6 (63.05)
(pg/mL)	(Range)	(51.7 – 819)	(58.0 – 912)
	(n)	(88)	(89)
AUC(0-t)	Gmean (gCV%)	941.7 (50.74)	1102 (46.02)
(pg*h/mL)	(Range)	(227 – 2190)	(261 – 2280)
	(n)	(89)	(89)
AUC	Gmean (gCV%)	1016 (47.12)	1151 (44.75)
(pg*h/mL)	(Range)	(248 – 2220)	(287 – 2340)
	(n)	(85)	(89)
t_{max}	Median	0.33	0.33
(h)	(Range)	(0.08 - 4.00)	(0.08 -3.00)
	(n)	(88)	(89)
$t_{1/2lz}$	Mean (SD)	4.111 (0.9920)	3.968 (0.9914)
(h)	(Range)	(2.46 – 6.15)	(2.23 – 6.29)
	(n)	(85)	(89)
CL/F	Mean (SD)	176.4 (101.6)	153.7 (81.00)
(L/h)	(Range)	(72.2 – 646)	(68.2 – 558)
	(n)	(85)	(89)
Vz/F	Mean (SD)	1002 (515.3)	827.4 (354.6)
(L)	(Range)	(393 – 3130)	(344 – 2770)
	(n)	(85)	(89)

A: Budesonide/Albuterol Sulfate metered dose inhaler (BDA MDI) - PT027 (Test); B: Budesonide metered dose inhaler (BD MDI) - PT008 (Reference).

CV%: coefficient of variation; SD: standard deviation.

n: number of data values; N: number of subjects in the pharmacokinetic analysis set.

(Source: Table 11-2 of Study LOGAN CSR).

Table 72. Relative Bioavailability of Budesonide Following a Single Dose of BDA MDI (160/180 µg) and BD MDI (160 µg) (Study LOGAN)

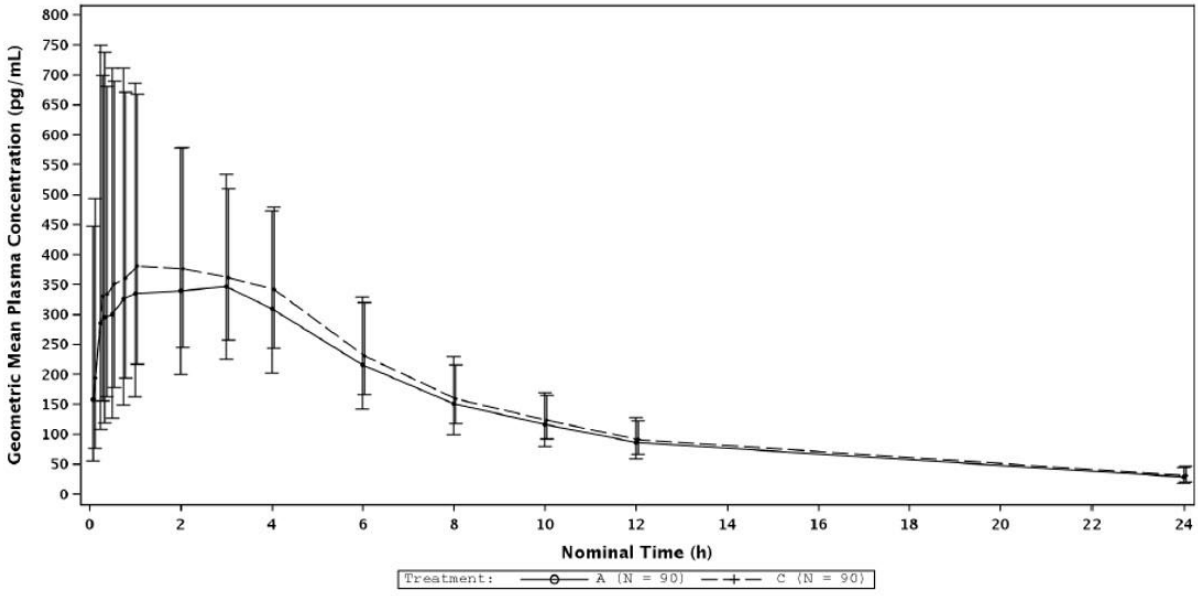
						Pairwise comparisons			
Parameter (unit)	Treatment	N	n	Geometric LS mean	95% CI	Pair	Geometric Mean Ratio (%)	90% CI	Intra-Subject CV%
Cmax (pg/mL)	A	90	87	274.80	[255.53, 295.52]				
	B	90	87	311.30	[289.47, 334.77]	A/B	88.28	[81.01, 96.20]	35.07
AUC(0-t) (pg.h/mL)	A	90	88	943.72	[895.23, 994.83]				
	B	90	88	1098.21	[1041.78, 1157.68]	A/B	85.93	[80.74, 91.46]	25.25
AUC (pg.h/mL)	A	90	84	1014.21	[962.11, 1069.14]				
	B	90	84	1156.04	[1096.65, 1218.65]	A/B	87.73	[82.43, 93.38]	24.62

A: Budesonide/Albuterol Sulfate metered dose inhaler (BDA MDI) - PT027 (Test); B: Budesonide metered dose inhaler (BD MDI) - PT008(Reference).
CI: confidence interval; LS: least squares; N: all subjects in the pharmacokinetic analysis set; n: all subjects included in the statistical comparison analysis.
Only the data for the comparison under investigation are included in the statistical analysis.
Result based on analysis of variance (ANOVA) of log-transformed PK parameter with treatment, sequence, period and volunteer within sequences as fixed effects.
Geometric mean ratio and corresponding 90% CI are back transformed and presented as percentages. Geometric LS mean and corresponding 95% CI are also back transformed.
The intra-subject CV% is calculated as 100 x [exp(MSE) - 1]^0.5 where the MSE is the mean square error from the ANOVA model.
(Source: Table 11-3 of Study LOGAN CSR).

AS PK Results

Following a single dose of BDA MDI (2× 80/90 µg) and AS MDI (2× 90 µg), the plasma PK profiles and PK parameters of AS are shown as below.

Figure 17. Geometric Mean (± Error) Plasma Concentration (pg/mL) Versus Time Profiles of Albuterol (Linear Scale) (Study LOGAN)



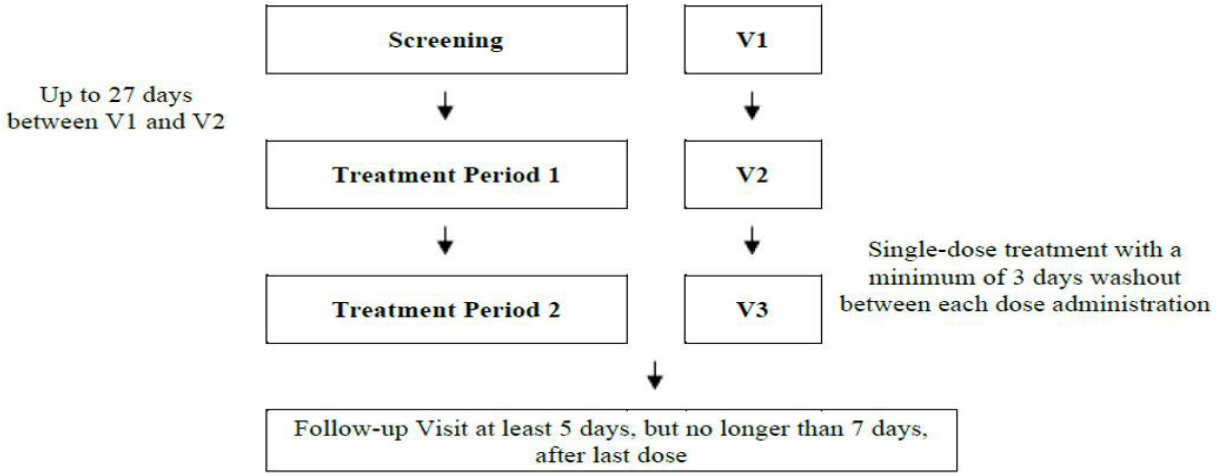
A: Budesonide/Albuterol Sulfate metered dose inhaler (BDA MDI) - PT027 (Test); C: Albuterol Sulfate metered dose inhaler (AS MDI) - PT007 (Reference).
LLOQ: lower limit of quantification for albuterol (1.00 pg/mL); N: Number of subjects.
Vertical lines represent the gmean±error.
Gmean+error: exp(mean(log(PK Conc))+SD(log(PK Conc))).
Gmean-error: exp(mean(log(PK Conc))-SD(log(PK Conc))).
(Source: Figure 11-3 of Study LOGAN CSR).

Table 73. Summary of Plasma PK Parameters of Albuterol (Study LOGAN)

PK Parameter (Units)	Summary Statistic	Treatment A (BDA MDI) (N=90)	Treatment C (AS MDI) (N=90)
C_{max}	Gmean (gCV%)	472.2 (51.20)	504.9 (37.97)
(pg/mL)	(Range)	(38.4 – 971)	(90.7 – 967)
	(n)	(89)	(90)
AUC(0-t)	Gmean (gCV%)	3373 (42.04)	3637 (30.13)
(pg*h/mL)	(Range)	(321 – 5620)	(911 – 8010)
	(n)	(89)	(90)
AUC	Gmean (gCV%)	3692 (41.03)	3935 (28.21)
(pg*h/mL)	(Range)	(378 – 6450)	(1070 – 6660)
	(n)	(87)	(89)
t_{max}	Median	1.00	1.00
(h)	(Range)	(0.08 – 6.05)	(0.23 – 6.02)
	(n)	(89)	(90)
$t_{1/2\lambda z}$	Mean (SD)	7.056 (1.263)	6.994 (1.296)
(h)	(Range)	(4.62 – 10.0)	(4.99 – 12.7)
	(n)	(87)	(89)
CL/F	Mean (SD)	54.89 (49.08)	47.86 (18.16)
(L/h)	(Range)	(27.9 – 476)	(27.0 – 168)
	(n)	(87)	(89)
Vz/F	Mean (SD)	565.7 (609.4)	485.8 (225.8)
(L)	(Range)	(215 – 5880)	(224 – 2030)
	(n)	(87)	(89)

A: Budesonide/Albuterol Sulfate metered dose inhaler (BDA MDI) - PT027 (Test); C: Albuterol Sulfate metered dose inhaler (AS MDI) - PT007 (Reference).
CV%: coefficient of variation; SD: standard deviation.
n: number of data values; N: number of subjects in the pharmacokinetic analysis set.
(Source: Table 11-4 of Study LOGAN CSR).

Table 74. Relative Bioavailability of Albuterol Following a Single Dose of BDA MDI (160/180 µg) and AS MDI (180 µg) (Study LOGAN)



V: visit.
(Source: Table 11-5 of Study LOGAN CSR).

Conclusions

- Following a single dose administration, the systemic exposure (C_{max} and AUC) of BD is comparable between BDA MDI (160/180 µg) and BD MDI (160 µg).
- Following a single dose administration, the systemic exposure (C_{max} and AUC) of AS is comparable between BDA MDI (160/180 µg) and AS MDI (180 µg).

14.3.2.2. Study ELBRUS (D6930C00011)

Title

A Phase 1, Randomized, Open-label, Single-dose, 2-way Cross-over Study to Compare the Pharmacokinetics of Budesonide Delivered by PT027 Compared with Pulmicort Flexhaler

Study Period

16 May 2019 – 10 Sep 2019

Objective

Primary

- Compare the systemic exposure of budesonide after single-dose administration of BDA MDI versus Pulmicort Flexhaler

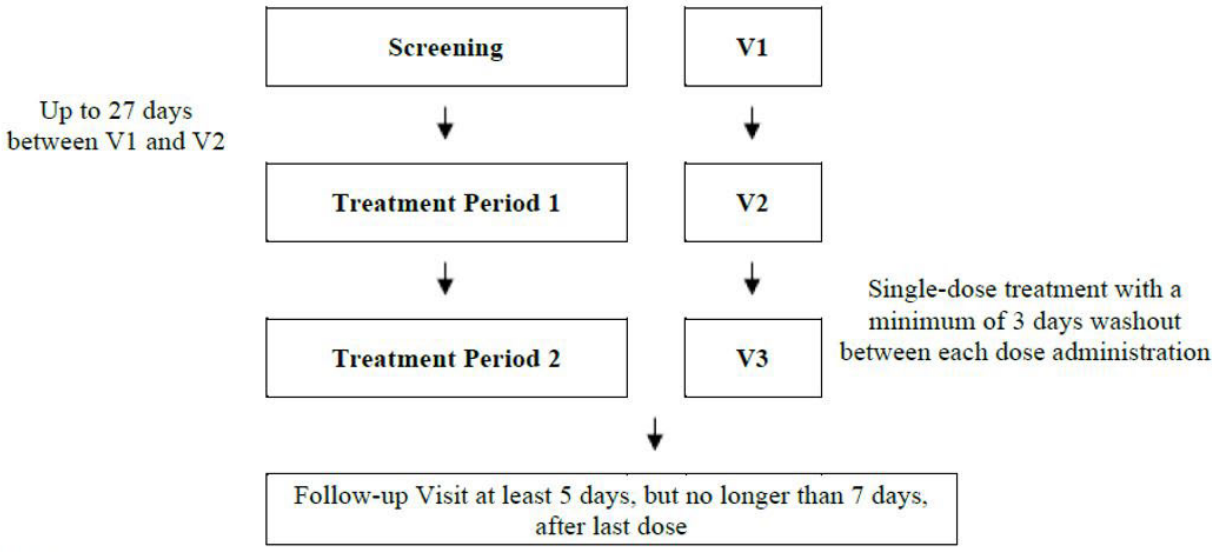
Secondary

- PK, safety, tolerability

Study Design

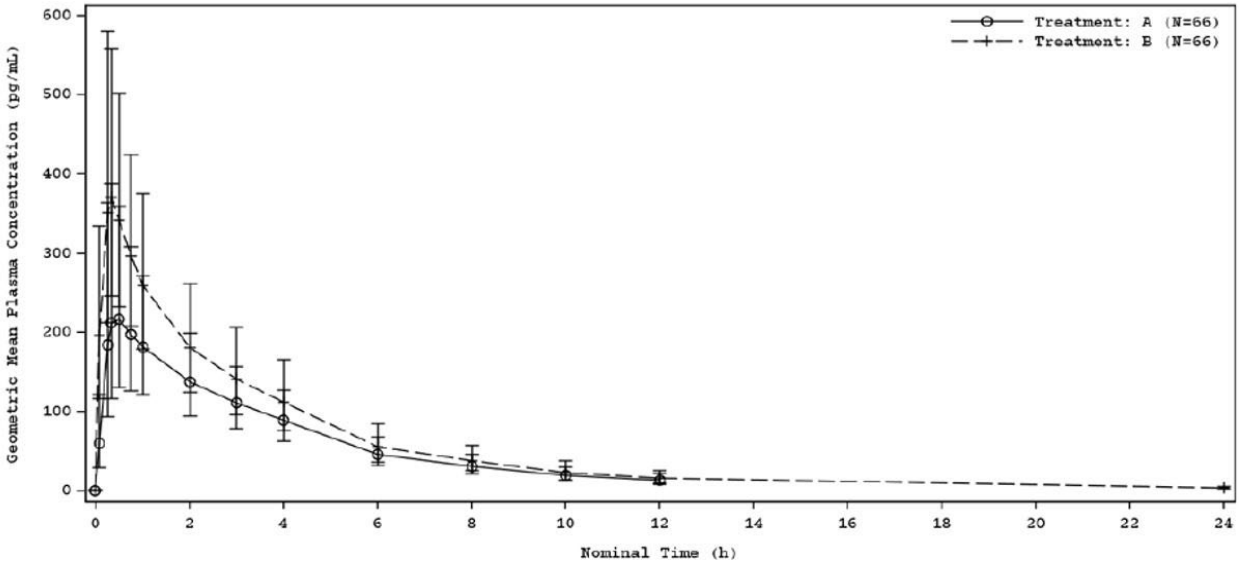
This was an open-label, single-center, randomized, 2-way cross-over study in healthy adult male and female subjects (n=67). The study comprised a screening period, 2 treatment periods and a final follow-up visit. During the 2 treatment periods subjects received either BDA MDI (80/90 µg, Test drug) or Pulmicort Flexhaler (90 µg, Reference). Subjects received a single dose of 2 inhalations of study treatment on Day 1 of each treatment period, under fasted conditions, and were discharged on the morning of Day 2. There was a minimum washout period of 3 days between each dose administration.

Figure 18. Design of Study ELBRUS



V: visit.
(Source: Figure 9-1 of Study ELBRUS CSR).

Table 75. Test Drug and Dose



A: Budesonide/Albuterol sulfate metered dose inhaler (BDA MDI) (Test); B: Pulmicort dry-powder inhaler (DPI) (Reference).

PK Samples

In each treatment period, plasma samples were collected pre-dose and 5, 15, 20, 30 and 45 minutes and 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours post dose.

Results

Following a single dose of BDA MDI (2× 80/90 µg) and Pulmicort Flexhaler (2× 90 µg), the plasma PK profiles and PK parameters of BD are shown as below.

Figure 19. Geometric Mean (+/-Error) Plasma Concentration (pg/mL) of Budesonide Versus Time by Treatment (Linear Scale) (Study ELBRUS)

PK Parameter (Units)	Summary Statistic	BDA MDI (Treatment A) (N = 66)	Pulmicort Flexhaler (Treatment B) (N = 66)
Cmax (pg/mL)	Gmean (gCV%) (Range) (n)	262.8 (49.72) (74.5 - 1010) (66)	417.3 (40.91) (190 - 898) (64)
AUC(0-t) (pg*h/mL)	Gmean (gCV%) (Range) (n)	916.2 (36.90) (386 - 1800) (66)	1235 (37.32) (456 - 2390) (66)
AUC (pg*h/mL)	Gmean (gCV%) (Range) (n)	968.5 (34.84) (464 - 1870) (65)	1279 (36.73) (475 - 2430) (65)
tmax (h)	Median (Range) (n)	0.36 (0.23 - 3.00) (66)	0.33 (0.23 - 1.00) (64)
t1/2λz (h)	Mean (SD) (Range) (n)	4.086 (1.516) (2.16 - 9.43) (65)	4.362 (1.572) (1.83 - 8.87) (65)
Vz/F (L/h)	Mean (SD) (Range) (n)	1001 (474.1) (360 - 2790) (65)	799.9 (361.7) (327 - 2350) (65)
CL/F (L)	Mean (SD) (Range) (n)	175.0 (62.33) (85.5 - 345) (65)	133.6 (53.53) (65.8 - 337) (65)

A: Budesonide/Albuterol Sulfate metered dose inhaler (BDA MDI) (Test); B: Pulmicort dry-powder inhaler (DPI) (Reference); CV%: coefficient of variation; SD: standard deviation; n: number of data values; N: number of subjects in the pharmacokinetic analysis set

(Source: Figure 11-1 of Study ELBRUS CSR).

