FDA Briefing Document

NDA# 214070

Drug name: budesonide/albuterol sulfate metered dose inhaler

Applicant: Bond Avillion 2 Development LP

Pulmonary-Allergy Drugs Advisory Committee Meeting

11/08/22

Division of Pulmonology, Allergy, and Critical Care

Office of Immunology and Inflammation

Office of New Drugs

Center for Drug Evaluation and Research

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Table of Contents

Table of Tables

Table of Figures

Glossary

AC	Advisory Committee
AE	adverse event
ACQ-5	Asthma Control Questionnaire-5
ACQ-7	Asthma Control Questionnaire-7
AQLQ12+	Asthma Quality of Life Questionnaire 12+
AS	albuterol sulfate
AUC	area under the curve
BD	budesonide
BDA	budesonide/albuterol sulfate metered dose inhaler
BID	twice daily
BRF	Benefit-Risk Framework
CAR	censoring at random
CDC	Centers for Disease Control and Prevention
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CMAX	maximum concentration
COVID-19	disease from SARS-CoV-2 infection
DB	double-blind
EIB	exercise-induced bronchoconstriction
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
FEV1	forced expiratory volume in one second
FEV1/FVC	ratio of forced expiratory volume in one second/forced vital capacity
FVC	forced vital capacity
GINA	Global Initiative for Asthma
HFA	hydrofluoroalkane
HR	hazard ratio
IA	integrated assessment
ICS	inhaled corticosteroid
IM	intramuscular
IND	Investigational New Drug
IP	investigational product
IV	intravenous
iPSP	Initial Pediatric Study Plan
LABA	long-acting $beta_2$-adrenergic agonist
LAMA	long-acting antimuscarinic antagonist
LTRA	leukotriene receptor antagonist
MDI	metered dose inhaler
NAEPP	National Asthma Education and Prevention Program
NDA	New Drug Application
OR	odds ratio

PAQLQ	Pediatric Asthma Quality of Life Questionniare
PC	placebo-controlled
PCD	primary completion date
PEF	peak expiratory flow
PG	parallel group
PIND	pre-Investigational New Drug
PRN	as needed
REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
RPM	Regulatory Project Manager
QD	daily
QID	four times daily
SABA	short-acting $beta_2$-adrenergic agonist
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SD	standard deviation
YO	years old

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The FDA is convening this Advisory Committee (AC) meeting to discuss whether the available data for a fixed dose combination metered dose inhaler of budesonide and albuterol sulfate support a favorable benefit risk assessment "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." An important focus of the panel discussion is the available data in pediatric patients.

1.2 Context for Issues to Be Discussed at the AC

The Applicant, Bond Avillion 2 LP, submitted an NDA for a fixed dose combination (FDC) metered dose inhaler (MDI) oral inhalation aerosol containing an inhaled corticosteroid (ICS), budesonide (BD), and a short-acting beta$_2$-adrenergic agonist (SABA), albuterol sulfate (AS), (herein referred to as BDA). The proposed indication is, "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 Applicant proposes two doses:

- BD 160 µg/AS 180 µg, delivered as 2 actuations of BD 80 µg/AS 90 µg for patients ≥12 years of age, not to exceed 6 doses or 12 inhalations in 24 hours (herein, BDA 160/180 or high dose); and
- BD 80 µg/AS 180 µg, delivered as 2 actuations of BD 40 µg/AS 90 µg for patients ≥4 to <12 years of age, not to exceed 6 doses or 12 inhalations in 24 hours (herein, BDA 80/180 or low dose).

There are several unique features about this application. BDA would be the first ICS/SABA combination product approved in the United States. The proposed indication and use to prevent severe 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 prevent or reduce the severity of exacerbations. FDA approval of an ICS-containing product as a reliever treatment for asthma (rather than as controller) would be new.

Asthma is a common and potentially serious chronic respiratory disease, characterized by recurring symptoms of wheezing, breathlessness, chest tightness, and coughing, caused by underlying airway inflammation and airway hyper-responsiveness. The goals of asthma management are to achieve symptom control and to minimize future exacerbations. Guidelines for asthma management categorize asthma medications as controller medications or reliever medications. BDA would represent a new reliever medication; however, the concept of as-needed (PRN) use of an ICS for asthma is not new. Published literature has evaluated the use of PRN ICS (with and without a beta-agonist) to prevent asthma exacerbations (refer to Section 2.1 for details). We note that recent updates to asthma guidelines recommend the use of an ICS/long-acting beta$_2$-adrenergic agonist (LABA) (formoterol) combination product not only as controller treatment, but also as a preferred reliever treatment for some patients. This is a concept known as SMART – single maintenance and reliever therapy; however, no ICS/LABA product is currently FDA-approved for PRN use. FDA does not make recommendations regarding asthma guidelines, but we do note that approval of BDA could impact current asthma guidelines.

1.3 Brief Description of Issues for Discussion at the AC

Key Aspects of Development Program

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,' i.e., the principle that in developing combination drugs, the program should demonstrate that "each component makes a contribution to the claimed effect," (*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. In terms of safety, our primary concern was assessment of the risks associated with increased corticosteroid exposure, particularly in children, given that BDA could be used in addition to controller ICS treatment.

With respect to drug development in pediatrics[1], applicants typically include adolescents (≥12 to <18 years of age) with adults in the original efficacy trial(s) for asthma development programs. Although the Agency has not always required statistical significance in the adolescent subgroup, this approach has generally provided sufficient data to support approval of a product in patients 12 years and older, pending efficacy and safety trends among adolescents are consistent with those in adults. Often, separate studies in children less than 12 are conducted following approval of a product in adults and adolescents. Given what is known about AS and BD, the Agency encouraged the Applicant not only to include adolescents, but also to evaluate younger children early in the BDA development program.