Table 76. Summary of Plasma PK Parameters of Budesonide (Study ELBRUS)

PK Parameter (Units)	Summary Statistic	BDA MDI (Treatment A) (N = 66)	Pulmicort Flexhaler (Treatment B) (N = 66)
Cmax (pg/mL)	Gmean (gCV%) (Range) (n)	262.8 (49.72) (74.5 - 1010) (66)	417.3 (40.91) (190 - 898) (64)
AUC(0-t) (pg*h/mL)	Gmean (gCV%) (Range) (n)	916.2 (36.90) (386 - 1800) (66)	1235 (37.32) (456 - 2390) (66)
AUC (pg*h/mL)	Gmean (gCV%) (Range) (n)	968.5 (34.84) (464 - 1870) (65)	1279 (36.73) (475 - 2430) (65)
tmax (h)	Median (Range) (n)	0.36 (0.23 - 3.00) (66)	0.33 (0.23 - 1.00) (64)
t1/2λz (h)	Mean (SD) (Range) (n)	4.086 (1.516) (2.16 - 9.43) (65)	4.362 (1.572) (1.83 - 8.87) (65)
Vz/F (L/h)	Mean (SD) (Range) (n)	1001 (474.1) (360 - 2790) (65)	799.9 (361.7) (327 - 2350) (65)
CL/F (L)	Mean (SD) (Range) (n)	175.0 (62.33) (85.5 - 345) (65)	133.6 (53.53) (65.8 - 337) (65)

A: Budesonide/Albuterol Sulfate metered dose inhaler (BDA MDI) (Test); B: Pulmicort dry-powder inhaler (DPI) (Reference); CV%: coefficient of variation; SD: standard deviation; n: number of data values; N: number of subjects in the pharmacokinetic analysis set

(Source: Table 11-3 of Study ELBRUS CSR).

Table 77. Relative Bioavailability of Budesonide for Key PK Parameters (Study ELBRUS)

						Pairwise comparisons			
Parameter (unit)	Treatment	N	n	Geometric LS mean	95% CI	Pair	Geometric Mean Ratio (%)	90% CI	Intra-Subject CV%
Cmax (pg/mL)	A	66	64	263.0	[242.0, 285.7]				
	B	66	64	419.0	[385.6, 455.3]	A/B	62.76	[56.89, 69.23]	34.16
AUC(0-t) (pg.h/mL)	A	66	66	916.2	[862.2, 973.6]				
	B	66	66	1235	[1162, 1312]	A/B	74.19	[69.05, 79.71]	25.09
AUC (pg.h/mL)	A	66	64	971.8	[916.8, 1030]				
	B	66	64	1280	[1207, 1357]	A/B	75.93	[70.88, 81.34]	23.64

A: Budesonide/Albuterol sulfate metered dose inhaler (BDA MDI) (Test); B: Pulmicort dry-powder inhaler (DPI) (Reference); CI: confidence interval; LS: least-squares; N: all subjects in the Pharmacokinetic analysis set; n: only data for subjects that have the respective PK parameter values for both treatments are included in the analysis.
Result based on analysis of variance (ANOVA) of log transformed PK parameter with treatment, sequence, period and volunteer within sequences as fixed effects.
Geometric mean ratio and corresponding 90% CI are back-transformed and presented as percentages. Geometric LS mean and corresponding 95%.
CI are also back transformed.
The intra-subject CV% is calculated as 100 x [exp(MSE) - 1]^0.5 where the MSE is the mean square error from the ANOVA model.

(Source: Table 11-4 of Study ELBRUS CSR).

Conclusions

Following a single dose of BDA MDI (2× 80/90 µg) and Pulmicort Flexhaler (2× 90 µg), budesonide systemic exposure (C_{max} and AUC) for BDA MDI did not exceed that for Pulmicort Flexhaler.

14.3.2.3. Study BLANC (AV006)

Title

A Phase 1, Randomized, Open-label, Single-dose, 2-way Crossover Study to Compare the Pharmacokinetics of Budesonide Delivered by PT027 to Pulmicort Respules in Children with Asthma Aged 4 to 8 Years

Study Period

6 May 2021 – 8 Jul 2021

Objective

- To determine and compare the systemic exposure of budesonide after single-dose administration of BDA MDI and Pulmicort Respules
- PK, safety, tolerability

Study Design

This was a randomized, open-label, single-dose, 2-way crossover study to compare the systemic exposure of budesonide delivered by the combination inhaler (BDA MDI) or Pulmicort Respules

in children with asthma, aged 4 to 8 years (inclusive), with at least 4 children aged 4 to 5 years. Eligible children were randomly assigned to a treatment sequence:

- A/B: BDA MDI (2 inhalations of 80/90 µg) at Visit 2 and Pulmicort Respules (1 mg) at Visit 3

OR

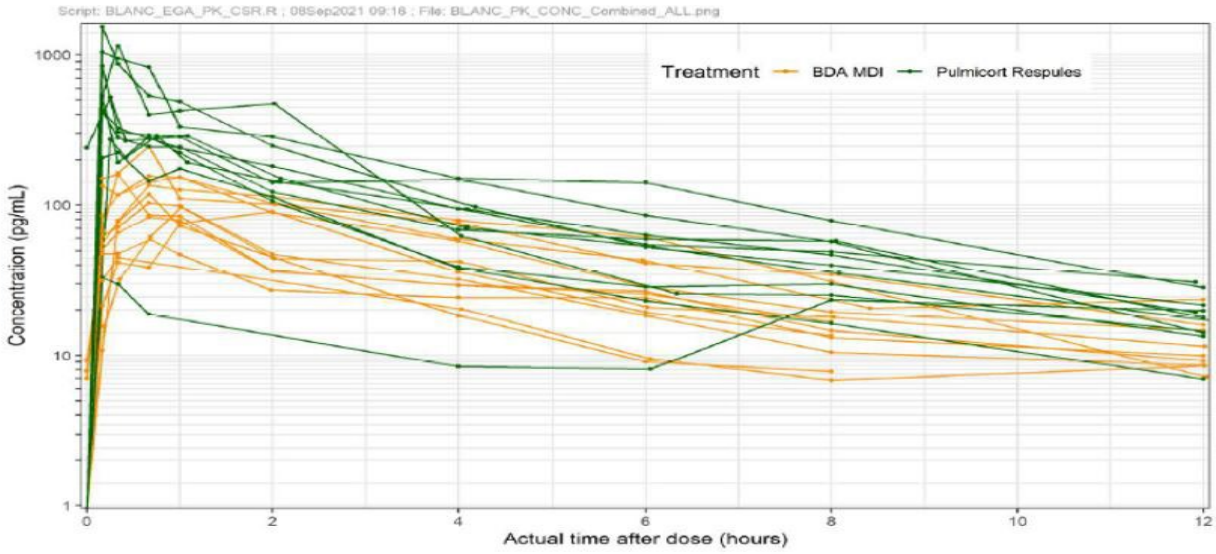
- B/A: Pulmicort Respules (1 mg) at Visit 2 and BDA MDI (2 inhalations of 80/90 µg) at Visit 3

Figure 20. Design of Study BLANC

	Treatment A (test product)	Treatment B (reference product)
Formulation:	BDA MDI	Pulmicort Respules
Supplier:	AstraZeneca	(b) (4)
Strength:	80/90 µg (budesonide/albuterol)	1 mg budesonide
Dose:	2 inhalations	1 ampule
Route of administration:	Oral inhalation	Oral inhalation
Regimen:	Single dose – 2 inhalations	Single nebulization dose
Special handling requirements:	Prime per instructions. Contamination avoidance procedures.	Nebulization until sputtering with nebulization cup as empty as possible. Contamination avoidance procedures.

Visit 3 occurred no less than 2 and no greater than 14 days after dosing on Visit 2 (i.e., washout of 2 to 14 days) during which children were dosed with a single dose of BDA MDI or Pulmicort Respules (A/B or B/A).
(Source: Figure 1 of Study BLANC CSR).

Table 78. Test Drug and Dose



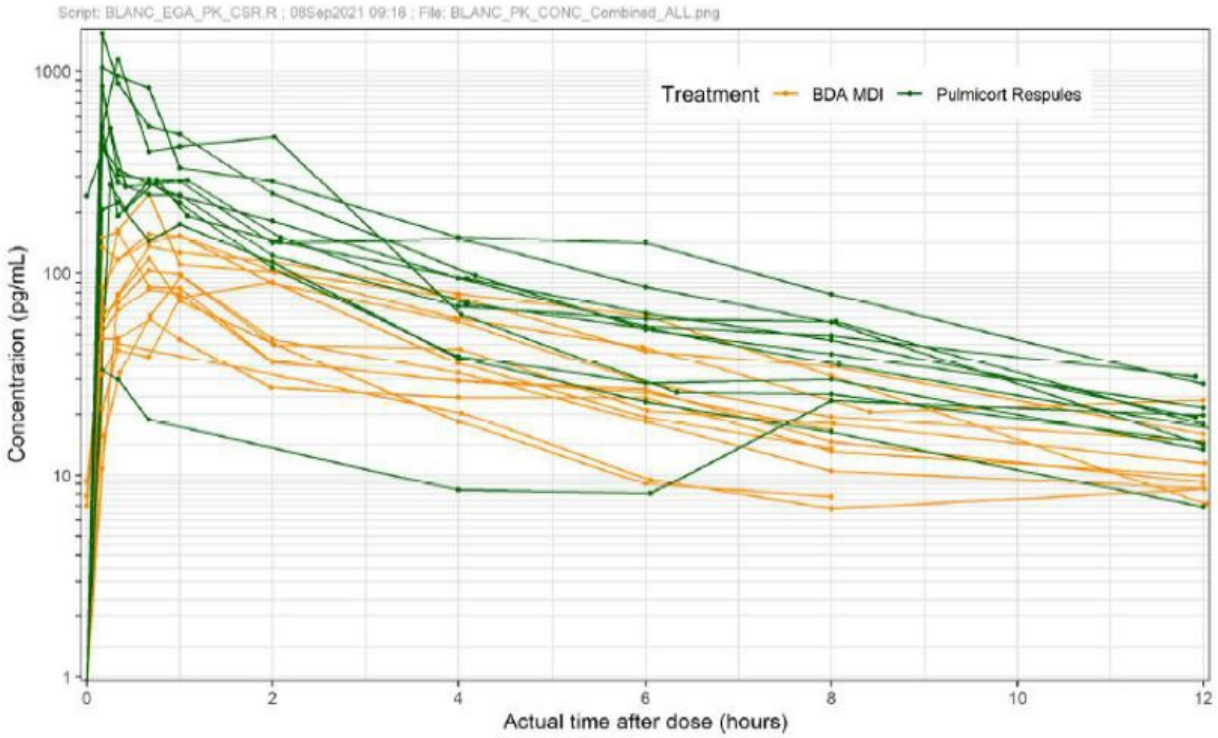
PK Samples

After each treatment, a total of 10 samples were taken at pre-dose and at 10, 20, 40 minutes and 1, 2, 4, 6, 8, 12 hours after dosing.

Results

The PK results were summarized as below.

Figure 21. Individual Budesonide PK Profiles After Administration of BDA MDI (2 inhalations of 80/90 µg) or Pulmicort Respules (1 mg) (Semi-log Scale) (Study BLANC)



(Source: Figure 2 of Study BLANC CSR).

Table 79. Individual PK Parameters and Summary Statistics After Administration of BDA MDI (Study BLANC)

Study: AV006/BLANC Treatment A: BDA MDI (160/180 µg)										
ID	C_{max} (pg/mL)	t_{max} (h)	C_{last} (pg/mL)	t_{last} (h)	AUC_{0-t} (h.pg/mL)	AUC_{0-8h} (h.pg/mL)	λz (1/h)	t1/2λz (h)	AUC_{inf} (h.pg/mL)	AUC_{ext} (%)
(b) (6)	246	0.667	23.6	12.0	668	580	0.161	4.30	814	18.0
	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	135	0.667	7.14	12.0	693	628	0.358	1.93	713	2.79
	160	0.333	16.7	8.00	326	326	NR	NR	NR	NR
	153	1.00	14.7	12.0	578	510	0.186	3.72	657	12.0
	45.2	0.333	8.52	12.0	199	168	NR	NR	NR	NR
	83.0	0.667	9.19	12.0	329	282	0.144	4.82	392	16.3
	118	0.667	7.78	8.00	241	241	0.333	2.08	264	8.84
	156	0.667	16.0	12.0	717	620	0.186	3.72	803	10.7
	103	0.667	8.59	12.0	344	306	0.180	3.84	392	12.2
	96.7	1.02	11.5	12.0	359	301	NR	NR	NR	NR
	90.3	2.00	13.5	8.00	327	327	NR	NR	NR	NR
N	11	11	11	11	11	11	7	7	7	7
Nmiss	1	1	1	1	1	1	5	5	5	5
Mean	126	-	12.5	-	435	390	NR	NR	NR	NR
SD	53.3	-	5.03	-	191	163	NR	NR	NR	NR
SE	16.1	-	1.52	-	57.5	49.2	NR	NR	NR	NR
Min	45.2	0.333	7.14	8.00	199	168	0.144	1.93	264	2.79
Median	118	0.667	11.5	12.0	344	326	NR	NR	NR	NR
Max	246	2.00	23.6	12.0	717	628	0.358	4.82	814	18.0
CV%	42.3	-	40.3	-	43.8	41.8	NR	NR	NR	NR
Geometric Mean	116	-	11.7	-	398	359	NR	NR	NR	NR
Geometric CV%	46.6	-	39.6	-	46.3	44.8	NR	NR	NR	NR

'-' = Not applicable; N =Number of derived PK parameters in treatment group; Nmiss = Number of PK parameters missing in treatment group; NR = Not reportable
(Source: Table 8 of Study BLANC CSR).

Table 80. Individual PK Parameters and Summary Statistics After Administration of Pulmicort Respules (Study BLANC)

Study: AV006/BLANC Treatment B: Pulmicort Respules (1 mg)										
ID	C_{max} (pg/mL)	t_{max} (h)	C_{last} (pg/mL)	t_{last} (h)	AUC_{0-t} (h.pg/mL)	AUC_{0-8h} (h.pg/mL)	λz (1/h)	t1/2λz (h)	AUC_{inf} (h.pg/mL)	AUC_{ext} (%)
(b) (6)	1160	0.333	14.5	12.0	1640	1562	NR	NR	NR	NR
	1550	0.167	21.7	12.0	1773	1653	NR	NR	NR	NR
	1040	0.167	28.3	12.0	2160	1963	0.266	2.61	2266	4.69
	32.9	0.167	19.8	12.0	193	107	NR	NR	NR	NR
	425	0.167	17.8	12.0	1004	868	0.221	3.14	1085	7.42
	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	224	0.333	6.94	12.0	590	546	0.210	3.30	623	5.31
	426	0.167	30.7	11.9	1163	1009	NR	NR	NR	NR
	289	0.750	19.3	11.9	1015	893	0.200	3.47	1112	8.68
	522	0.167	13.4	12.0	760	678	0.257	2.70	813	6.42
	846	0.167	14.1	12.0	1340	1217	0.292	2.37	1388	3.47
N	10	10	10	10	10	10	6	6	6	6
Nmiss	2	2	2	2	2	2	6	6	6	6
Mean	651	-	18.7	-	1164	1050	NR	NR	NR	NR
SD	480	-	7.09	-	587	561	NR	NR	NR	NR
SE	152	-	2.24	-	186	177	NR	NR	NR	NR
Min	32.9	0.167	6.94	11.9	193	107	0.200	2.37	623	3.47
Median	474	0.167	18.6	12.0	1089	951	NR	NR	NR	NR
Max	1550	0.750	30.7	12.0	2160	1963	0.292	3.47	2266	8.68
CV%	73.6	-	38.0	-	50.5	53.4	NR	NR	NR	NR
Geometric Mean	447	-	17.3	-	985	847	NR	NR	NR	NR
Geometric CV%	156	-	44.5	-	78.7	99.9	NR	NR	NR	NR

(Source: Table 9 of Study BLANC CSR).

Table 81. Statistical Analysis of Budesonide PK Parameters After Administration of BDA MDI (2 inhalations of 80/90 µg) or Pulmicort Respules (1 mg) (Study BLANC)

Study: AV006/BLANC								
				Geometric LS means		BDA MDI vs Pulmicort Respules		
PK Parameter	Treatment	N	n	Estimate	95%CI	GMR (%)	90%CI	ISCV (%)
AUC_{0-t} (h.pg/mL)	A: BDA MDI	12	9	432	[325,574]	46.2	[33.4,63.7]	37.0
	B: Pulmicort Respules	12	9	937	[705,1245]			
C_{max} (pg/mL)	A: BDA MDI	12	9	131	[72.6,236]	32.4	[16.6,63.0]	85.7
	B: Pulmicort Respules	12	9	404	[224,728]			

Source: Table 14.2.3
ANOVA=analysis of variance; AUC_{0-t} = Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; BDA = Budesonide/albuterol sulfate; C_{max} = Maximum observed plasma concentration; CI=confidence interval; GMR=geometric mean ratio; ISCV=intra-subject coefficient of variation; LS=least squares; MDI = Metered-dose inhaler; N=Number of subjects in treatment group; n=Number of subjects included in analysis; PK=pharmacokinetic
Treatment A: Budesonide/albuterol sulfate metered-dose inhaler (BDA MDI) 2 * 80/90 µg.
Treatment B: Pulmicort Respules 1 mg ANOVA with treatment, sequence, period, and subject within sequence as fixed effects.
(Source: Table 10 of Study BLANC CSR).

Conclusions

Following a single-dose inhalation of BDA MDI (2 inhalations of 80/90 µg) or Pulmicort Respules (1 mg) in children, the systemic budesonide exposure of BDA MDI was lower than the systemic exposure of Pulmicort Respules.

14.3.2.4. Study ASPEN (D6930C00002)

Title

Albuterol Sulfate Pressurized Inhalation Suspension (PT007) Cumulative Dose Study in Subjects With Mild to Moderate Asthma

Study Period

29 Dec 2017 – 26 March 2018

Objective

Primary

- Assess the efficacy of AS MDI compared to Proventil on lung function after cumulative doses of up to 1440 µg.

Secondary

- Assess the extrapulmonary PD effects.
- Compare the relative systemic bioavailability of albuterol delivered by AS MDI and Proventil after cumulative doses up to 1440 µg.
- Assess the safety.

Study Design

This was a randomized, cumulative-dose, open-label, 2-period crossover, multicenter study to assess the safety, efficacy, PK, and extrapulmonary PD of cumulative doses of AS MDI compared with cumulative doses of Proventil (active control) in subjects with mild to moderate asthma.