The Applicant submitted results from a clinical program that included 3 pivotal clinical trials: MANDALA, DENALI, and TYREE. The primary source of efficacy and safety data is MANDALA; thus, we will focus the discussion on MANDALA. DENALI provides data to support the combination rule and data to support safety for both a mild asthma severity population and a higher dose of BDA. TYREE is an exercise-induced bronchospasm trial that does not contribute significant clinically meaningful data to support the proposed indication, so we do not plan to discuss this trial.

MANDALA was an event-driven, randomized, double-blind, parallel group, active comparator-controlled trial in 3,132 subjects with moderate to severe asthma randomized to BDA 160/180, BDA 80/180, or AS 180, which was self-administered PRN, on top of background maintenance therapy. Subjects were instructed to use the investigational product (IP) as they would their pre-enrollment SABA, PRN in response to symptoms or triggers (including 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 emergency department (ED) visit or hospital admission).

The Applicant proposed to include children down to 6 years of age in the exacerbation study; however, the Agency encouraged the Applicant to include pediatric patients down to 4 years of age, since both AS

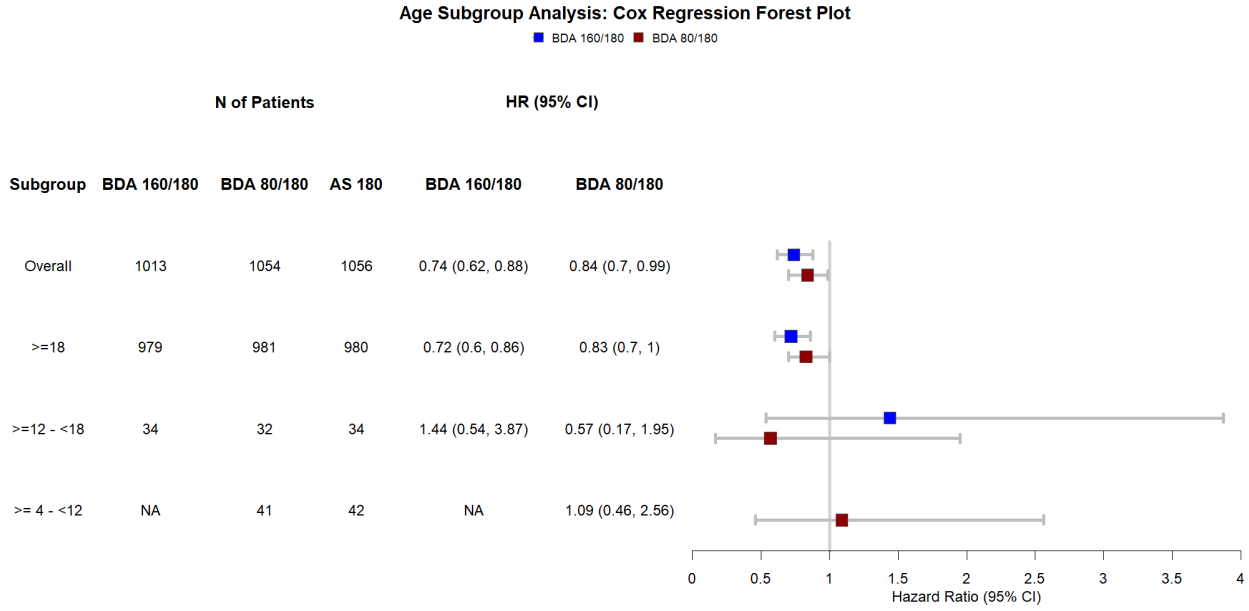
[1] Herein, we use the term "pediatric" to mean less than 18 years of age. We will sometimes refer to subgroups of the pediatric population as "adolescents," meaning 12 to 17 years of age, or "children," meaning younger than 12.

and BD are approved for children 4 years and older. 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.

Key Results

Results from MANDALA showed 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 3.1.3. Figure 1 shows results for the primary endpoint of MANDALA for the overall population and by age-based subgroups.

Figure 1. Forest Plot for Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand, Age-Based Subgroups (MANDALA, Full Analysis Set; All Ages)



Source: Statistical Reviewer and Statistical Analyst using adtte.xpt. Full Analysis Set: all randomized subjects who received at least 1 inhalation of investigational product (IP), analyzed according to randomized treatment arm.HR, hazard ratio.

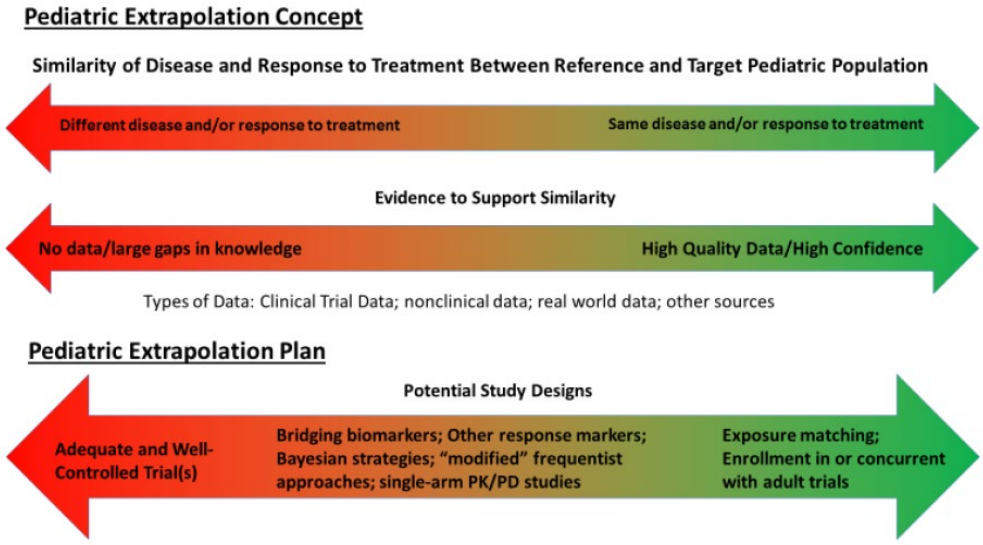
For the first analysis in our default hierarchy, an analysis grouping together all subjects enrolled in the study (≥4 years old (yo) for the low dose BDA, ≥12 yo for the high dose BDA) supports efficacy. Similarly, the next analysis in the hierarchy, for the adult subgroup (≥18 yo), also supports efficacy. Efficacy in the two pediatric subgroups (≥12 to <18 yo and ≥4 to <12 yo) is uncertain because the upper confidence limits for the hazard ratios exceed 1. We hypothesize the wide confidence intervals and high degree of uncertainty may be a function of small sample sizes. The uncertainty of the data in pediatric subjects is an important focus of the AC panel discussion.