At V1 of the screening period, subjects were instructed to discontinue their current asthma medications and initiate Sponsor-provided asthma medications. Subjects using only a SABA as needed prior to Visit 1 initiated Sponsor-provided Ventolin HFA (Ventolin) to be used as needed until 48 hours before Visit 2. Subjects were then instructed to discontinue Ventolin and initiate Sponsor-provided Atrovent HFA (Atrovent) for the duration of the study, to be used as needed up until 8 hours before each study visit. Subjects who were receiving an inhaled corticosteroid (ICS) or ICS/long-acting β2-agonist (LABA) regimen prestudy were switched to Sponsor-provided Pulmicort Flexhaler BID, in addition to the Sponsor-provided Ventolin and Atrovent. The minimum Screening/Run-In Period durations for subjects on SABA and ICS (or ICS/LABA) regimens prestudy were 3 and 14 days, respectively; for all subjects, the maximum Screening/Run-In Period duration was 28 days. All subjects had to demonstrate forced expiratory volume in 1 second (FEV1) reversibility to Ventolin, defined as an improvement in FEV1 of ≥15% after Ventolin treatment, during the Screening Period; only 2 reversibility test attempts were allowed.

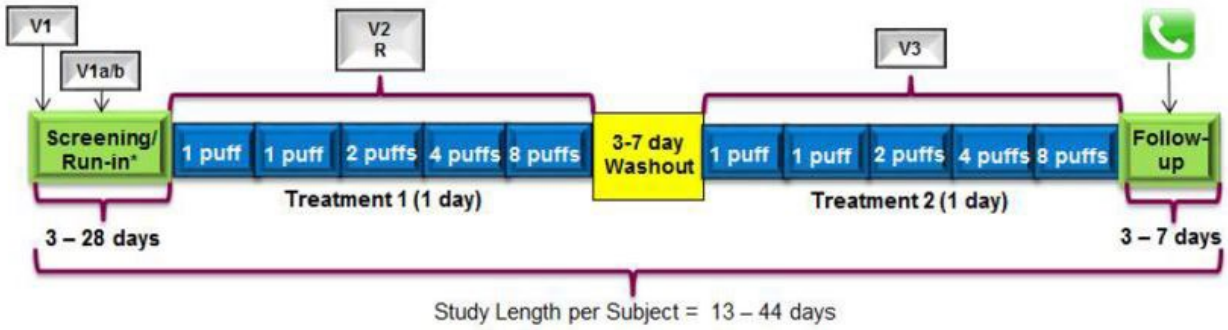
Subjects who met all screening and randomization requirements were eligible for randomization into the Treatment Period, which comprised Visits 2 and 3 of the study.

Eligible subjects were randomized to receive the following 2 cumulative-dose treatments in one of 2 possible treatment sequences:

- AS MDI, given as 1+1+2+4+8 actuations of AS MDI 90 µg (doses of 90, 90, 180, 360, and 720 µg, respectively).
- Proventil, given as 1+1+2+4+8 actuations of Proventil 90 µg (doses of 90, 90, 180, 360, and 720 µg, respectively).

During Visits 2 and 3, subjects received 5 doses of open-label study drug (i.e., AS MDI or Proventil) separated by 30 minutes. Visits 2 and 3 were separated by a 3- to 7-day washout period.

Figure 22. Design of Study ASPEN



Abbreviations: R=randomization; V=Visit.
*Subjects on ICS or ICS/LABA before Visit 1 received run-in Pulmicort Flexhaler 180 or 360 µg BID for a minimum of 14 days.

(Source: Figure 1 of Study ASPEN CSR).

Test Drug and Dose

5 cumulative doses of AS MDI (90 µg) or Proventil (90 µg) were administered 30 minutes apart as 1+1+2+4+8 inhalations for a total albuterol dose of 1440 µg.

Table 82. Test Drug and Dose

Study Drug	Dosage Form, Strength/ Fill Count	Batch Number	Expiration Date
AS MDI 90 µg	MDI, AS MDI 90 µg/actuation[a]/ 120 actuations	N17-012-PK-001	September 2018
Proventil 90 µg	MDI, Albuterol 90 µg/actuation[a]/ 200 actuations	170181	June 2019

Note: All study drugs were administered by oral inhalation.
[a] Each inhalation contained 108 µg albuterol sulfate corresponding to 90 µg albuterol base per actuation.

PK Samples

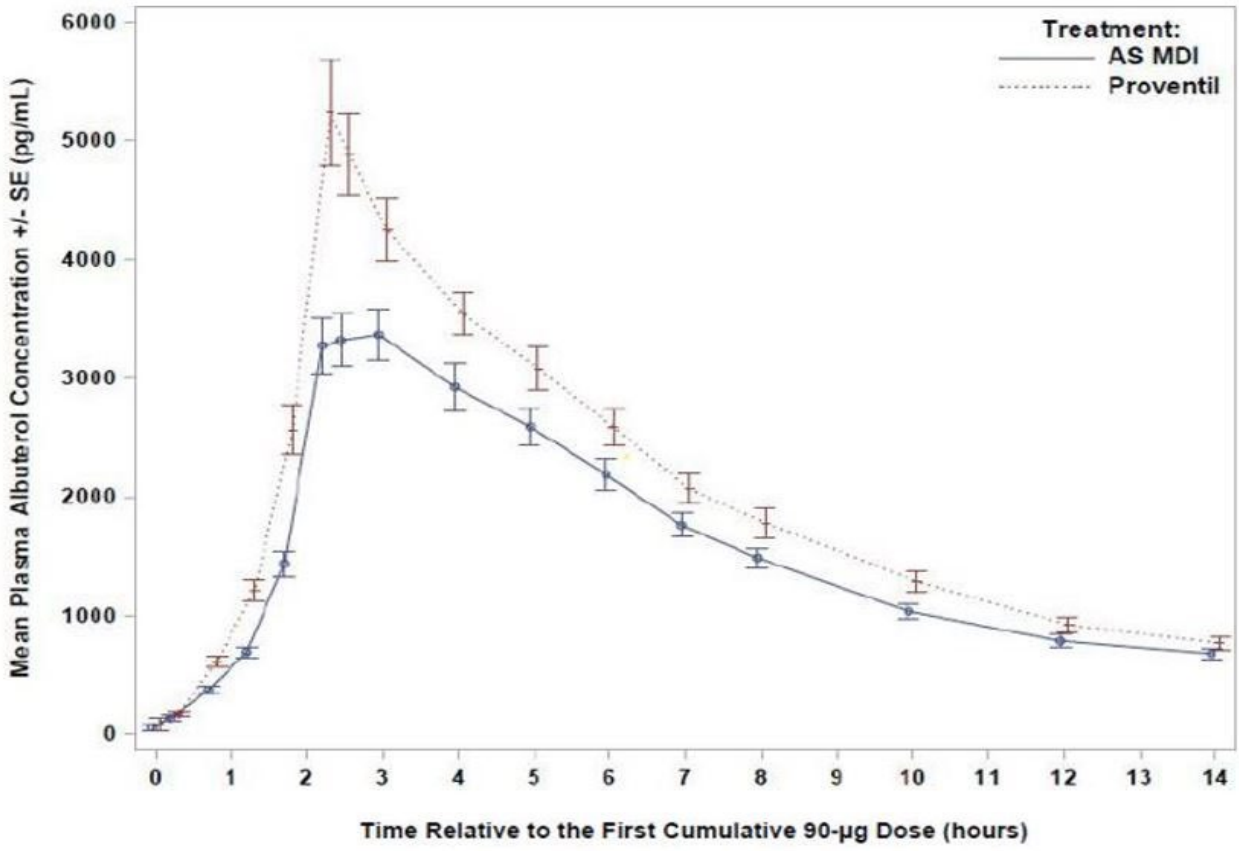
A subset of subjects participated in a PK sub-study. PK samples were collected 15 minutes after each cumulative dose. After the last dose of study drug, PK samples were collected at 15, 30 minutes, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours.

Results

Efficacy

The primary efficacy endpoint, i.e., the change from baseline in FEV1 30 minutes after each cumulative dose, is presented as below.

Table 83. Change From Baseline in FEV1 (mL) 30 Minutes After Each Cumulative Dose (mITT Analysis Set) (Study ASPEN)

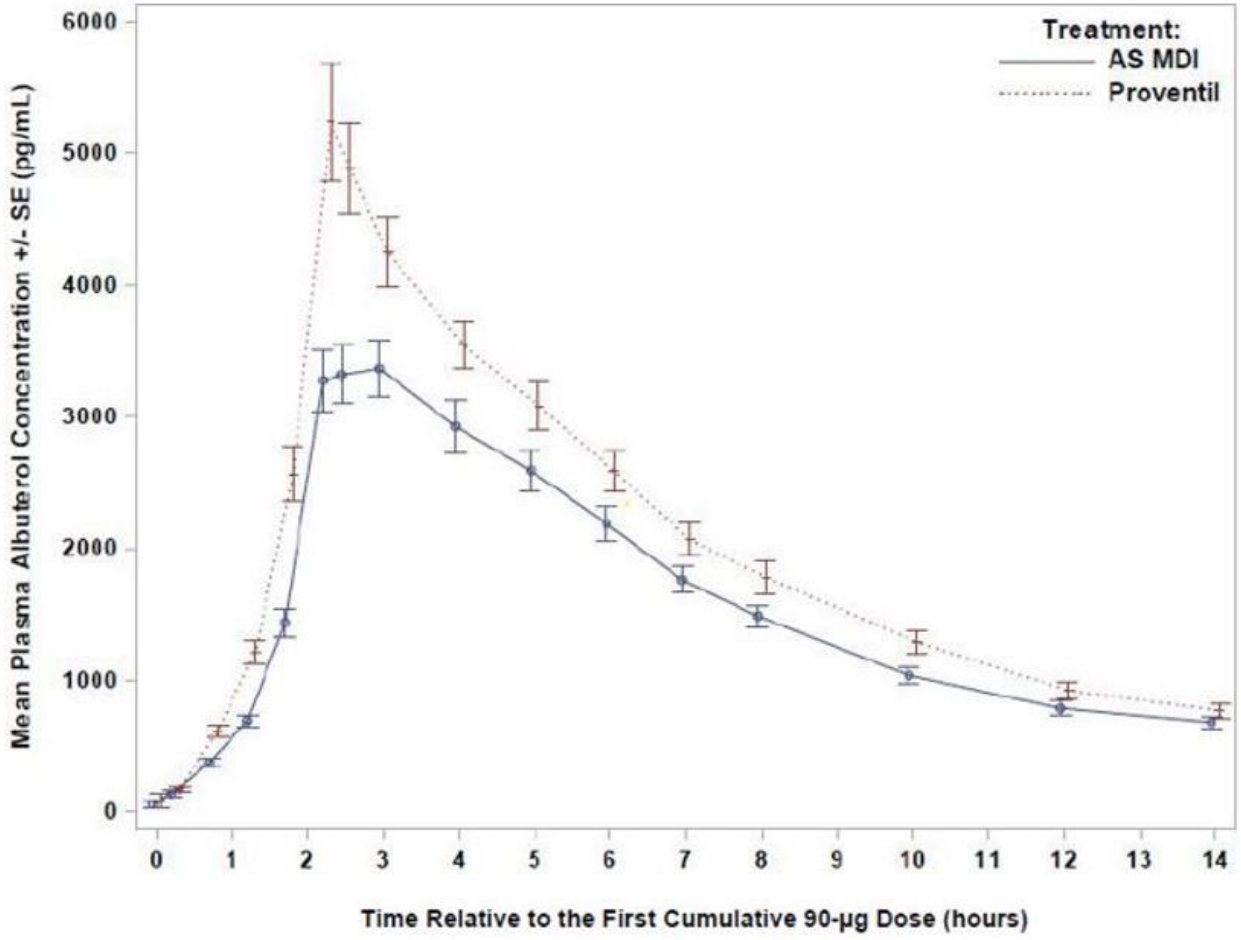


Abbreviation: LLOQ=lower limit of quantification.
Note: Values below the LLOQ (50 pg/mL) were set to LLOQ/2, except those that occurred at predose, which were set to 0.
(Source: Table 18 of Study ASPEN CSR).

PK Results

Following the cumulative dose administration of AS MDI and Proventil during the Treatment Periods, the mean albuterol plasma PK profiles and PK analysis are shown as below.

Figure 23. Mean (±SE) Plasma Albuterol Concentration-Time Profile Following the Cumulative Dose (1+1+2+4+8 Actuations, a Total Albuterol Dose of 1440 µg) Administration of AS MDI (90 µg) and Proventil (90 µg) (Linear Scale, Study ASPEN)



Abbreviation: LLOQ=lower limit of quantification.
Note: Values below the LLOQ (50 pg/mL) were set to LLOQ/2, except those that occurred at predose, which were set to 0.
(Source: Figure 4 of Study ASPEN CSR).

Table 84. Albuterol PK Parameters Following the Cumulative Dose (1+1+2+4+8 Actuations, a Total Albuterol Dose of 1440 µg) Administration of AS MDI (90 µg) and Proventil (90 µg) (Study ASPEN)

	Study Drug	
PK Parameter	AS MDI (N=25)	Proventil (N=25)
C_{max} (pg/mL), n	25	25
Mean (%CV)	3847.6 (26.3)	5456.8 (37.2)
SD	1010.8	2028.3
Median	3850.0	5380.0
Minimum, maximum	1990.0; 5400.0	2290.0; 10800.0
Geometric mean (CV%)	3710.8 (28.7)	5099.2 (39.7)
AUC_{0-t} (pg•hr/mL), n	25	25
Mean (%CV)	22233.8 (27.0)	28235.1 (26.9)
SD	6002.0	7607.1
Median	21032.5	28423.7
Minimum, maximum	13766.1; 36307.4	15213.4; 46952.1
Geometric Mean (CV%)	21514.6 (26.3)	27245.3 (28.2)
T_{max} (hr), n	25	25
Median	2.6	2.4
Minimum, maximum	2.23; 5.02	2.20; 5.05

Note: For the purposes of parameter estimation, plasma concentration values below the LLOQ were set to missing in the NCA with the exception of those values reported at predose. Predose concentrations that are below the LLOQ were set to 0 for the NCA. Albuterol LLOQ=50.0 pg/mL.
Source: Table 2.12.2.
(Source: Table 21 of Study ASPEN CSR).

Table 85. Albuterol PK Comparison Following the Cumulative Dose (1+1+2+4+8 Actuations, a Total Albuterol Dose of 1440 µg) Administration of AS MDI (90 µg) and Proventil (90 µg) (Study ASPEN)

	Geometric LS Mean			
PK Parameter	AS MDI (N=25)	Proventil (N=25)	Geometric Mean Ratio (90% CI)[a]	Intrasubject CV[b]
C_{max} (pg/mL)	3706.62	5104.88	72.61 (66.48–79.30)	18.20
AUC_{0-t} (pg•hr/mL)	21495.79	27269.15	78.83 (73.39–84.67)	14.71

[a] Ratio (expressed as %) of exponentiated mean difference of ln-transformed PK parameter. The CI is from a mixed model with a random subject effect and fixed effects for study drug and period.
[b] 100*sqrt[exp(residual)–1], where residual represents the residual variance component.
(Source: Table 22 of Study ASPEN CSR).

Conclusions

Following the same cumulative dose (1+1+2+4+8 actuations, a total albuterol dose of 1440 µg) administration of AS MDI (90 µg) and Proventil (90 µg), the systemic exposure of albuterol with AS MDI is lower than with Proventil.

14.3.3. OCP Appendix III: Pharmacometrics Review

Population PK Analysis

In NDA214070, the Applicant submitted a population PK report to characterize the PK profile of budesonide delivered via a metered dose inhaler for as-needed dosing in adults and children on top of maintenance therapy with budesonide delivered via dry powder inhaler or Pulmicort Respules. The final population PK models for adults and children were used to predict steady-state budesonide exposure under a variety of dosing scenarios in the Phase 3 program for BDA MDI in adults and children 4 years and older.

The pharmacometrics review focused on the assessment of the appropriateness of the sponsor's population PK models for simulations. Independent analyses were conducted to simulate the exposure of budesonide in children under worse case scenarios.

Review Summary

In general, the applicant's population PK analyses are considered acceptable for the purpose of predicting exposure parameters of budesonide delivered via metered dose inhaler in adults and children on top of maintenance therapy with budesonide delivered via dry powder inhaler or Pulmicort Respules. The final population PK models appeared adequate to characterize the PK profiles of budesonide as indicated in the applicant's goodness-of-fit plots and VPC plots. The applicant's population analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 86.

Additional simulations were performed to mimic the 'worst-case scenario' daily use in adults and children: i.e., 12 inhalations of high dose BDA (6 doses of BDA 160/180 µg) plus the maximum BD controller dose. Results showed that, in this situation, the total systemic exposure ($AUC_{0\text{-}24hours}$) of BD in adolescents and children aged 4 to 11 years is still expected to be lower than the value in adults (Table 12)

Table 86. Specific Comments on Applicant's Population PK Analyses

Utility of the Final Model	Reviewer's Comments
Derive population PK parameters of budesonide in adults and children to simulate budesonide exposure	Two population PK models were developed, one for adults and one for children. The applicant's final models for adults and children are acceptable and deemed appropriate for simulations.
Compare the total budesonide exposure ($AUC_{0\text{-}24hours}$) between adults and children under the worst-case scenario use (12 Inhalations BDA MDI/daily plus the maximum BD DPI maintenance dose)	See Table 12. Independent simulations were conducted by the reviewer with the applicant's final models. Under the worst-case scenario, the total systemic exposure ($AUC_{0\text{-}24hours}$) of BD in adolescents and children aged 4 to 11 years is still expected to be lower than the value in adults.

The Applicant's population PK analyses are summarized as below.

Objectives

The primary objectives of the analysis varied by age group and are listed below.

Adults and Children ≥6 Years of Age

- Using data from two phase 1 trials, update an existing pharmacokinetic (PK) model of budesonide delivered in a metered dose inhaler (MDI), to characterize budesonide exposure with delivery via BDA MDI or BD DPI in adults.
- Simulate budesonide exposure under scenarios involving frequent dosing as studied in the phase 3 program for BDA MDI (e.g., 4 times per day in DENALI and PRN in MANDALA, on top of BD DPI maintenance therapy), and compare to exposure under currently approved dosing regimens for BD DPI in the US.

Pediatrics

- Using the developed BDA MDI budesonide model in adults as a starting point, develop a pediatric budesonide PK model by incorporating data from the pediatric study BLANC, for budesonide delivered via BDA MDI or Pulmicort Respules.
- Simulate budesonide exposure in children under dosing scenarios studied in the phase 3 program for BDA MDI (e.g., 4 times per day in DENALI and PRN in MANDALA) with or without Pulmicort Respules maintenance therapy.

Data

Population PK analysis of budesonide was based on PK data from three Phase I studies, two in healthy adult volunteers and one in children aging 4-8 with asthma. Description of Studies is summarized in Table 87.