Regarding safety results, we focused our review on the additive effects of ICS (i.e., BDA in addition to controller ICS), as well as results in pediatric subjects. Our review did not identify new safety signals of concern. The data were consistent with the known risk profiles of AS and BD. We did not observe significant differences between age cohorts or evidence of increased risk from PRN ICS use in subjects <18 yo. We acknowledge that limitations to the safety data include the small number of pediatric subjects enrolled and the inability to assess potential long-term effects of ICS given the study duration.

Pediatric Considerations

Although pediatric patients were enrolled concurrently with adults in MANDALA, the number of pediatric subjects was small and there are considerable uncertainties with respect to the efficacy results in the pediatric subgroups. Pediatric extrapolation will be an important consideration for this program. 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 2, from the recent *FDA Draft Guidance for Industry: E11A Pediatric Extrapolation* (FDA 2022), provides a visualization of key considerations for pediatric extrapolation.

Figure 2. Pediatric Extrapolation in Drug Trials



Source: FDA Draft Guidance for Industry: E11A Pediatric Extrapolation

Bayesian methods can provide a quantitative framework for extrapolation. The FDA and the Applicant utilized Bayesian methods to evaluate the utility of borrowing adult data to support efficacy in pediatric subpopulations. Through Bayesian methods, we can evaluate the relationship between the degree of borrowing and the strength of evidence in support of efficacy. For reference, when borrowing is zero, Bayesian analyses produce the same results as the 'frequentist' analyses, which we usually employ to assess statistical significance. 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 detailed results are discussed in Section 3.1.3. We note that these analyses were conducted *post hoc*. In ideal circumstances, the degree of borrowing from adult data is pre-specified, based upon clinical considerations regarding similarity in population, disease, and response to treatment.

The high degree of Bayesian borrowing required to achieve meaningful results in pediatric subgroups suggests that almost complete extrapolation would be necessary to demonstrate efficacy (statistical significance). Figure 2 suggests that this degree of extrapolation 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. Although use of a Bayesian approach was mentioned at a Type B meeting between the Agency and the Applicant, there was no discussion or agreement on either the degree of borrowing or the specific statistical model to be used.

Inhalation products for asthma are locally acting, and extrapolation based upon pharmacokinetic data is not applicable for these products. Clinical data is required in pediatric patients. As stated previously, the Agency has 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. An important distinction is that, to date, most 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.

We ask the AC panel to consider the uncertainties regarding the available pediatric data. Given the novelty of this product, we request AC discussion on the role of this product in pediatrics and whether extrapolation is appropriate to establish the benefit of BDA in pediatric patients or if additional data are needed.

Thank you for your participation in this AC meeting. We are bringing this application to an AC because we believe the findings warrant public discussion. We look forward to your input on the BDA program and the following topics for discussion.

1.4 Draft Points for Consideration

- Discuss the data to support the efficacy of BDA 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. Specifically address available data in adolescents (12 to <18) and young children (4 to < 12) and use of extrapolation in these age groups.
- Discuss the safety data for BDA for the proposed indication. Discuss any specific pediatric safety concerns.
- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥18 years of age with asthma? If not, what additional data are needed?
- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥12 to <18 years of age with asthma? If not, what additional data are needed?
- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥4 to <12 years of age with asthma? If not, what additional data are needed?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

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 step-wise 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, particularly for the small subset of patients with severe disease. Acute 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. Asthma affects both children and adults, with an estimated pediatric incidence of approximately eight percent in the United States (CDC 2018), representing one of the most common childhood diseases. 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.

Current Asthma Management

Historically, patients with mild or intermittent asthma were started on PRN SABA, 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 controller medications, such as LABA or long-acting antimuscarinic antagonists (LAMA). Guidelines now recommend the initiation of SMART with an ICS/LABA relatively early in disease severity. In the absence of SMART, Global Initiative for Asthma (GINA) guidelines recommend use of an ICS in combination with SABA as the preferred alternative reliever treatment in patients as young as 6 years old with mild disease. Similarly, National Asthma Education and Prevention Program (NAEPP) guidelines recommend a PRN ICS with SABA for patients ≥12 with mild disease. Refer to Section 6.1 for more detail regarding recent guideline revisions.

Over a dozen inhaled asthma therapies are currently approved and marketed in the US. Two broad categories comprise the foundation of asthma treatment: controller (e.g., ICS, LABA, LAMA) medications and reliever (SABA) medications. There is only one drug class (SABA) approved as a reliever treatment for asthma symptoms in the US, and AS accounts for the vast majority of clinical use. There are no reliever treatments that carry the indication to prevent severe asthma exacerbations. There is a need for more safe and effective treatments for asthma. A new reliever therapy that could prevent severe exacerbations would represent a meaningful addition to the therapeutic armamentarium for all severities of adult and pediatric asthma.