Table 87. Brief Description of Studies With PK Sampling Included in Population PK Analyses of Budesonide

Study Number	Study Design	Population	Formulations	Number of subjects with evaluable plasma concentrations	Blood sampling schedule
D6930C00003 (Phase 1, LOGAN)	Single dose, three-period, randomized, open-label, crossover.	Healthy adult volunteers	BDA MDI (80/90µg x2) Budesonide & Albuterol delivered separately (not used in this analysis)	89	Pre-dose, 5, 15, 20, 30, 45 min, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours after dose.
D6930C00011 (Phase 1, ELBRUS)	Single dose, two-period, randomized, open-label, crossover.	Healthy adult volunteers	BDA MDI (80/90µg x2) BD DPI (90µg x2)	65	Pre-dose, 5, 15, 20, 30, 45 min, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours after dose.
Study Number	**Study Design**	**Population**	**Formulations**	**Number of subjects with evaluable plasma concentrations**	**Blood sampling schedule**
AV006 (Phase 1, BLANC)	Single dose, two-period, randomized, open-label, crossover.	Children age 4 to 8 with asthma	BDA MDI (80/90µg x2) Pulmicort Respules (1 mg)	10	Pre-dose, 10, 20, 40 min, 1, 2, 4, 6, 8 and 12 hours after dose.
BD = budesonide; DPI = dry power inhaler; MDI = metered dose inhaler.					

Source: Table 1 on page 16-17 of Applicant's population PK report.

PK Population and Demographics

For budesonide population PK analyses, the final PK dataset included 3305 plasma PK samples from 155 adult subjects and 199 samples from the 10 evaluable pediatric subjects. After

excluding samples that were pre-dosed or under BLQ, a total of 3145 samples were used for model development. Summary of concentration data used in the analysis is shown in Table 88.

Table 88. Summary of Concentration Data Used in the Analysis by Study and Formulation

Study	Number of samples included in analysis	BDA MDI	BD DPI	Pulmicort Respules
PT027003	1190	1190 (100%)	0	0
PT027011	1777	885 (49.8%)	892 (50.2%)	0
Adult total	2967	2075 (69.9%)	892 (30.1%)	0
AV006	178	88 (49.4%)	0	90 (50.6%)
TOTAL	3145	2163 (68.8%)	892 (28.4%)	90 (2.86%)
BD = budesonide; DPI = dry power inhaler; MDI = metered dose inhaler. Data source: PT027_NMadultpaeds_BD.csv; r-script: s02_ExploratoryDataAnalysis_BD.R Output: BD_Summary_Formulation.csv; 2021-10-22 16:54:55				

Source: Table 6 on page 36 of Applicant's population PK report.

A summary of subject demographic and baseline characteristics for the pooled budesonide PK population is provided in Table 89.

Table 89. Summary of Continuous and Categorical Covariates from All Studies (N=165)

Summary of Continuous Covariates for all Studies					
Covariate median (min-max)	**PT027003 (N=89)**	**PT027011 (N=66)**	**ADULT TOTAL (N=155)**	**AV006 (N=10)**	**TOTAL (N=165)**
Age at baseline [years]	37 (19-55)	34 (18-55)	36 (18-55)	7 (4-8)	34 (4-55)
Weight at baseline [kg]	71.2 (50.6-95.5)	76.3 (60.6-99)	73.4 (50.6-99)	32.4 (14.1-54.4)	72.9 (14.1-99)
Height at baseline [cm]	172 (154-188)	173 (157-196)	173 (154-196)	121 (96.5-142)	172 (96.5-196)
BMI at baseline [kg/m2]	24.1 (19-29.9)	25.4 (20.2-30)	24.8 (19-30)	20.3 (15.1-26.9)	24.5 (15.1-30)
Estimated (normalized) GFR at baseline [mL/min/1.73m2]	105 (74.5-140)	108 (72.8-143)	106 (72.8-143)	118 (95-147)	106 (72.8-147)
Estimated absolute GFR at baseline [mL/min]	112 (84.4-149)	121 (85.5-168)	116 (84.4-168)	71.1 (33.4-105)	114 (33.4-168)
Creatinine clearance at baseline[mL/min]	116 (80.6-166)	116 (77.8-188)	116 (77.8-188)	113 (54-208)	116 (54-208)
BMI = body mass index; GFR = glomerular filtration rate.					

Summary of Categorical Covariates for all Studies						
Covariate N (%)		**PT027003 (N=89)**	**PT027011 (N=66)**	**ADULT TOTAL (N=155)**	**AV006 (N=10)**	**TOTAL (N=165)**
Sex	Female	38	24	62 (40%)	7 (70%)	69
		(42.7%)	(36.4%)			(41.8%)
	Male	51(57.3%)	42 (63.6%)	93 (60%)	3 (30%)	96(58.2%)
Race	White	62(69.7%)	14(21.2%)	76 (49%)	6 (60%)	82(49.7%)
	Black/African American	14(15.7%)	51(77.3%)	65 (41.9%)	3 (30%)	68(41.2%)
	Asian	5 (5.62%)	0	5 (3.23%)	0	5 (3.03%)
	Native	0	1 (1.52%)	1 (0.645%)	0	1
	Hawaiian/Other					(0.606%)
	Pacific Islander					
	Other	8 (8.99%)	0	8 (5.16%)	1 (10%)	9 (5.45%)

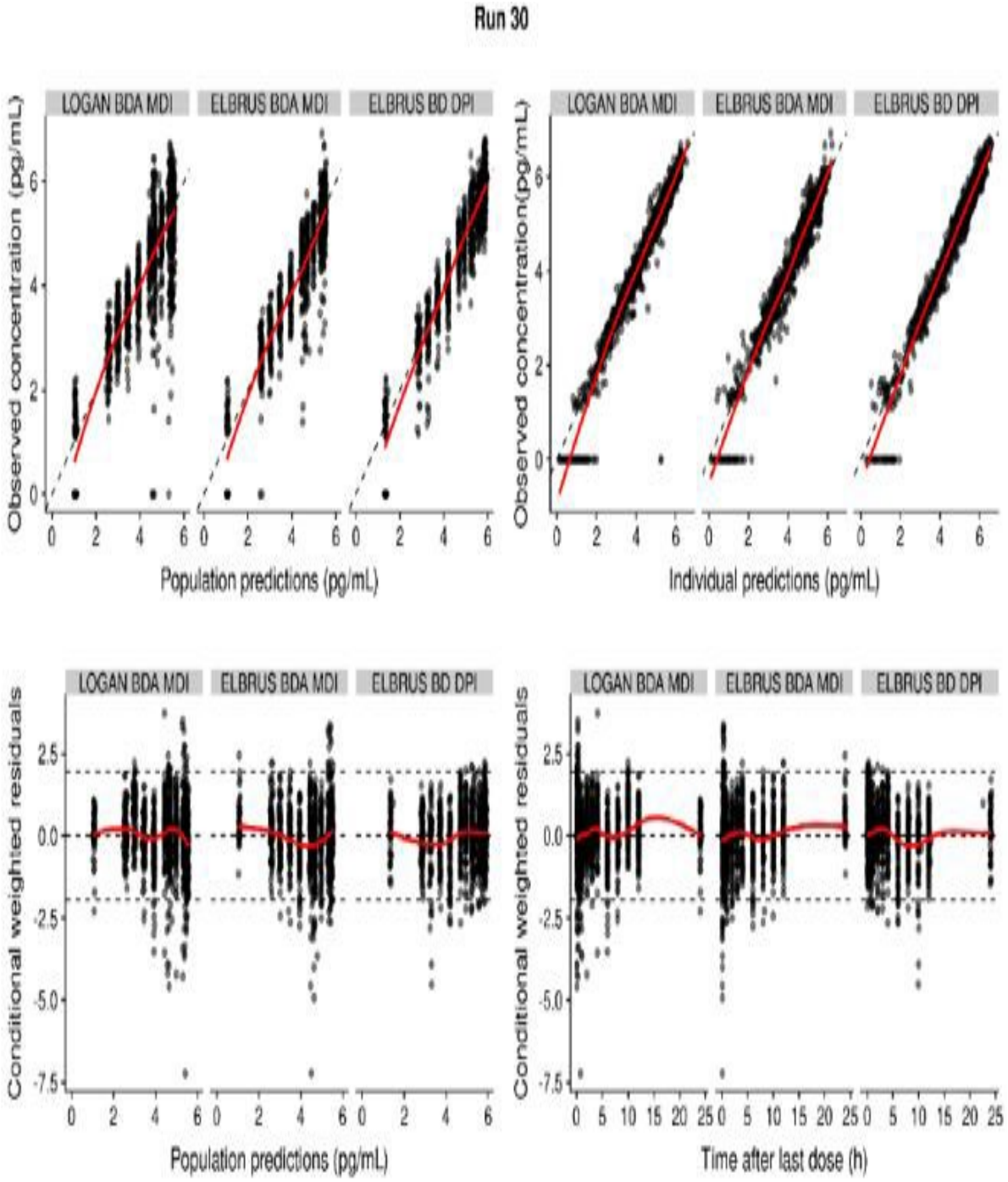
Source: Adapted from Table 7 and 8 on page 40-41 of Applicant's population PK report.

14.3.3.1. Population PK Model Development

Adult Population PK Model

The final model for budesonide was a three-compartment model with formulation-specific first order absorption and relative bioavailability, a combined residual error model, with a study specific proportional residual error (approximately proportional error on log-scale), log-normally distributed between subject variability on ka_MDI, ka_DPI, CL/F, and Vc/F, with a correlation between the individual estimates of CL/F and Vc/F, and a covariate effect of body weight on Vc/F (increasing volume with increasing body weight). Parameter estimates for the final covariate model are reported in Table 90.

Table 90. Population Pharmacokinetic Parameter Estimates of Budesonide -Final Model for Adults (Run 30)

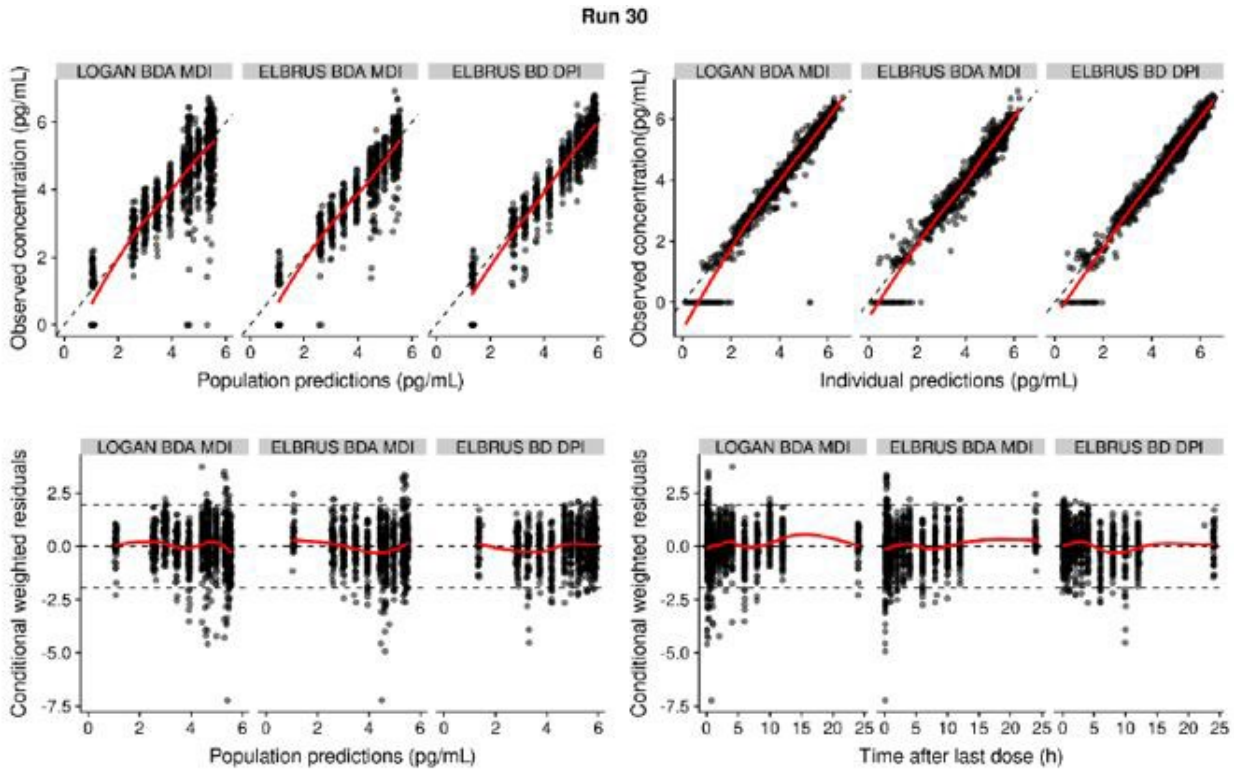


Source: Table 12 on page 54 of Applicant's population PK report.

Model Evaluation

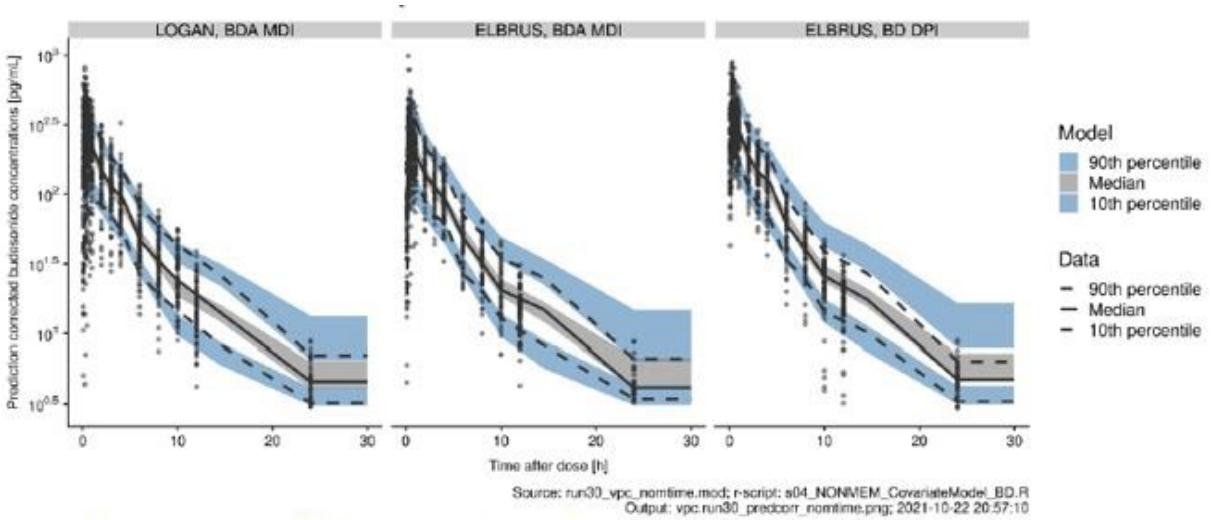
The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs). The goodness-of-fit plots for the final model are displayed in Figure 24 and the VPCs plots are demonstrated in Figure 25.

Figure 24. Goodness of Fit Plot for the Final Adult Budesonide Population PK Model, by Study and Formulation (Log Scale)



Source: Figure E-2 on page 110 of Applicant's population PK report.

Figure 25. Prediction Corrected VPCs at Steady State, Stratified on Formulation and Study



BD = budesonide; DPI = dry power inhaler; MDI = metered dose inhaler.

Source: Figure 10 on page 56 of Applicant's population PK report.

Posthoc PK Parameter Estimation A posterior predictive check was performed to evaluate the model's ability to predict AUC and C_{max}. The results are summarized in Table 91.

Table 91. Posterior Predictive Check for AUC and C_{max} (Run 30)

Study/Formulation	Data	Predicted
AUC (pg/mL*hr)	median (90%CI) [IQR]	
Overall	1050 (453-1840) [777-1360]	1050 (546-1980) [807-1370]
LOGAN BDA MDI	1010 (337-1860) [745-1270]	973 (519-1750) [756-1240]
ELBRUS BDA MDI	945 (517-1530) [746-1150]	974 (518-1750) [755-1250]
ELBRUS BD DPI	1270 (603-2080) [1000-1640]	1280 (680-2310) [992-1640]
C_{max} (pg/mL)	median (90%CI) [IQR]	
Overall	324 (105-700) [228-443]	264 (105-648) [181-383]
LOGAN BDA MDI	311 (73-591) [207-421]	236 (98.3-546) [165-334]
ELBRUS BDA MDI	261 (128-477) [205-345]	233 (96.8-536) [163-330]
ELBRUS BD DPI	437 (219-758) [300-560]	353 (146-798) [248-498]
AUC = area under the concentration-time curve; BD = budesonide; BID = bis in die (twice daily dosing); C_{max} = maximum concentration; DPI = dry power inhaler; MDI = metered dose inhaler. Datasource: run30, r-script: s05_PPC.R, 2021-10-22 20:17:02		

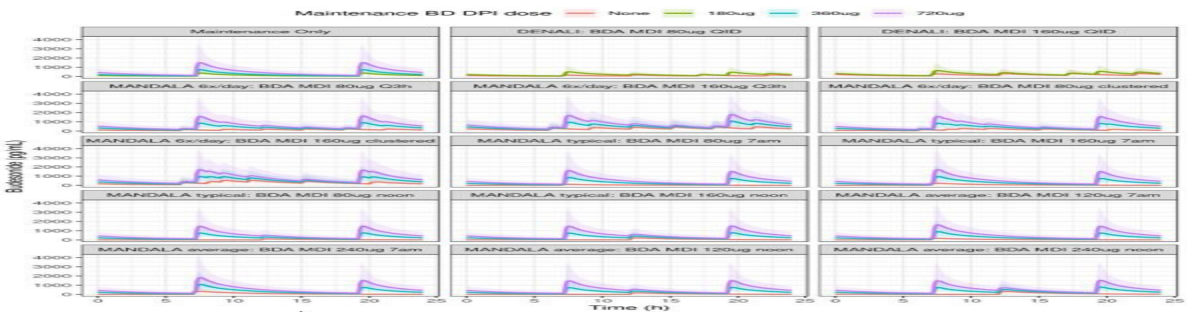
Source: Table 13 on page 58 of Applicant's population PK report.

Dosing Scenario Simulations for Adults and Adolescents 12 Years and Older

Various dosing scenarios were simulated, with or without background therapy with BD DP, to explore budesonide exposures in phase 3 program for BDA MDI, I. For each scenario, 10,000 individuals were bootstrapped from the individual participants aged 12 years and up randomized in DENALI and/or MANDALA (n=4033 with recorded body weight). The 24-hour AUC and C_{max} at steady state were calculated for each simulated individual and summarized using the median and 90% prediction interval (PI) for each exposure metric. BD DPI 720µg BID was used as a reference case for comparing total budesonide dose, C_{max}, and AUC over 24 hours. The results are summarized in Table 92 and demonstrated in Figure 26. Relative budesonide exposure under different dosing scenarios for adults and adolescents 12 years and older is show in Figure 27.

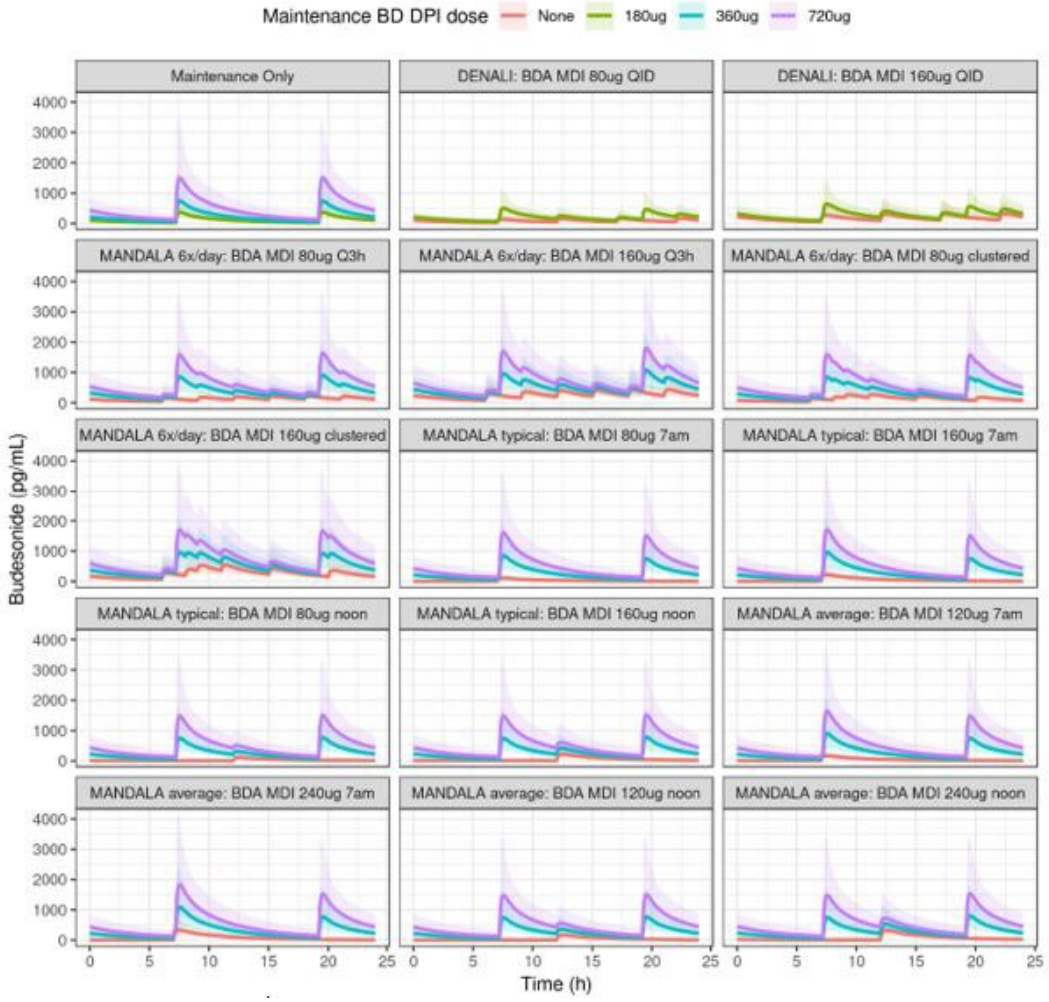
Table 92. Summary of Relative Budesonide Exposure Metrics Under Different Dosing Scenarios for Adults and Adolescents 12 Years and Older

24hr AUC, relative to BD DPI 720µg BID	Maintenance BD DPI Dose			
BDA MDI Dosing	**None**	**180µg**	**360µg**	**720µg**
Maintenance Only		0.247	0.495	1
DENALI: BDA MDI 80ug QID	0.188	0.43		
DENALI: BDA MDI 160µg QID	0.375	0.617		
MANDALA 6x/day: BDA MDI 80µg Q3h	0.28		0.775	1.25
MANDALA 6x/day: BDA MDI 160µg Q3h	0.559		1.05	1.53
MANDALA 6x/day: BDA MDI 80µg clustered	0.281		0.778	1.26
MANDALA 6x/day: BDA MDI 160µg clustered	0.562		1.06	1.56
MANDALA typical: BDA MDI 80µg 7am	0.0464		0.544	1.04
MANDALA typical: BDA MDI 160µg 7am	0.0938		0.588	1.08
MANDALA typical: BDA MDI 80µg noon	0.0468		0.543	1.03
MANDALA typical: BDA MDI 160µg noon	0.0928		0.587	1.07
MANDALA average: BDA MDI 120µg 7am	0.071		0.559	1.05
MANDALA average: BDA MDI 240µg 7am	0.14		0.638	1.13
MANDALA average: BDA MDI 120µg noon	0.0705		0.563	1.06
MANDALA average: BDA MDI 240µg noon	0.141		0.636	1.13
C_{max}, relative to BD DPI 720µg BID	**Maintenance BD DPI Dose**			
BDA MDI Dosing	**None**	**180µg**	**360µg**	**720µg**
Maintenance Only		0.245	0.492	1
DENALI: BDA MDI 80µg QID	0.11	0.332		
DENALI: BDA MDI 160µg QID	0.218	0.424		
MANDALA 6x/day: BDA MDI 80µg Q3h	0.144		0.603	1.08
MANDALA 6x/day: BDA MDI 160µg Q3h	0.288		0.709	1.19
MANDALA 6x/day: BDA MDI 80µg clustered	0.181		0.569	1.06
MANDALA 6x/day: BDA MDI 160µg clustered	0.361		0.661	1.14
MANDALA typical: BDA MDI 80µg 7am	0.0755		0.567	1.07
MANDALA typical: BDA MDI 160µg 7am	0.152		0.638	1.13
MANDALA typical: BDA MDI 80µg noon	0.0771		0.508	0.995
MANDALA typical: BDA MDI 160µg noon	0.153		0.516	1.01
MANDALA average: BDA MDI 120µg 7am	0.117		0.598	1.09



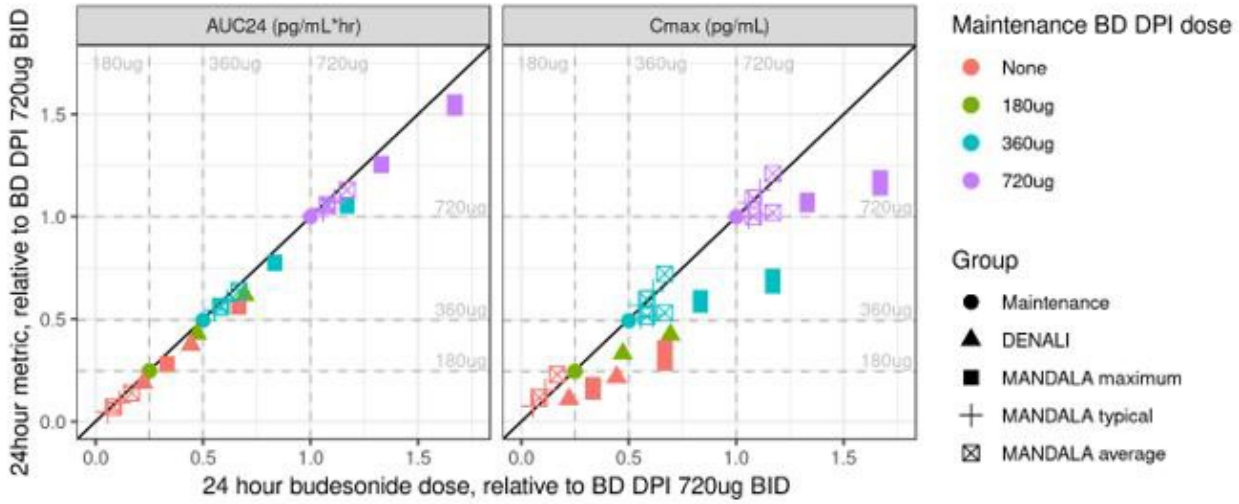
Source: Table 16 on page 62 of Applicant's population PK report.

Figure 26. Predicted Budesonide Plasma Concentrations in Adults and Adolescents 12 years and Older Under Different Dosing Scenarios



Note: X-axis shows time from midnight on a representative day at steady-state. Lines are median and ribbons are 90% prediction intervals. All maintenance BD DPI doses were given BID.
AUC24 = area under the concentration-time curve in 24 hours; BD = budesonide; BID = bis in die (twice daily dosing); C_{max} = maximum concentration; DPI = dry power inhaler; MDI = metered dose inhaler.
Source: Figure 14 on page 63 of Applicant's population PK report.

Figure 27. AUC and C_{max} for Budesonide, Relative to Exposure with BD DPI 720µg BID, Under Different Dosing Scenarios in Adults and Adolescents 12 Years and Older

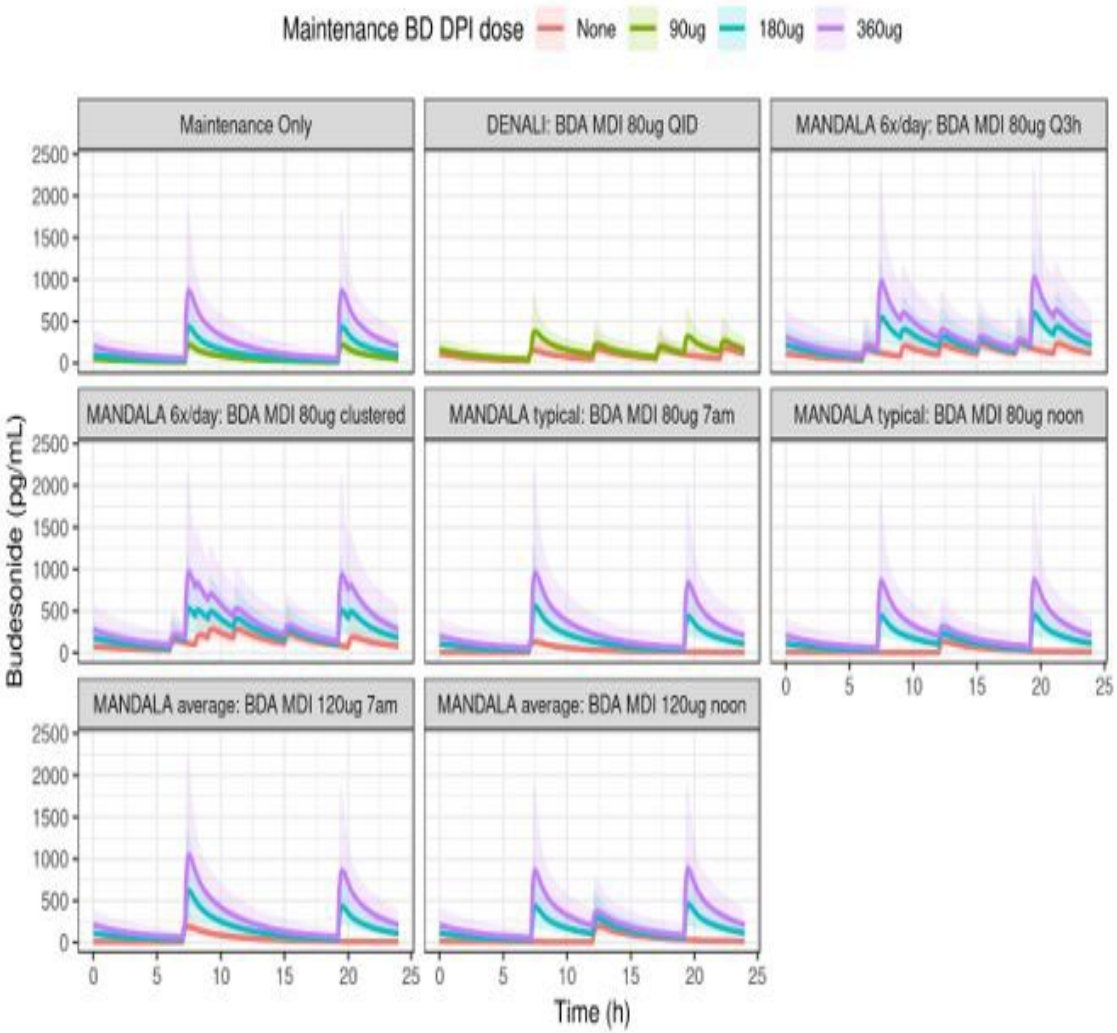


Source: Figure 15 on page 65 of Applicant's population PK report.

Dosing Scenario Simulations for 6-11 Year Old Children

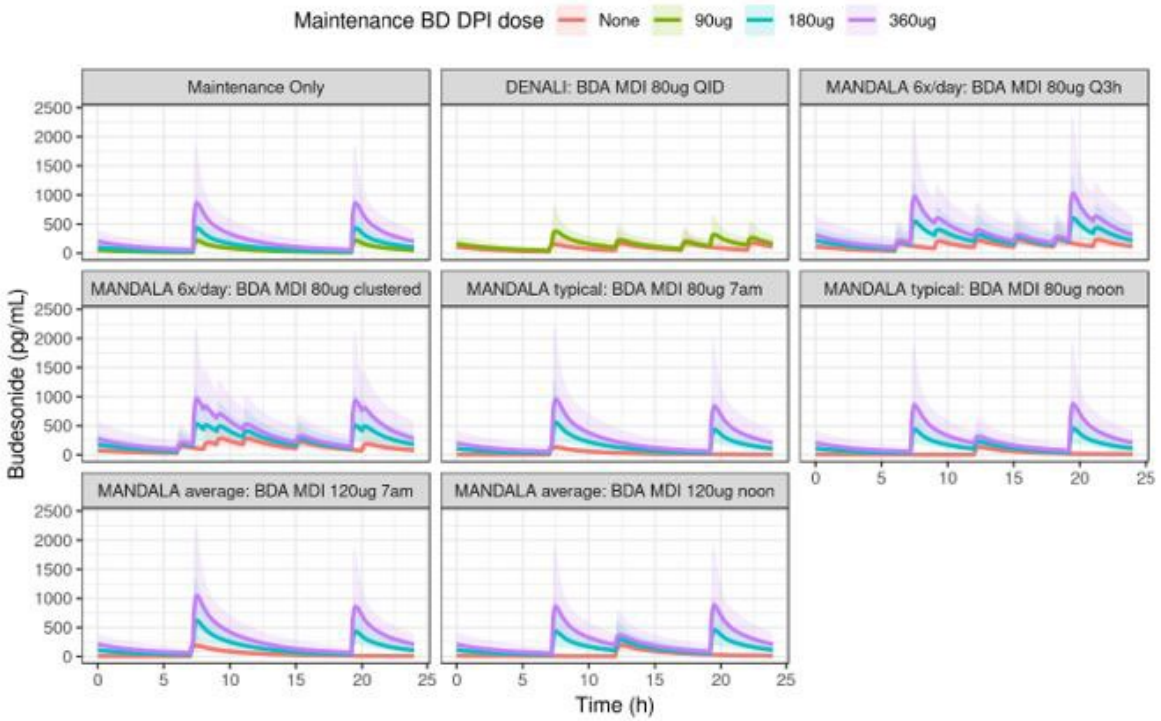
Adolescents (aged 6-11 years old) from DENALI and MANDALA were simulated separately, as the recommended dosing for this age group was different than for adults. As only 88 6-11 year old subjects with recorded baseline body weight were randomized in DENALI or MANDALA, this group was sampled 1,000 times with replacement. Summary of budesonide exposure in this group of population is summarized in Figure 28 and shown in Figure 30.

Figure 28. Summary of Budesonide Exposure Metrics Under Different Dosing Scenarios for Children 6-11 Years Old



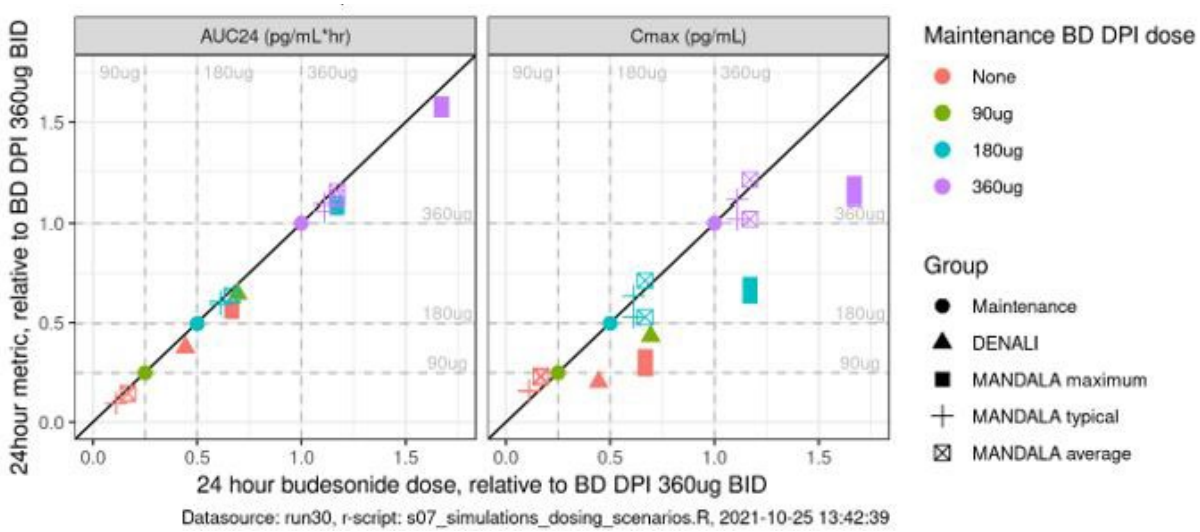
Source: Table 17 on page 66 of Applicant's population PK report.

Figure 29. Predicted Budesonide Plasma Concentrations in Children 6-11 Years Old Under Different Dosing Scenarios



Note: X-axis shows time from midnight on a representative day at steady-state. Lines are median and ribbons are 90% prediction intervals.
AUC24 = area under the concentration-time curve in 24 hours; BD = budesonide; BID = bis in die (twice daily dosing); C_{max} = maximum concentration; DPI = dry power inhaler; MDI = metered dose inhaler.
Source: Figure 16 on page 67 of Applicant's population PK report .

Figure 30. AUC and C_{max} for Budesonide, Relative to Exposure With BD DPI 360µg BID, Under Different Dosing Scenarios in Children 6-11 Years Old



Note: 24-hour budesonide dose calculated using labeled dose for each formulation. For BD DPI, the labeled dose is 90µg, while the dose delivered from the mouthpiece is 80µg per inhalation.
AUC24 = area under the concentration-time curve in 24 hours; BD = budesonide; BID = bis in die (twice daily dosing); C_{max} = maximum concentration; DPI = dry power inhaler; MDI = metered dose inhaler.