Several of the currently approved medications contain BD or AS. The BDA development program leveraged the available data for Pulmicort Flexhaler, Pulmicort Respules, and Proventil HFA. These are known as the Reference Listed Drugs (RLDs). As shown in Table 1, BDA administered at its maximum recommended frequency (6 times daily or 12 inhalations) results in a lower dose than the RLDs of BD and a comparable dose of AS. Note that these doses indicate the maximum dose from use of the product itself and do not account for additive exposure of ICS, assuming BDA is administered in addition to a background ICS. For further information on cumulative exposure, refer to pharmacologic simulation results in Section 3.2.3.

Table 1. BDA and Reference Listed Drug Dose Ranges and Maximum Recommended Doses

Drug Product	Indication	Age Groups	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 (1440 µg QD) • 6 to <18 years: 180 µg BID; max dose 360 µg BID (720 µg QD)
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; max dose 1080 µg QD
Proposed BDA MDI for oral inhalation	As-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations; Do not take >6 doses (12 inhalations) in 24 hours	≥4 years of age	• ≥12 years: BDA 160 µg/180 µg PRN • 4-11 years: BDA 80 µg/180 µg PRN • Max dose BD 480 µg in 4-11; and BD 960 µg in ≥12 • Max dose AS 1080 µg

Source: Clinical and clinical pharmacology reviewers.
Abbreviations: EIB, exercise-induced bronchoconstriction; HFA, hydrofluoroa kane; max, maximum; BID, twice daily; QD, daily; Q4-6H, every 4-6 hours

Summary of Pre-Existing Experience with ICS as Reliever Treatment

Approval of BDA would represent a novel indication and intended use for ICS in asthma; however, the concept of symptom-triggered use of an ICS to abort or prevent asthma exacerbations is not new to clinical practice or research. Numerous trials have previously evaluated the use of PRN ICS with or without concomitant SABA or LABA to prevent exacerbations. 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 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). These data are also incorporated into the guidelines for some patients (refer to Section 6.1).

2.2 Pertinent Drug Development and Regulatory History

A summary of the key regulatory activity for BDA development is provided in Table 2. Overall, the Applicant and FDA agreed upon a development program that included a factorial design trial with scheduled administration of treatments to fulfill the combination rule and a large trial comparing BDA to AS, administered PRN, with asthma exacerbations as the primary endpoint to provide the primary data to support the efficacy of BDA.

Table 2. Summary of Key Regulatory History

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.
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 6 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 available 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 yo 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 yo 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	• Agency expressed concerns regarding EIB indication. 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.

Source: Clinical Reviewer.
Abbreviations: PIND, pre-Investigative New Drug; iPSP, initial Pediatric Study Plan

3 Summary of Issues for the AC

3.1 Efficacy Issues

In the key efficacy trial, MANDALA, results for the overall population showed benefit, but there is considerable uncertainty regarding the benefit in adolescents (≥12 to <18 years) and younger children (≥4 to <12 years).

3.1.1 Sources of Data for Efficacy

The Applicant submitted results from 3 pivotal clinical trials: MANDALA, DENALI, and TYREE, as shown in Table 3.

Table 3. Efficacy Trials Submitted to Support Registration

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 yo 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 FAS, all ages: 3123 ≥4 - <12 yo: 83 ≥12 - <18 yo: 100 ≥18 yo: 2940	Centers: 296 Countries: 11
DENALI AV004 D6930C00004 NCT03847896	Subjects ≥4 yo with asthma requiring treatment with PRN SABA alone or low dose ICS + PRN SABA	12-week, R, DB, PC, PG	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 FAS, all ages: 999 ≥4 - <12 yo: 10 ≥12 - <18 yo: 25 ≥18 yo: 964	Centers: 110 Countries: 7
TYREE AV005 D6930C00006 NCT04234464	Subjects ≥12 yo with asthma and EIB treated with PRN SABA only or ICS + PRN SABA	Single dose R, DB, PC, Crossover	Number treated: 60 Placebo/BDA 160/180 (31), BDA 160/180/Placebo (29)	Primary: Maximum % fall in FEV1 Secondary: % subjects with maximum % fall in FEV1 <10%	60 randomized, 60 treated FAS: 60	Centers: 6 Countries: 1

Source: Clinical Reviewer. FAS = full analysis set, defined as all subjects who were randomized to treatment and took any amount of investigative product (IP), analyzed according to the treatment they were assigned at randomization. R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group

The primary source of efficacy and safety 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. As a result, the focus of the briefing document is on the design and results from MANDALA.

DENALI is a 12 week, factorial design trial in which BDA, AS, BD, and placebo administration was scheduled four times daily (QID) to assess the contribution of AS and BD to the effect of BDA on FEV1, i.e. to help satisfy the combination rule. DENALI provides confirmatory evidence of the efficacy of BDA and safety data on use of BDA in subjects with milder disease. Safety data from DENALI is relevant since BDA was administered QID, which is more frequent usage than the median and mean use of BDA in MANDALA. While these are important considerations for the clinical program, our review did not identify concerns related to the efficacy and safety results from DENALI. We have included a brief summary of the study design and relevant results in Section 6.5 for completeness, but DENALI will not be a focus of the briefing document.

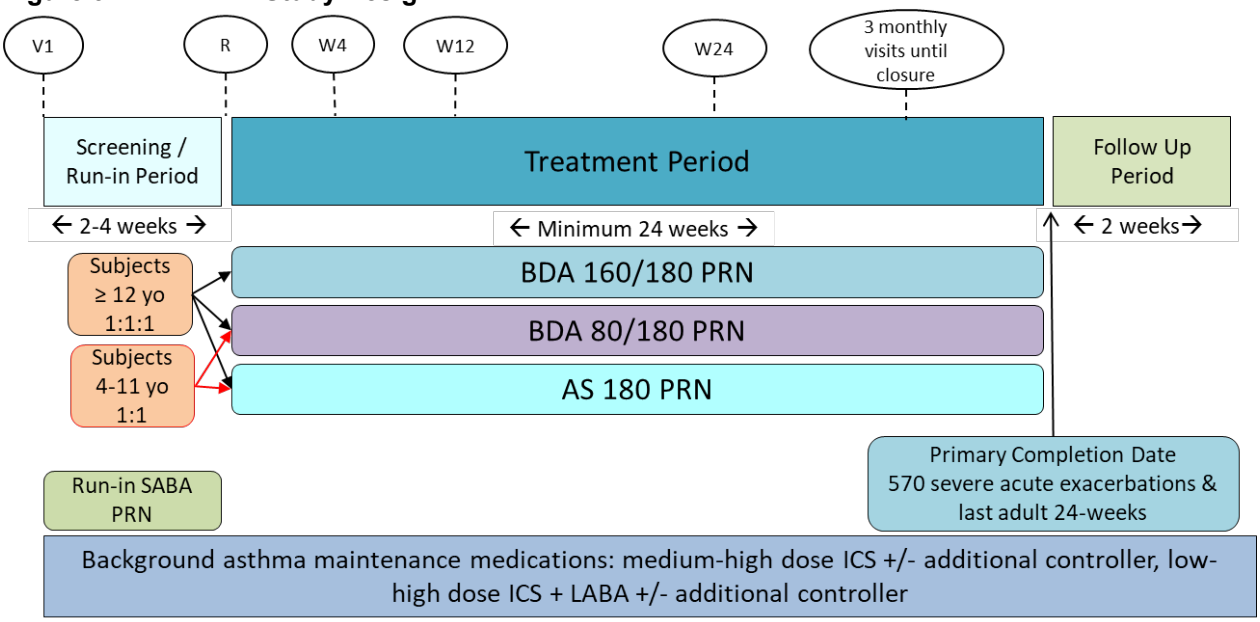
TYREE is a trial that evaluated the use of BDA for exercise-induced bronchospasm. The Agency had recommended that TYREE should be designed to show the contribution of BD, since AS is known to be safe and effective for EIB. Since TYREE was a single-dose study comparing BDA to placebo alone, it does not provide information beyond what is already established for AS in EIB. We do not plan to discuss TYREE during the AC meeting.

3.1.2 Efficacy Summary

The design of MANDALA is presented in Figure 3. MANDALA was an event-driven, randomized, double-blind, parallel group, active comparator-controlled trial in 3132 subjects with moderate to severe asthma. Patients were randomized to BDA 160/180, BDA 80/180, or AS 180, which was self-administered PRN, on top of background controller therapy. Subjects were instructed to use the IP as they would their pre-enrollment SABA, PRN in response to symptoms or triggers (including prior to exercise). MANDALA enrolled 100 subjects ≥12 to <18 years of age and 83 subjects ≥4 to <12 years of age. Subjects <12 years of age were not randomized to high dose BDA treatment. Whether the available pediatric data are sufficient to support a favorable benefit risk assessment is the key question for this AC panel.

The primary endpoint of MANDALA was time to first severe acute asthma exacerbation (defined as loss of symptom control and worsening lung function (by 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). Efficacy endpoints were measured at the Primary Completion Date (PCD), once 570 severe acute exacerbations occurred and the last enrolled adult reached 24 weeks. Key secondary endpoints included annualized severe exacerbation rate, total annualized dose of systemic corticosteroids (SCS) (mg/subject), and the Asthma Control Questionnaire-5 (ACQ-5).

Figure 3. MANDALA Study Design



Source: Clinical Reviewer. PRN=as needed; Run-In SABA PRN=Applicant-provided Ventolin HFA to replace pre-enrollment SABA prior to randomization. Note that no adjustments to pre-enrollment maintenance therapy were during the run-in period. Additional controller= LAMA, leukotriene modifier, or theophylline; use of biologics was an exclusion criterion for enrollment. V1=Visit 1; R=randomization; W4=week 4; W12=week 12; W24=week 24.

MANDALA Statistical Analysis Plan (SAP)

The SAP for MANDALA is described in Section 6.3. All efficacy analyses were conducted in the full analysis set (FAS), defined as all subjects who were randomized to treatment and took any amount of IP, analyzed according to randomized treatment arm. The FAS population is largely adults ≥18, who account for 2,940 out of 3,123 subjects, or 94 percent. The primary endpoint, time to first severe asthma exacerbation, was analyzed using a Cox proportional hazards regression model to compare treatment arms. The summary measure to compare treatments was the estimated hazard ratio, which was presented with the corresponding 95% confidence interval and p-value. Comparisons of BDA 80/180 vs AS and BDA 160/180 vs AS for the primary endpoint, time to first severe exacerbation using the efficacy estimand, were conducted using Hochberg's step-up method. The secondary endpoints were tested only if the primary endpoint was significant for both comparisons of the high dose BDA vs AS and the low dose BDA vs AS. The type-I error was controlled for secondary endpoint treatment comparisons via a hierarchical testing procedure.