Pediatric Population PK Model

The final pediatric model, fit to data from LOGAN, ELBRUS, and BLANC, was a three compartment model with formulation-specific first-order absorption, formulation and adult/pediatric-specific relative bioavailability, a combined residual error model with a study specific proportional error term (approximately proportional error on a log-scale), log-normally distributed between-subject variability on ka_MDI, ka_DPI, CL/F, and Vc/F, and a covariate effect of body weight on Vc/F (increasing volume with increasing weight). Parameter estimates for the final pediatric model are reported in Table 93, The VPC plots are shown in Figure 31.

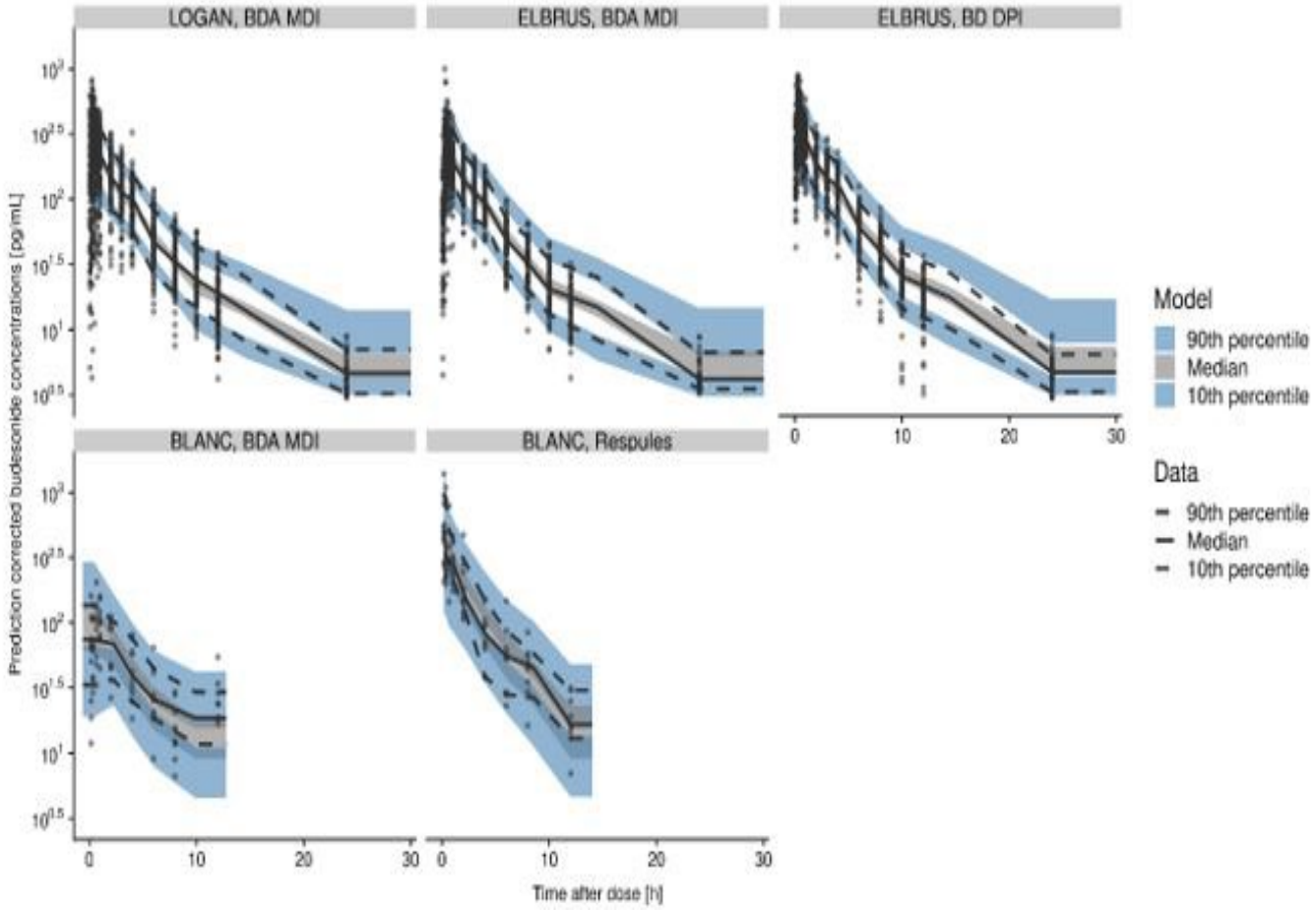
Table 93. Population Pharmacokinetic Parameter Estimates for the Final Pediatric Covariate Model (Run 105)

24hr AUC, relative to Pulmicort Respules 1mg QD	Maintenance Pulmicort Respules Dose		
BDA MDI Dosing	**None**	**1mg QD**	**0.5mg BID**
Maintenance Only		1	0.985
DENALI: BDA MDI 80µg QID	0.729	1.7	1.74
MANDALA 6x/day: BDA MDI 80µg Q3h	1.1	2.07	1.99
MANDALA 6x/day: BDA MDI 80µg clustered	1.12	2.11	2.16
MANDALA typical: BDA MDI 80µg 7am	0.184	1.18	1.13
MANDALA typical: BDA MDI 80µg noon	0.188	1.18	1.17
MANDALA average: BDA MDI 120µg 7am	0.28	1.28	1.29
MANDALA average: BDA MDI 120µg noon	0.277	1.28	1.26
24 hr AUC [90% PI] (pg/mL*hr)	**Maintenance Pulmicort Respules Dose**		
BDA MDI Dosing	**None**	**1mg QD**	**0.5mg BID**
Maintenance Only		1290 [693-2490]	1270 [656-2430]
DENALI: BDA MDI 80µg QID	938 [502-1820]	2190 [1140-4250]	2250 [1160-4240]
MANDALA 6x/day: BDA MDI 80µg Q3h	1410 [754-2690]	2660 [1370-5240]	2560 [1340-4960]
MANDALA 6x/day: BDA MDI 80µg clustered	1440 [740-2750]	2720 [1370-5180]	2780 [1350-5020]
MANDALA typical: BDA MDI 80µg 7am	237 [115-464]	1520 [797-3000]	1450 [787-2830]
MANDALA typical: BDA MDI 80µg noon	242 [120-475]	1520 [792-2990]	1510 [795-2850]
MANDALA average: BDA MDI 120µg 7am	361 [182-729]	1650 [809-3120]	1660 [838-3100]
MANDALA average: BDA MDI 120µg noon	357 [187-657]	1650 [840-3110]	1630 [848-3230]

BD = budesonide; BID = bis in die (twice daily dosing); DPI = dry power inhaler; MDI = metered dose inhaler; QD = quaque die (once per day dosing); QID = quarter in die (four times per day dosing).

Source: Table 21 on page 74 of Applicant's population PK report.

Figure 31. Prediction Corrected VPCs at Steady State for the Final Pediatric Model Stratified on Formulation and Study



Source: Figure 19 on page 76 of Applicant's population PK report.

Pediatric Dosing Scenario Simulations

Dosing scenarios from the phase 3 DENALI and MANDALA trials that are relevant to 4-8 year old children were simulated, with or without background therapy of Pulmicort Respules 1mg QD or 0.5mg BID as the representative maintenance ICS.

Simulated budesonide exposure under different dosing scenarios for Children 4-8 years old are summarized in Table 94 and budesonide plasma concentrations are shown in Figure 32. AUC for Budesonide under different dosing scenarios with BDI MDI Only, compared in Adults, Adolescents, and Children is shown in Figure 33.

Total 24-hour budesonide doses in the scenarios ranged from 80µg to 1480µg, with median 24-hour AUC ranging from 237pg/mL*hr to 2,780pg/mL*hr (Table 94). Overall, AUC scaled linearly

with dose, regardless of maintenance Pulmicort Respules use, and the timing of budesonide dosing did not have a large impact on the AUC.

In the simulated cases without maintenance Pulmicort Respules , the 24-hour AUC with BDA MDI reached a maximum of 1.12-fold higher than the reference case of Pulmicort Respules 1mg QD (Table 94). In the DENALI: BDA MDI 80 µg QID case without maintenance therapy, the 24-hour AUC was 73% of that with Pulmicort Respules 1mg QD. With maintenance Pulmicort Respules, the median budesonide AUC estimate reached 2.16-fold higher than with Pulmicort Respules 1mg QD alone (Table 94), MANDALA maximum use scenarios with Pulmicort Respules 0.5mg BID maintenance therapy and BDA MDI use six times per day at 80µg).

Table 94. Summary of Budesonide Exposure Metrics Under Different Dosing Scenarios for Children 4-8 Years Old

24hr AUC, relative to Pulmicort Respules 1mg QD	Maintenance Pulmicort Respules Dose		
BDA MDI Dosing	**None**	**1mg QD**	**0.5mg BID**
Maintenance Only		1	0.985
DENALI: BDA MDI 80µg QID	0.729	1.7	1.74
MANDALA 6x/day: BDA MDI 80µg Q3h	1.1	2.07	1.99
MANDALA 6x/day: BDA MDI 80µg clustered	1.12	2.11	2.16
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MANDALA average: BDA MDI 120µg 7am	0.28	1.28	1.29
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24 hr AUC [90% PI] (pg/mL*hr)	**Maintenance Pulmicort Respules Dose**		
BDA MDI Dosing	**None**	**1mg QD**	**0.5mg BID**
Maintenance Only		1290 [693-2490]	1270 [656-2430]
DENALI: BDA MDI 80µg QID	938 [502-1820]	2190 [1140-4250]	2250 [1160-4240]
MANDALA 6x/day: BDA MDI 80µg Q3h	1410 [754-2690]	2660 [1370-5240]	2560 [1340-4960]
MANDALA 6x/day: BDA MDI 80µg clustered	1440 [740-2750]	2720 [1370-5180]	2780 [1350-5020]
MANDALA typical: BDA MDI 80µg 7am	237 [115-464]	1520 [797-3000]	1450 [787-2830]
MANDALA typical: BDA MDI 80µg noon	242 [120-475]	1520 [792-2990]	1510 [795-2850]
MANDALA average: BDA MDI 120µg 7am	361 [182-729]	1650 [809-3120]	1660 [838-3100]
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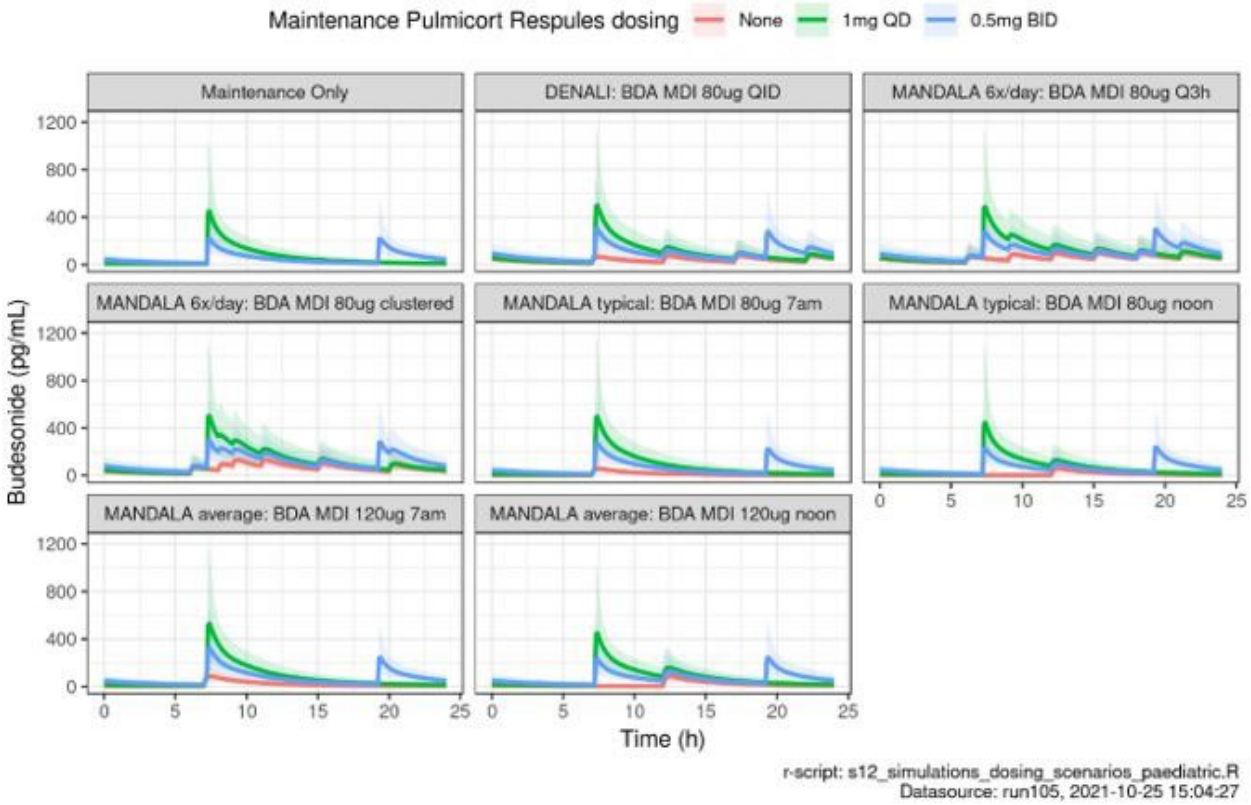
BD = budesonide; BID = bis in die (twice daily dosing); DPI = dry power inhaler; MDI = metered dose inhaler; QD = quaque die (once per day dosing); QID = quarter in die (four times per day dosing).

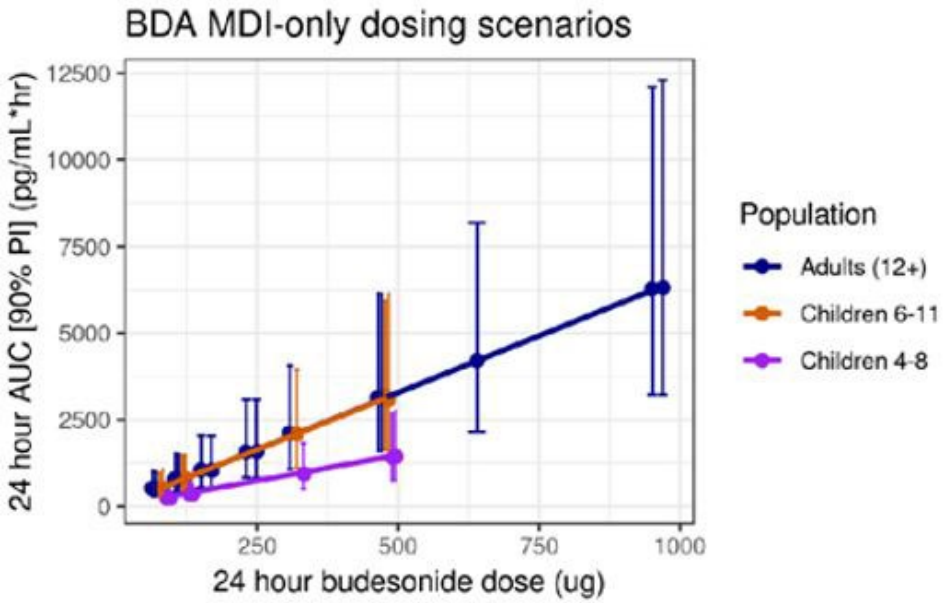
Source: Table 23 on page 79 of Applicant's population PK report.

Figure 32. Predicted Budesonide Plasma Concentrations in 4-8 Year Old Children Under Different Dosing Scenarios



Note: X-axis shows time from midnight on a representative day at steady-state. Lines are median and ribbons are 90% prediction intervals.BD = budesonide; MDI = metered dose inhaler; QD = quaque die (once per day dosing); QID = quarter in die (once per day dosing).
Source: Figure 22 on page 80 of Applicant's population PK report.

Figure 33. AUC for Budesonide Under Different Dosing Scenarios with BDI MDI Only, Compared in Adults, Adolescents, and Children



Source: Figure 24 on page 82 of Applicant's population PK report.

Reviewer's comments: *The Applicant's population PK modeling and simulations analyses for budesonide are acceptable. The reviewer was able to repeat and verify the Applicant's analyses with no significant discordance identified. Overall, the final population PK models appeared adequate to characterize the PK profile of budesonide delivered via a metered dose inhaler for as-needed dosing in adults and children as indicated in the applicant's goodness-of-fit plots and VPC plots. However, there are uncertainties in PK of adolescents. The reviewer noticed that the PK sample size in children was too limited. Only 7 pediatric subjects 4-8 years provided PK samples for modeling analyses, and there were no PK samples collected in children 9 to 17 years old.* (b) (4) .

Based on the modeling analyses, budesonide exposures following same dosage treatment with BDA MDI were lower in 4-8 year old children than predicted by the adult model, due to lower systemic bioavailability. The applicant attributed this as a result of differences in airway geometry and inhalation technique. Relative bioavailability of BDA MDI in 4-8 year old children was estimated to be 44.5% of that in adults, and relative bioavailability of Pulmicort Respules in children was estimated to be 19.3% of that of BDA MDI in adults.

Additional simulations were conducted by the reviewer to mimic the 'worse-case scenario' daily use in children. i.e., 12 inhalations of high dose BDA (6 doses of BDA 160/180) plus the maximum BD controller dose. In this situation, the total systemic exposure ($AUC_{0\text{-}24hours}$) of BD in

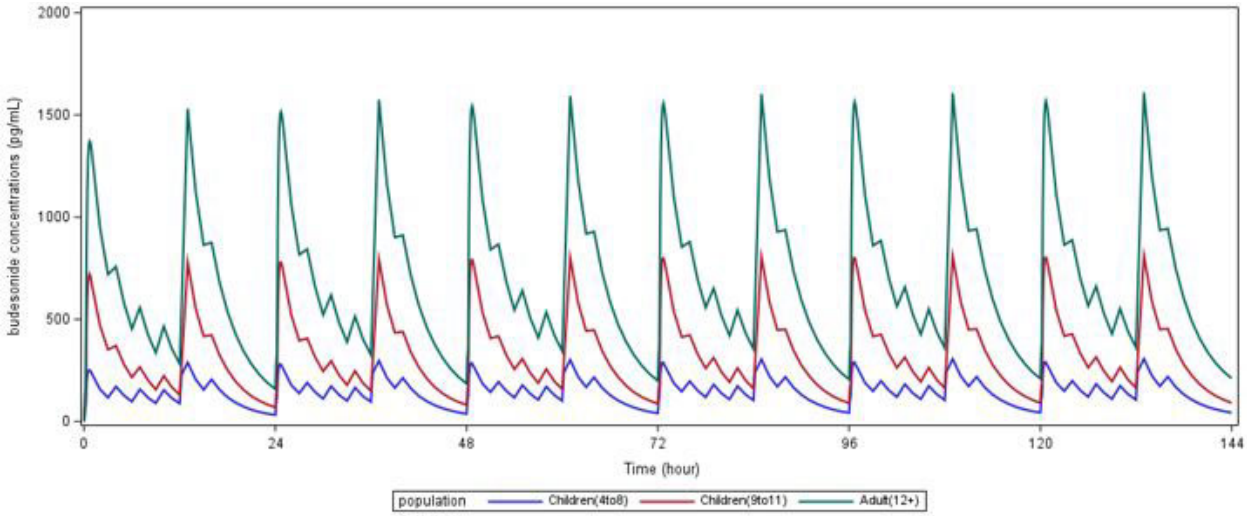
adolescents and children aged 4 to 11 years is still expected to be lower than the value in adults. Our simulation results are shown in Table 95 and Figure 34. Note that there is no observed PK data available in children aged 9 to <18 years from the BDA clinical development program; therefore, our simulation assumed the same bioavailability of BD in subjects ≥9 years old via the inhalational route. This decision is considered conservative, because all approved BD inhalational products (Pulmicort Flexhaler, Pulmicort Respules, and Symbicort) have demonstrated comparable or lower bioavailability and systemic exposure of BD in pediatric patients compared to adults.

Table 95. Comparison of Total Budesonide Systemic Exposure ($AUC_{0\text{-}24hours}$) Between Adults and Children Under the Worst-Case Scenario Use (12 Inhalations BDA MDI/Daily Plus the Maximum BD DPI Maintenance Dose)

Age Group	BDA MDI Maximum Dose[1]	Maximum BD DPI Maintenance Dose	Total BD Exposure in Children Relative to Adults Under Worst-Case Scenario Use
Adults	12 inhalations (960 µg)/day	720 µg BID[2]	1.0
Adolescents (≥12 years)[2,4]	12 inhalations (960 µg)/day	360 µg BID[2]	0.68
Children 9-11 years[2,4]	12 inhalations (480 µg)/day	360 µg BID[2]	0.48
Children 4-8 years	12 inhalations (480 µg)/day	1000 µg QD or 500 µg BID[3]	0.21

Source: Clinical Pharmacology Reviewer.
DPI : dry powdered inhaler.
[1] As proposed by the Applicant.
[2] Approved maximum BD dose from Pulmicort Flexhaler (6 to 17 years of age)
[3] Approved maximum BD dose from Pulmicort Respule (1 to 8 years of age)
[4] No observed PK data in children 9 to 18 years of age from the BDA program, the simulated results are based on adult bioavailability value

Figure 34. Simulated Budesonide PK Profiles of Children and Adults Under Scenarios of Maximum Use



Source: Reviewer's simulations based on Applicant's final population PK models for adults and children.

14.4. Bayesian Analysis for Pediatric Efficacy

Overview

Bayesian analyses provide a formal framework to incorporate prior information into the design and analysis of clinical trials. The source of such prior information may incorporate expert opinion and analyses of trial data from other sources. Proper use of prior information may reduce the need for enrollment of additional patients to determine efficacy or safety.

Consider, for example, a case where we believe it may be appropriate to incorporate some information from an adult study to help determine efficacy in adolescents. First, we represent our 'prior' belief regarding efficacy in adolescents by combining the 'informative' element, which consists of results from the adult study, with a 'non-informative' element, which is completely or nearly agnostic as to what results might be in the target adolescent population. The informative and non-informative elements are combined by weighting the informative element by the probability that experts think the informative element is truly applicable to the target population, with the remaining probability allocated as a weight to the non-informative element. This formulation of prior belief is a 'mixture' because it includes informative and non-informative elements and, as we shall see, is 'robust' because the non-informative element is given greater weight during the analysis if the data from the target (adolescent) population is inconsistent with the informative (adult) element of the prior. This formulation of prior belief is thus called a 'robust mixture prior.'

Next, data from the target population we are concerned with, in this case adolescents, are combined with the previously constructed robust mixture prior to form a distribution of posterior belief, which represents the Bayesian estimate of efficacy in the target population. This 'posterior' distribution of belief can be summarized using point estimates such as the mean and median, as well as by the Bayesian 95% credible interval[1] for efficacy in the target population.

Combining the robust mixture prior with data from the target to estimate a posterior distribution for the target population is performed in three steps: (i) the informative and noninformative elements of the robust mixture prior are each updated to include the new target data; (ii) the weight on the informative prior element is updated according to the extent that the actual data from the target population is consistent with the informative prior. If there is good consistency between the informative element of the prior and actual data, then the weight on that informative element will be increased and the weight on the non-informative element of the prior will be decreased. Conversely, if the actual data from the target population is inconsistent with the informative element of the prior, the weight on the informative element will be decreased and the weight on the non-informative element of the prior will be increased. This updating of the weighting of the informative and non-informative elements

[1] For a 95% credible interval, the probability that the efficacy measure of interest lies within its upper and lower bounds is 95%.

based on the consistency is often called 'dynamic borrowing;' and (iii) the updated elements and weights are combined to form the posterior distribution that will be used for performing inferences in the target population.

In addition to the probability weightings discussed above, the degree of borrowing needed to meet a decision rule (e.g., that the two-sided 95% credible interval from the posterior distribution excludes the null hypothesis) can be quantified by calculating the "effective sample size" of patients borrowed from the informative element.

This submission also borrows data from adults and adolescents to evaluate efficacy in children. To support this evaluation, the Applicant similarly constructed a robust mixture prior based on the trial results from adults and adolescents.

As one last note, the robust mixture prior is just one of many Bayesian methods which can be used to incorporate trial results with other sources of information.

Mathematical Implementation

Mathematical implementation of the Bayesian borrowing framework described above closely follows the steps provided in the Overview above.

First, we construct our robust mixture prior. Let θ be the efficacy parameter we're trying to estimate in the target population - for this particular submission it is the log(hazard ratio), let M_{inform} be the model for the informative element of the prior, let $M_{noninform}$ be the model for the (ideally) non-informative element of the prior, let $\pi(\theta|M_{inform})$ be the distribution of θ given the informative element of the robust mixture prior is true, and let $\pi(\theta|M_{noninform})$ be the distribution of θ given the non-informative element of the robust mixture prior is true. Further, let $0 \leq p(M_{inform}) \leq 1$ be the weight representing the level of confidence from expert opinion, in this case the Advisory Committee opinion, that the informative element truly represents the target population of interest, i.e. that response to treatment in adults represents that in adolescents, with the prior probability that the non-informative is true equal to:

$$\mathrm{p}(M_{noninform}) = 1 - \mathrm{p}(M_{inform}).$$

Then the robust mixture prior is:

$$\pi(\theta) = \mathrm{p}\left(M_{inform}\right) \times \pi\left(\theta \middle| M_{inform}\right) + \left(1 - \mathrm{p}\left(M_{inform}\right)\right) \times \pi\left(\theta \middle| M_{noninform}\right) \qquad [A.1]$$

Second, the robust mixture prior is updated in three steps to form the posterior distribution.

(i) Given the observed adolescent data *y*, the weight $\mathrm{p}\left(M_{inform}\right)$ for the informative element is updated to $\mathrm{p}\left(M_{inform}|y\right)$. In particular, let $\mathrm{f}\left(y\middle|M_{inform}\right)$ be the likelihood, from our

predefined statistical analysis, of getting the observed adolescent data given that the informative component of the prior is true, let $f\left(y\middle|M_{noninform}\right)$ be the likelihood of getting the observed adolescent data given that the non-informative element of the prior is true. Then the estimated probability that the informative element is true given data *y* can be calculated as

$$p\left(M_{inform}|y\right) = \frac{f\left(y\middle|M_{inform}\right)p(M_{inform})}{f\left(y\middle|M_{inform}\right)p(M_{inform}) + f\left(y\middle|M_{noninform}\right)p(M_{noninform})} \quad \text{[A.2]}$$

Schmidli et al. provide formulas proportional to the likelihoods in equation [A.2] to calculate $p\left(M_{inform}|y\right)$ (Schmidli et al. 2014).

(ii) The data from the target population, *y*, are incorporated into the informative and non-informative prior elements to form the posterior distributions $\pi\left(\theta\middle|y, M_{inform}\right)$ and $\pi\left(\theta\middle|y, M_{noninform}\right)$. Schmidli et al (ibid) provide closed form posterior solutions for θ under a variety of conjugate one-parameter exponential families.

(iii) The posterior distribution function, from which we can determine point estimates and credible intervals for efficacy in the target population, is given below in the same form as our robust prior of equation [A.1] above, with the informative and non-informative elements of the prior and the weight on the informative element updated to reflect data from the target population.

$$\pi(\theta|y) = p\left(M_{inform}|y\right) \times \pi\left(\theta\middle|y, M_{inform}\right) + \left(1 - p\left(M_{inform}|y\right)\right) \times \pi\left(\theta\middle|y, M_{noninform}\right) \quad \text{[A.3]}$$

In general, there are no closed form solutions for the posterior, and Markov chain Monte Carlo simulations are required to obtain approximate solutions. However, for special 'conjugate,' distributions, closed form solutions are indeed possible and are often used to save computing time. Best et al., for example, discuss the use where appropriate of analyses based on the normal distribution, with likelihoods based on single units from the informative or noninformative populations, and they outline closed form solutions for that case (Best et al. 2021). This corresponds to our current example, in which the confidence intervals for log hazard ratio for both the prior adult data and the new adolescent data are estimated using Wald intervals based on the normal distribution.

Third, we want to assess the amount of borrowing needed to achieve a high level of confidence of efficacy, e.g., for our superiority evaluations, that the two-sided equal-tailed 95% credible interval from the posterior distribution excludes the null hypothesis of no treatment effect. For example, if treatment effect greater than zero indicates efficacy, we first determine the prior weight on the informative element needed to satisfy

$$Prob(\ \theta > 0 \mid \pi(\theta|y)\ ) \geq 0.975. \quad \text{[A.4]}$$

Then, from the model with that prior weight, we calculate the realized amount of borrowing from the informative element. The realized amount of borrowing can be quantified as the effective proportion of data in the posterior distribution which originates from the informative element, defined as the effective sample size of the prior, ESS_{prior}, divided by the total effective sample size, ESS_{total}. One calculation method for ESS is the expected local information-ratio, or ELIR (Neuenschwander et al. 2020). Unlike other methods, ELIR consistently provides an expected posterior effective sample size for a sample of size N which is the sum of the prior ESS and N. For conjugate distributions effective sample sizes from ELIR are similar to many other methods. For example, given a normal distribution with known target variance σ^2 and a normal prior with variance of estimate $\sigma_0^2 = {\sigma^2}/{n_0}$, the ELIR effective sample size contributed from the prior is $\sigma^2 / \sigma_0^2 = n_0$.

If the proportion of data borrowed from the informative element of the prior is large, it will be important to confirm with medical experts such as this Advisory Committee, but that the populations contributing to the informative element and the target are nearly identical in the course of disease and response to treatment.

Programming

Programming code for analysis of robust mixture priors with data from conjugate distributions was adapted from a supplement to Best et al (ibid) using the RBesT (R Bayesian Evidence Synthesis Tools) package in R by Weber et al(Weber et al. 2021).

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/s/

KELLY D STONE
01/10/2023 10:40:11 AM

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 214070
Supporting document/s:	1, 22, 25
Applicant's letter date:	March 10, 2022
CDER stamp date:	March 10, 2022, December 15, 2022, December 28, 2022
Product:	AIRSUPRA (budesonide/albuterol sulfate) MDI
Indication:	As-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in adult patients with asthma
Applicant:	Bond Avillion 2 Development LP
Review Division:	Division of Pulmonary, Allergy, and Critical Care Products
Reviewer:	Jessica A. Bonzo, Ph.D.
Supervisor:	Carol M. Galvis, Ph.D.
Clinical Division Director:	Sally Seymour, M.D.
Project Manager:	Elaine Sit, Pharm. D.

Template Version: September 1, 2010

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214070 are owned by Bond Avillion 2 Development LP or are data for which Bond Avillion 2 Development LP has obtained a written right of reference.
Any information or data necessary for approval of NDA 214070 that Bond Avillion 2 Development LP does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214070.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

This review evaluates the nonclinical information in Highlights and Sections 8, 12, and 13 proposed in the label for AIRSUPRA (budesonide/albuterol sulfate) MDI. The PROVENTIL HFA (albuterol sulfate) label is not in PLR- and PLLR-compliant format. Therefore, the Applicant referenced labeling for VENTOLIN-HFA (albuterol sulfate), which is in the approved PLR and PLLR format, for the albuterol sections of the label. The Applicant referenced the PLR- and PLLR-compliant PULMICORT FLEXHALER® and PULMICORT RESUPULES® labels for the budesonide sections of the label.

1.2 Brief Discussion of Nonclinical Findings

The majority of nonclinical labelling changes were based on maintaining consistency with the VENTOLIN-HFA label for albuterol sulfate. The budesonide sections were consistent with the PULMICORT labels.

1.3 Recommendations

1.3.3 Labeling

Highlights of Prescribing Information

Under the Indications and Usage section, the Applicant proposed [(b) (4)], the Indication statement should only use the EPC. There are no EPCs that specify the [(b) (4)]. Therefore, "[(b) (4)]" was removed and replaced with "a corticosteroid". It is noted that there is inconsistency among the various FDA-approved inhaled budesonide labels in regards to the use of "[(b) (4)]" and "a corticosteroid". [(b) (4)]. The recommend language for the AIRSUPRA Indications and Usage section at the time of this review is:

AIRSUPRA is a combination of albuterol, a beta$_2$-adrenergic agonist, and budesonide, a corticosteroid, indicated for the as-needed treatment or prevention of bronchoconstriction or the prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older. (1)

Section 8 Use In Specific Populations

8.1 Pregnancy

Changes were made to this section to comply with the PLR and PLLR. The general statement that animal reproduction studies have not been conducted with AIRSUPRA was moved up to the Risk Summary [(b) (4)]. The albuterol animal risk statement was omitted in the initial proposed label. The albuterol animal risk statement from the VENTOLIN-HFA label was incorporated into the Risk Summary as follows:

Animal reproduction studies have not been conducted with AIRSUPRA, however, animal studies are available with its individual components, albuterol and budesonide.

Administration of albuterol to mice and rabbits during the period of organogenesis revealed evidence of adverse developmental outcomes (cleft palate in mice, delayed ossification in rabbits) at less than the maximum recommended human daily inhalation dose (MRHDID) (*see Data*).

In animal reproduction studies, budesonide, administered by the subcutaneous route, caused structural abnormalities, was embryocidal, and reduced fetal weights in rats and rabbits at less than the maximum recommended human daily inhalation dose (MRHDID) in adults, but these effects were not seen in rats that received inhaled doses approximately 2.5 times the MRHDID in adults *(see Data)*. Experience with oral corticosteroids suggests that rodents are more prone to structural abnormalities from corticosteroid exposure than humans.

Under the animal data portion of Section 8.1 Pregnancy, it was noted that the Applicant converted the margin multiples for the albuterol nonclinical studies from using the albuterol sulfate dose to the albuterol base. This change differs from the values in VENTOLIN-HFA and other albuterol labels. The margins were corrected to the calculations using the albuterol sulfate doses to be consistent with VENTOLIN-HFA. It is presumed the Applicant used the albuterol base dose for calculations as the albuterol base and albuterol sulfate equivalences have to be listed in the Highlights of Prescribing Information. The updated animal data for Section 8.1 is as follows:

Albuterol
In a study in pregnant mice, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure less than the MRHDID in adults (on a mg/m2 basis at a maternal dose of 0.25 mg/kg) and in 10 of 108 (9.3%) fetuses at approximately 9 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 2.5 mg/kg). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol, another $beta_2$-agonist.

In a study in pregnant rabbits, orally administered albuterol sulfate produced cranioschisis in 7 of 19 fetuses (37%) at approximately 750 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 50 mg/kg).

In a study in pregnant rabbits, an albuterol/HFA-134a formulation administered by inhalation produced enlargement of the frontal portion of the fetal fontanelles at approximately one third of the MRHDID on a mg/m^2 basis.

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

Budesonide
In a fertility and reproduction study, male rats were subcutaneously dosed with budesonide for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were dosed up until weaning of their offspring. Budesonide caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at doses 0.2 times the MRHDID in adults (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and above). No such effects were noted at a dose 0.05 times the MRHDID in adults (on a mcg/m2 basis at a maternal subcutaneous dose of 5 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at doses 0.5 times the MRHDID in adults (on a mcg/m^2 basis at a maternal subcutaneous dose of 25 mcg/kg/day). In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, budesonide produced similar adverse fetal effects at doses approximately 5 times the MRHDID in adults (on a mcg/m^2 basis at a

maternal subcutaneous dose of 500 mcg/kg/day). In another embryo-fetal development study in pregnant rats, no structural abnormalities or embryocidal effects were seen at doses approximately 2.5 times the MRHDID in adults (on a mcg/m^2 basis at maternal inhalation doses up to 250 mcg/kg/day).

In a peri- and post-natal development study, rats were dosed from gestation day 15 to postpartum day 21. Budesonide had no effects on delivery but did have an effect on growth and development of offspring. Offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at doses 0.2 times the MRHDID in adults and higher (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

Section 12 Clinical Pharmacology

12.1 Mechanism of Action

The Applicant separated the mechanism of action section into two parts for albuterol and budesonide. The Applicant stated that the albuterol section was obtained from the VENTOLIN-HFA label. Upon comparison between the PROVENTIL-HFA and VENTOLIN-HFA label, several changes were noted. [Note: There are a few minor word changes between PROVENTIL-HFA and VENTOLIN-HFA but not substantial differences]. It appears as though the Applicant has included wording (b) (4) . To maintain consistency with the PROVENTIL-HFA and VENTOLIN-HFA labels, it is recommended to replace this section with the same wording as found in VENTOLIN-HFA as follows:

Albuterol

In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on $beta_2$-adrenergic receptors compared with isoproterenol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective $beta_2$-agonists may have cardiac effects.

Activation of $beta_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenyl cyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [see Warnings and Precautions (5.3)].

Section 13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Similar to Section 8.1, the Applicant changed the margin calculations in the VENTOLIN-HFA label for albuterol from using albuterol sulfate to albuterol base. The margin calculations were corrected to the albuterol sulfate as follows. Also, mention of (b) (4)

[redacted] have been removed from both the albuterol and budesonide sections as [redacted].

Albuterol

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg/day (approximately 15 times the MRHDID for adults on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg/day (approximately 1,900 times the MRHDID for adults on a mg/m^2 basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg/day (approximately 250 the MRHDID for adults , on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg/day (approximately 380 times the MRHDID for adults on a mg/m^2 basis).

Budesonide

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats receiving an oral dose of 50 mcg/kg/day (approximately 0.5 times the MRHDID in adults on a mcg/m^2 basis). No tumorigenicity was seen in male rats at oral doses up to 25 mcg/kg/day (approximately 0.5 times the MRHDID in adults on a mcg/m^2 basis) and in female rats at oral doses up to 50 mcg/kg/day (approximately 0.5 times, the MRHDID doses in adults on a mcg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg/day (approximately 0.5 times the MRHDID in adults on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg/day (approximately 0.5 times the MRHDID in adults on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisone and triamcinolone acetonide) in these two studies showed similar findings.