BDA Use Pattern in MANDALA

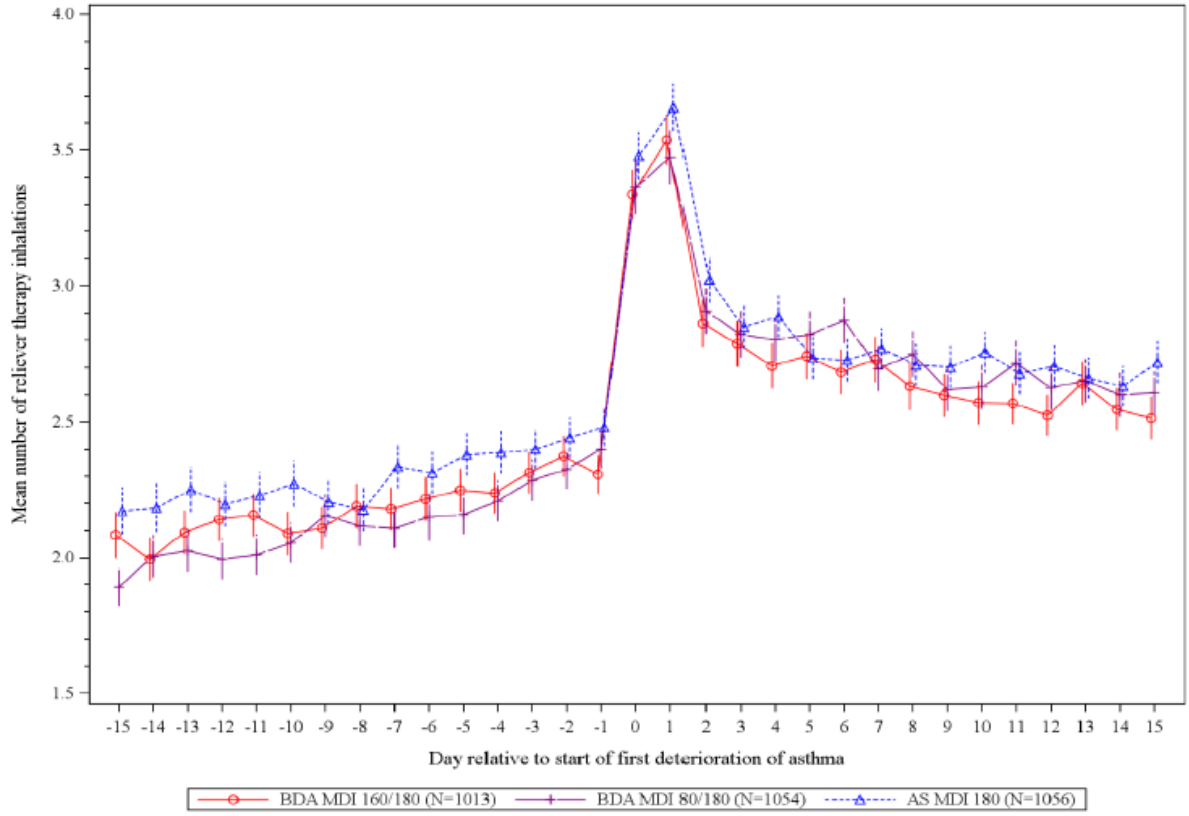
It is important to understand how BDA was used in MANDALA, since IP use frequency and duration of possible exposure to IP were variable. The event-driven design resulted in subjects experiencing varied treatment periods, depending on when they were enrolled relative to the PCD. The mean number of days subjects were eligible for exposure to PRN IP was 305 (44 weeks), with 310 for BDA 160/180, 306 for BDA 80/180, and 290 for AS. Of all subjects, 88% were exposed for ≥24 weeks and 30% for at least a year by the time of primary database lock. Of note, for subjects <12 yo, the mean treatment duration was shorter at 234 days (33 weeks), with 55 (66%) exposed for ≥24 weeks and 18 (22%) for ≥1 year, a

result of late randomization relative to the PCD. At the time of primary database lock, 38 subjects <18 yo were still enrolled, and 37 were still participating in the randomized treatment period.

IP usage and deterioration of asthma—(defined as PEF decline ≥20% from baseline; reliever therapy use >4 puffs/day and ≥2X baseline; night-time symptom score that is > baseline *and* ≥2 *or* a daytime score that is > baseline and =3)—were captured as exploratory endpoints. Overall, the average daily number of inhalations was 2.6 for both BDA arms and 2.8 for the AS arm. *Post hoc* analysis of MANDALA showed that subjects of all ages used ≤2 inhalations on approximately 55% of study days, ≤4 inhalations on approximately 85% of study days, and >8 inhalations on fewer than 2% of study days. In a subgroup analysis of subjects ≥12 to <18 yo, subjects used ≤4 inhalations on approximately 85% of study days and >8 inhalations on less than 1% of study days. In children 4 to <12 years, subjects used ≤2 inhalations on more than 50% of study days, ≤4 inhalations on more than 80% of study days, and >8 inhalations on less than 1% of study days. In pediatric subjects, there was not a significant pattern of difference in BDA usage frequency compared to AS—in subjects <12, the mean number of daily inhalations was 2.1 for BDA 80/180 vs 1.8 for AS.

The average daily number of IP inhalations from 15 days before to 15 days after first asthma deterioration for all ages is summarized in Figure 4. This pattern demonstrates a gradual increase in number of daily IP inhalations from day 10 followed by a sharp increase around the time of the deterioration, consistent across all treatment arms. The peak numbers of daily IP inhalations were numerically lower in the BDA arms compared with the AS arm.

Figure 4. Average Daily Number of Investigation Product Inhalations from 15 Days Before to 15 Days After Start of First Deterioration of Asthma from MANDALA (Full Analysis Set; All Ages)



Source: Applicant. Clinical Study Report Mandala AV003 Figure 9 (p.129).

MANDALA Efficacy Results

Baseline demographic characteristics of the MANDALA study population were balanced across treatment arms. The majority of subjects were female (65%) and white (81%). The baseline asthma characteristics are shown in Table 4. The population is largely composed of subjects with 1 severe exacerbation in the previous year (79%) and an FEV1 ≥60% (68%), maintained on medium dose ICS (47%) in combination with a LABA, LAMA or leukotriene modifier (LTRA) (76%). This represents a population with moderate to severe disease with reasonable probability of another exacerbation within the following year, but not with out-of-control or life-threatening disease. These disease characteristics were well-balanced across treatment arms.

Table 4. Baseline Asthma Characteristics, Full Analysis Set Population

Characteristic	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: Clinical Reviewer. OCS Analysis Studio, Custom Table Tool, adexsum.xpt.

Table 5 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. This analysis, which conflates all age groups, supports efficacy for BDA, demonstrating a larger treatment effect and more robust statistical significance for the high dose BDA relative to the low dose. (For missing data sensitivity analysis results, refer to Section 6.4.) The Applicant proposes the high dose, BDA 160/180, as the marketed dose for subjects ≥12 and the low dose for children 4 to 11. In Section 3.1.3, we revisit pediatric subgroup analyses in more detail.

Table 5. Primary Analysis of Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand[a] (MANDALA, Full Analysis Set[b])

		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, a buterol 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, 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] 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.

The key secondary efficacy endpoints for MANDALA are presented in Table 6.

Table 6. Key Secondary Efficacy Endpoints, Efficacy Estimand (MANDALA, 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, a buterol 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.

All key secondary endpoints shown in Table 6 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 ACQLQ+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 yo. Pooling of subjects <12 yo into the analysis for the BDA 80/180 comparison to AS dilutes the magnitude of the treatment effect.

In subjects ≥18 yo (and in analyses grouping in subjects ≥12 yo), MANDALA met the FDA-agreed upon endpoints. BDA 160/180 demonstrated benefit in reducing severe asthma exacerbations and reducing systemic corticosteroid use.

3.1.3 Efficacy Issues in Detail

MANDALA was powered for primary efficacy comparisons in subjects ≥12 yo, and subjects <12 yo 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. Although sample sizes were small, the trends of the efficacy results among subjects <18 yo were inconsistent with those in adults across both primary and key secondary endpoints. Given the novel indication and use, we ask the committee to consider the uncertainties regarding the pediatric data; whether, despite these uncertainties, there is a role for BDA in the management of pediatric asthma; and whether extrapolation of adult data constitutes an appropriate method to bridge those uncertainties. In this section, we provide further detail on the pediatric subgroup analyses in MANDALA. We also elaborate on the role of Bayesian analysis, a quantitative framework for extrapolation. Of note, both the Applicant and Agency conducted Bayesian analyses to examine the role of extrapolation of adult data to support efficacy in pediatrics, but these analyses were all conducted *post hoc* without prespecifications.

As described in Section 1, we evaluated the efficacy in pediatric subgroups in a stepwise manner, using a default hierarchy. The results from Figure 1 are again shown in tabular format in Table 7. To evaluate efficacy in these pediatric subgroups without a predefined analysis hierarchy, we took an approach described by Rothmann et al. (2012) and Freidlin and Korn (2022), investigating efficacy in subgroups only if a primary analysis on the entire population under study demonstrates efficacy. To further reduce 'cherry picking' of subgroup results, we ordered subsequent analyses of subgroups in a default hierarchy reasonable for this design, with: (i) the adult subgroup (≥18 years of age) first, which was the majority of the enrolled study population; (ii) the adolescent subgroup next, since they are most likely to be similar in treatment response and course of disease to the adults, and then; (iii) the younger pediatric patients (≥4 to <12 years of age).

Table 7. 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.

As illustrated in Table 7, point estimates for the summary measure, hazard ratio (HR), for time to first severe asthma exacerbation favor AS vs high dose BDA among subjects ≥12 to <18 yo. The confidence intervals are wide, prohibiting any clear interpretation of these results, likely, because the sample sizes are small and the event of severe asthma exacerbation was relatively rare. In subjects <12, in whom only low dose BDA was studied, the results, although limited, do not support benefit of BDA 80/180 in preventing severe acute exacerbations. Although only 21 severe exacerbation events occurred, we note that the rate (approximately 25%) was the same as that in adults. We again note that at the time of primary database lock, 38 subjects <18 yo were still enrolled, 37 of whom had not yet completed 24 weeks of randomized treatment; however, separate analysis of that data did not alter these findings. Among subjects ≥12 to <18 yo, the HR for BDA 160/180 vs AS did not suggest benefit of BDA, again complicated by wide confidence intervals and a small sample size. Of note, the low dose BDA (which the Applicant does not propose to market for this age group) had a more favorable trend for both the primary endpoint and secondary endpoints, as shown below; however, we note the very small number of events in this arm (4 or 12.5%). The clinical significance of this pattern is not clear.

Given the uncertainties described, we turn to a Bayesian approach as a potential method for providing clarity regarding efficacy within a quantitative framework. In the Bayesian analyses provided directly below, we focus our attention 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.

For the analysis of the high dose in adolescents (Table 8), data were borrowed from the adults treated with the high dose or AS alone. For the analysis of the low dose in children (Table 9), data were borrowed from adolescents and adults treated with the low dose or AS alone.