There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 mcg/kg/day (equal to the MRHDID in adults on a mcg/m^2 basis). Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg/day (approximately 0.8 times the MRHDID in adults on a mcg/m^2 basis). At a subcutaneous dose of 20 mcg/kg/day (approximately 0.2 times the MRHDID in adults on a mcg/m^2 basis), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/kg/day (approximately 0.05 times the MRHDID in adults on a mcg/m^2 basis).

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/s/

JESSICA A BONZO
01/09/2023 12:49:00 PM

CAROL M GALVIS
01/09/2023 12:52:55 PM
I concur.

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 214070
Supporting document/s:	1
Applicant's letter date:	March 10, 2022
CDER stamp date:	March 10, 2022
Product:	AIRSUPRA (budesonide/albuterol sulfate) MDI
Indication:	As-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in adult patients with asthma
Applicant:	Bond Avillion 2 Development LP
Review Division:	Division of Pulmonary, Allergy, and Critical Care Products
Reviewer:	Jessica A. Bonzo, Ph.D.
Supervisor:	Carol M. Galvis, Ph.D.
Clinical Division Director:	Sally Seymour, M.D.
Project Manager:	Elaine Sit, Pharm D.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214070 are owned by Bond Avillion 2 Development LP or are data for which Bond Avillion 2 Development LP has obtained a written right of reference. Any information or data necessary for approval of NDA 214070 that Bond Avillion 2 Development LP does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214070.

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1 Executive Summary

1.1 Introduction

Bond Avillion 2 Development LP (the Applicant) submitted a 505(b)(2) NDA on March 10, 2022 for a fixed-dose combination drug-device product, budesonide/albuterol sulfate metered dose inhaler (BDA MDI). This product was developed in partnership with Pearl Therapeutics, Inc, a member of AstraZeneca. The proposed indication is for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in adult patients with asthma. The Applicant is relying upon the FDA's previous findings of safety and efficacy from PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol for use of albuterol. The Applicant has obtained right of reference for PULMICORT RESPULES® (budesonide), Inhalation Suspension (AstraZeneca), PULMICORT FLEXHALER® (budesonide), Inhalation Powder, BEVESPI AEROSPHERE® (glycopyrrolate and formoterol fumarate), Inhalation Aerosol (Astra Zeneca), BREZTRI™ AEROSPHERE® (budesonide, glycopyrrolate, formoterol fumarate), Inhalation Aerosol (AstraZeneca), and HFA-134a safety data ((b) (4)) to support use of budesonide, the porous particle excipient, and the propellant HFA-134a.

The primary container closure system (CCS) consists of a can, valve, actuator, dose indicator, desiccant, and foil overwrap. The Applicant states that the can and valve are (b) (4) to those used by BEVESPI AEROSPHERE® and BREZTRI AEROSPHERE®.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical pharmacology or toxicology studies were requested or submitted. The Applicant submitted a study of extractables with the CCS, leachable studies under accelerated and long-term storage conditions, and a foreign particulate matters study. There were two compounds present above the Product Quality Research Institute (PQRI) guidance "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (2006) Qualification Threshold of 5 ug/day: (b) (4) . The Applicant performed a toxicological risk assessment to justify the safety of the levels of these leachables. Upon review, the maximum daily exposure to the (b) (4) and (b) (4) individually appear to be safe. Furthermore, the leachable profile in the BDA MDI is similar to those found in the approved drug products BEVESPI AEROSPHERE® and BREZTRI AEROSPHERE® which use the same CCS.

1.3 Recommendations

1.3.1 Approvability

Overall, there are no safety concerns regarding the potential extractables and leachables identified in the BDA MDI.

1.3.3 Labeling

The Proventil HFA label is not in PLR- and PLLR-compliant format. Therefore, the Applicant referenced labeling for Ventolin HFA, which is in the approved PLR and PLLR format, for the albuterol sections of the label. The Applicant referenced the PLR- and PLLR-compliant PULMICORT FLEXHALER® and PULMICORT RESUPULES® labels for the budesonide sections of the label.

2 Drug Information

2.1 Drug

CAS Registry Number
51333-22-3

Generic Name
Budesonide

Code Name
N/A

Chemical Name
Epimer A: (22S)-16α,17α-Butylidenedioxy-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione

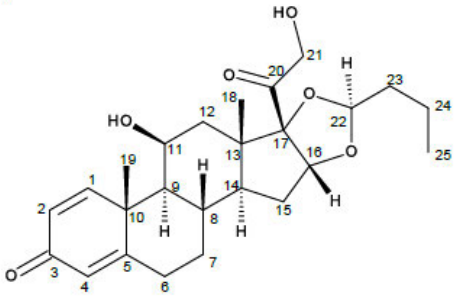
Epimer B: (22R)-16α,17α-Butylidenedioxy-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione

Molecular Formula/Molecular Weight
$C_{25}H_{34}O_6$ / 430.534 g/mol

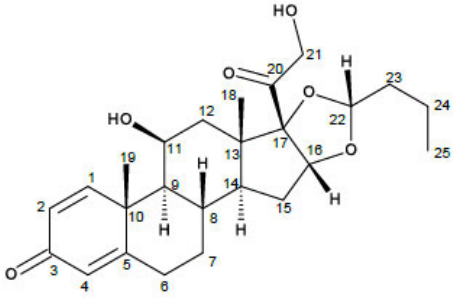
Structure or Biochemical Description
Budesonide is a mixture of two epimeric forms, epimer A (22S) and epimer B (22R).

Figure 1 Budesonide Structures

Epimer A:



Epimer B:



Excerpted from DMF (b) (4), Module 3.2.S.1.2 Structure

Pharmacologic Class

Corticosteroid

CAS Registry Number

51022-70-9

Generic Name

Albuterol sulfate

Code Name

N/A

Chemical Name

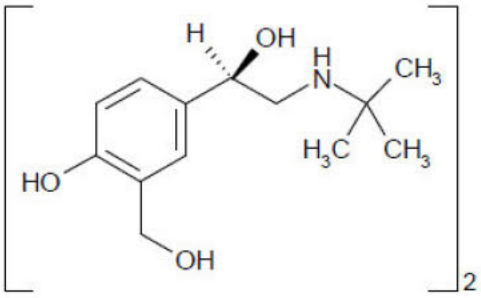
Bis[(1RS)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol]sulphate
or
1,3-benzenedimethanol, α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1) salt
or
α^1-[(tert-Butylamino)methyl]-4-hydroxy-m-xylene-α,α'-diol sulfate (2:1) salt

Molecular Formula/Molecular Weight

$(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ / 576.7 g/mol

Structure or Biochemical Description

Figure 2 Albuterol sulfate structure



H_2SO_4 and enantiomer

Excerpted from DMF (b) (4), Module 3.2.S.1.2 Structure

Pharmacologic Class

Beta-1 adrenergic agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

DMF (b) (4) - Letter of Authorization
DMF (b) (4) Letter of Authorization
DMF (b) (4) - Letter of Authorization
DMF (b) (4) Letter of Authorization
DMF (b) (4) - Letter of Authorization

NDA 020929 PULMICORT RESPULES® (budesonide), Inhalation Suspension (AstraZeneca)-Letter of Authorization

NDA 021949 PULMICORT FLEXHALER® (budesonide), Inhalation Powder (AstraZeneca)- Letter of Authorization

NDA 208294 BEVESPI AEROSPHERE® (glycopyrrolate and formoterol fumarate), Inhalation Aerosol (Astra Zeneca)- Letter of Authorization

NDA 212122 BREZTRI™ AEROSPHERE® (budesonide, glycopyrrolate, formoterol fumarate), Inhalation Aerosol (AstraZeneca)- Letter of Authorization

NDA 020503 PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol, (Kindeva Drug Delivery)-No Right of Reference, relying upon FDA's previous finding and/or published literature to support labeling, nonclinical pharmacology and toxicology, general safety and efficacy

Table 1 Summary of Letters of Authorization Obtained by Applicant

Holder	Use/Material Description	DMF or NDA Number
		(b) (4)
AstraZeneca Pharmaceuticals LC	Nonclinical safety of budesonide; clinical pharmacodynamics (mechanism of action); clinical pharmacokinetics; clinical reproductive safety	NDA 021949 (Pulmicort Flexhaler)
AstraZeneca Pharmaceuticals LC	Nonclinical safety of budesonide; clinical pharmacokinetics; clinical reproductive safety	NDA 020929 (Pulmicort Respules)
AstraZeneca AB	Nonclinical safety of excipients; Quality information for micronised budesonide	NDA 212122 (Breztri Aerosphere)
AstraZeneca Pharmaceuticals LC	Nonclinical safety of excipients	NDA 208294 (Bevespi Aerosphere)

Excerpted from Applicant, NDA 214070, SD1, Module 1.4.2 Statement of Right to Reference

2.3 Drug Formulation

The drug product is a combination of budesonide (40 or 80 mcg) and albuterol (90 mcg) per inhalation. The propellant is HFA-134a. The porous particle excipient is composed of the phospholipid 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and calcium chloride ($CaCl_2$).

Table 2 Composition of the BDA MDI Drug Product for the 120 Inhalations per Canister Packaging

Name	Function	Standard	MDI 40 µg Budesonide and 90 µg Albuterol			MDI 80 µg Budesonide and 90 µg Albuterol		
			Quantity per Canister	Metered Dose (ex-valve)	Delivered Dose (ex-actuator)	Quantity per Canister	Metered Dose (ex-valve)	Delivered Dose (ex-actuator)
Budesonide, micronized	API	USP/NF	(b) (4)			(b) (4)	88.3 µg	80.0 µg
Albuterol, micronized	API	USP/NF					99.3 µg	90.0 µg
Porous particles[b]	Cosuspending agent	*AstraZeneca*						(b) (4)
HFA-134a	Propellant	(b) (4						

API = active pharmaceutical ingredient; BDA = budesonide and albuterol; $CaCl_2$ = calcium chloride; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; HFA = hydrofluoroalkane propellant; MDI = metered-dose inhaler; NF = National Formulary; USP = United States Pharmacopeia.

[a] = Equivalent to (b) (4) mg albuterol sulfate.

[b] = Porous particles are comprised of (b) (4)% DSPC and (b) (4)% $CaCl_2$.

Excerpted from Applicant, NDA 214070, Module 2.4 Nonclinical Overview, p10

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product formulation. Porous particles (DSPC + $CaCl_2$) are found (b) (4) in NDA 208294 BEVESPI AEROSPHERE® and NDA 212122 BREZTRI™ AEROSPHERE® which the Applicant has obtained Right of Authorizations to reference the nonclinical safety of the excipients found in these products.

2.5 Comments on Impurities/Leachables & Extractables

The container closure system (CCS) for the to-be marketed product is comprised of a can, valve, actuator, dose indicator, desiccant, and foil overwrap. The Applicant states that the can and valve are (b) (4) to those used by BEVESPI AEROSPHERE® and BREZTRI AEROSPHERE® (Figure 3 BDA MDI – Exploded View).

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Excerpted from Applicant, Module 3.2.P.2. Pharmaceutical Development-Attachment 3, pg3.

Components likely to be in contact with the drug product were assessed for extractables using four different solvents: hexane, isopropanol, methylene chloride, water. Extractables were grouped based on the construction materials.

Table 3 Studies for Organic Extractables and Elemental Impurities

Studied component	Extraction solvents	Methods of analysis[a, b]
(b) (4)	Hexane, isopropanol, methylene chloride, water	GC-MS, LC-DAD-MS, ICP-MS
	Hexane, isopropanol, methylene chloride, water	GC-MS, LC-DAD-MS, ICP-MS
	Hexane, isopropanol, methylene chloride, water	GC-MS, LC-DAD-MS, ICP-MS
	Hexane, isopropanol, methylene chloride, water	GC-MS, LC-DAD-MS, ICP-MS
	Hexane, isopropanol, methylene chloride, water	GC-MS, LC-DAD-MS, ICP-MS
	Water	GC-MS, LC-DAD-MS, ICP-MS

[a] Organic extractables were analyzed from the hexane, isopropanol and methylene chloride extracts using GC-MS and LC-DAD-MS. For (b) (4) water was the solvent for all analyses.

[b] Elemental impurities were analyzed from the water extracts using ICP-MS.

Excerpted from Applicant, Module 3.2.P.2. Pharmaceutical Development-Attachment 3, pg3.

The (b) (4) consisted mainly of (b) (4) components. From (b) (4) components, the primary extractable species were (b) (4) and (b) (4) and (b) (4). No elemental impurities extracted from the (b) (4) components was predicted to exceed the PDE. The Phase 3 drug product contained (b) (4). (b) (4) can be found in the approved products BEVSPI® and BREZTRI®. The marketed product will contain (b) (4). Extractable studies identified (b) (4) and (b) (4) as extractables unique to (b) (4). (b) (4) were selected as targeted leachables specific to the (b) (4).

The extraction studies of the (b) (4) did not identify any organic extractables exceeding the reporting limit. No elemental impurities were observed exceeding the individual PDE limits.

The extractable profile of the (b) (4) did not identify organic extractables above the reporting limit. Elemental impurities did not exceed the individual PDE limits.

Per the Applicant, the (b) (4) does not have continuous contact with the drug formulation therefore, extraction studies were only conducted with water. There were no organic extractables above the PQRI limit. There were no elemental impurities exceeding PDE limits in the aqueous extraction of the (b) (4).

Leachables studies were conducted using at least 3 unique container closure system lots and stored at 25°C/60% RH and 40°C/75% RH. In addition, two different BDA MDIs were studied which differed in the (b) (4) used ((b) (4) for Phase 3 and (b) (4) for marketing). Results from the extractable studies were used to identify targeted compounds for the analysis in the leachable studies. The analytical evaluation threshold (AET) was set based on a safety concern threshold (SCT) of (b) (4) ug total daily intake (TDI). The AET is considered (b) (4) ug/canister (see Figure 5).

Figure 5 AET Calculation

$$AET\ (\frac{\mu g}{canister}) = $$ (b) (4)

Where:

SCT = (b) (4) µg/day

Actuations/canister = (b) (4)

Actuations/day = (b) (4)

(b) (4) = Uncertainty factor (from USP/PQRI)

Final AET = (b) (4) µg / canister

Excerpted from Applicant, Module 3.2.P.2. Pharmaceutical Development-Attachment 3, pg14.

The targeted leachables for quantitation are listed in Table 4. In addition to the leachables listed in Table 4, (b) (4) were included in the analysis at these leachables were occasionally observed in the BEVESPI AEROSPHERE® and BREZTRI AEROSPHERE® products.

Table 4 BDA MDI Target Leachables

Leachable	Analytical method	Limit of quantitation (µg/can)
(b) (4)	Leachables by LC-UV	(b) (4)
	Leachables by LC-UV	
	Leachables by LC-UV	
	Leachables by LC-UV	
	Leachables by LC-UV	
	Leachables by LC-UV	
	Leachables by LC-UV	
	Leachables by LC-UV	
	Leachables by GC-MS	
	Leachables by GC-MS	

[a] Targeted in BDA MDI with (b) (4) only.
[b] Targeted in BDA MDI with only.

Excerpted from Applicant, Module 3.2.P.2. Pharmaceutical Development-Attachment 3, pg16.

Table 5 Summary of Leachables Safety Assessment in BDA MDI

Species	Max Leach – 25°C/60% RH	Max Leach – 40°C/75% RH	Maximum daily exposure (µg/day)[a]	Recommend Safe Limit (µg/day)[b]	Recommend Safe Limit – Converted to (µg (b) (4)[c]
(b) (4)	(b) (4)				(b) (4)

ADI = acceptable daily intake; Leach = leachable; (b) (4); RH = relative humidity; TTC = threshold of toxicological concern.
[a] = Using the maximum leachable content identified and based on (b) (4) actuations/canister and up to a maximum of (b) (4) actuations/day.
[b] = Recommend Safe Limit may be ADI, TTC, etc. and is specific to each compound's safety assessment provided in Section 2.4.4.6.1.
[c] = Recommend Safe Limit – Converted to (µg/can) = Recommended Safe Limit (µg/day) × (b) (4) (actuations/can) / (b) (4) (actuations/day).
[d] = BDA MDI with (b) (4) only.
[e] = BDA MDI with only.

Excerpted from Applicant, Module 2.4 Nonclinical Overview, pg 14.

A summary of the targeted leachable quantities identified in the drug product is found in Table 6. Leachables below the threshold of toxicological concern (TTC, ICH M7(R1)) of 1.5 ug/day are considered to pose a negligible risk to human health. This review

focuses on the safety assessment for those leachables potentially above the TTC of 1.5 ug/day: (b) (4) and (b) (4).

(b) (4) (b) (4) do not pose a human safety risk as determined by the European Food Safety Authority (EFSA, 2009). In addition, the EFSA 2009 report states that the (b) (4) are not associated with genotoxicity and no genotoxicity is expected from the (b) (4). (b) (4) with minimal to no local adverse toxicity findings across several nonclinical species. (b) (4) are found at a maximum daily exposure of (b) (4) ug/day. Per the Product Quality Research Institute (PQRI) guidance "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (2006), nongenotoxic organic compounds (i.e., nonmetal) found below the threshold of 5 ug/day are considered qualified for safety.

(b) (4)
The levels of (b) (4) exceed the PQRI threshold of 5 ug/day at maximum potential daily exposure of (b) (4) ug/day. Per a 2018 safety assessment conducted for (b) (4) supplied in the NDA, (b) (4) was found to be negative for mutagenic and carcinogenic potential and assigned as a Class 4 compound per ICH M7 guideline. A permissible daily exposure was calculated from available studies and set as (b) (4) ug/50-kg person/day (b) (4) ug/kg/day) in the (b) (4) report. (b) (4) . The Applicant provided calculations of a second PDE of (b) (4) mg/day based on toxicology profiles from the family of (b) (4) and (b) (4) is on the EPA Safer Chemical Ingredient List (SCIL) as a chemical of low concern. Based on the totality of this information, the levels of (b) (4) are considered qualified for safety.

2.6 Proposed Clinical Population and Dosing Regimen

The originally proposed indication for the BDA MDI is as-need treatment and prevention of bronchoconstriction and prevention of exacerbations in patients with asthma 4 years of age and older. The dosing regimen for patients aged 12 years and older is 2 inhalations of BDA MDI (80 mcg budesonide, 90 mcg albuterol sulfate per inhalation) as needed, with a maximum of 12 inhalations in a 24-hour period. The dosing regimen for patients aged 4 to less than 12 years of age is 2 inhalations of BDA MDI (40 mcg budesonide and 90 mcg albuterol sulfate per inhalation) as needed, with a maximum of 12 inhalations in a 24-hour period. After discussion of the safety and efficacy data at an Advisory Committee meeting and internal discussions with management, the Division decided to approve the product only for adult patients.

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/s/

JESSICA A BONZO
11/28/2022 02:22:20 PM

CAROL M GALVIS
11/28/2022 02:31:44 PM
I concur.