Table 8. 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 6.6
[b] Calculated as borrowed adult events ÷ (borrowed adult events + events among children + 1)

Table 9. 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 6.6
[b] Calculated as borrowed adult and adolescent events ÷ (borrowed adult and adolescent events + events among children + 1)

The analyses in Table 8 and Table 9, as well as Bayesian analyses provided by the Applicant, show that demonstration of efficacy among the pediatric subgroups requires borrowing large amounts of adult data relative to the collected pediatric data. For either dose to achieve efficacy (i.e., upper limit of 'credible interval'—Bayesian equivalent of confidence interval—to be <1) in the respective age cohorts, a minimum of 95% of data must be borrowed from adults. Therefore, the question becomes one of whether extrapolation is appropriate, based on careful clinical and pharmacologic considerations.

MANDALA Secondary Endpoints

Secondary endpoints from MANDALA, analyzed in the pediatric subgroups, are presented in order of hierarchical ranking by the Applicant. These *post hoc* analyses are exploratory, but we include them to support discussion of any clinical insights into differential treatment responses between age groups. Table 10 summarizes the secondary endpoint of annualized rate of severe exacerbations. Given the small numbers, no clear pattern emerges. Rates are relatively balanced between arms, with the exception of point estimates that are suggestive of benefit for the low dose, BDA 80/180, in adolescents. 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.

Table 10. 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			
	Subjects With ≥24 Weeks Exposure					
	≥ 4 - <12 years	BDA MDI 80/180 (N=32)	10	0.80	0.24, 2.62	0.71
		AS MDI 180 (N=30)	11			
	≥12 - <18 years	BDA MDI 160/180 (N=28)	8	0.66	0.18, 2.43	0.53
		BDA MDI 80/180 (N=28)	6	0.43	0.11, 1.70	0.23
		AS MDI 180 (N=28)	9			

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

Table 11 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 11. 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		
	Subjects With ≥24 Weeks Exposure				
	≥4 - <12 years	BDA MDI 80/180 (N=41)	32	-24.5	0.88
		AS MDI 180 (N=42)	30		
	≥12 - <18 years	BDA MDI 160/180 (N=34)	28	-74.5	0.95
				-85.2	0.59
		BDA MDI 80/180 (N=32)	28		
		AS MDI 180 (N=34)	28		

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

Table 12 and Table 13 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 12. Subgroup Analysis by Age—Asthma Control Questionnaire 5-Item Version Minimal Important Difference 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
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)			
	Subjects With ≥24 Weeks Exposure					
	≥ 4 - <12 years	BDA MDI 80/180 (N=30)	21 (70.0)	1.07	0.35, 3.25	0.91
		AS MDI 180 (N=29)	20 (69.0)			
	≥12 - <18 years	BDA MDI 160/180 (N=28)	17 (60.7)	1.60	0.55, 4.67	0.39
		BDA MDI 80/180 (N=28)	21 (75.0)	3.21	1.03, 10.03	0.045
		AS MDI 180 (N=28)	14 (50.0)			

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

Table 13. 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)			
	Subjects With ≥24 Weeks Exposure					
	≥12 - <18 years	BDA MDI 160/180 (N=26)	12 (46.2)	1.64	0.52, 5.20	0.40
		BDA MDI 80/180 (N=28)	15 (53.6)	2.33	0.75, 7.25	0.14
		AS MDI 180 (N=28)	9 (33.3)			

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

3.2 Safety Issues

Our review of the safety data for BDA development did not identify safety signals that were unexpected or inconsistent with the known effects of BD and AS. The rates of adverse events (AEs) in subjects <18 yo were low. Both the Applicant and the Agency performed independent analyses of AEs in a variety of subgroups, defined by age and background ICS, for example. Findings were reassuring and consistent with the well-defined class effects of both ICS and SABA. We, therefore, do not present a particular safety concern to the committee for discussion. Instead, we provide an overview of the safety data, with a brief and focused review of findings in subjects <18 yo and AEs related to the known risks of ICS. We also invite the committee to consider potential safety issues in subjects <18 yo based on anticipated real-world use and the existing literature, not captured by the BDA development program.

3.2.1 Sources of Data for Safety

The Applicant and Agency agreed *a priori* that safety data would not be pooled for analysis because of the disparate designs and enrolled populations of the pivotal trials. Safety data from MANDALA, DENALI, and TYREE were presented and reviewed separately. As with our review of efficacy data, the focus was on MANDALA given its design and scope. For all three studies, safety analysis was conducted in the Safety Analysis Set (SAS), defined as all subjects who received any amount of IP, classified by treatment actually received. Table 14 summarizes the size of the safety database for review. We consider the sample size in subjects ≥18 to be adequate for review. As we will discuss in Section 3.2.3, the total incidence, distribution among treatment arms, and nature of AEs in subjects <18 yo were reassuring; however, we acknowledge the limited size of the safety database for this population to support definitive conclusions.

Table 14. Safety Database for BDA Development

Trial	Safety N
MANDALA	• Randomized: 3132 • SAS total: 3127 • ≥4 to <12: 83 • ≥12 to <18: 100 • ≥18: 2944
DENALI	• Randomized: 1001 • SAS total: 1000 • ≥4 to <12: 10 • ≥12 to <18: 25 • ≥18: 965
TYREE	• Randomized: 60 • SAS total: 60 • ≥4 to <12: 0 • ≥12 to <18: 2 • ≥18: 58
Total	4187

Source: Clinical Reviewer.
Abbreviations: N, number; SAS, safety analysis set

3.2.2 Safety Summary

The known risks of BD are well-described and include localized infection (e.g. oral candidiasis); immunosuppression and worsening of infections; hypercorticism and adrenal suppression; and other long-term effects of hypercorticism, such as growth restriction, glaucoma, and reduction in bone density. The most common adverse reactions are nasopharyngitis, nasal congestion, pharyngitis, rhinitis, viral upper respiratory tract infection, nausea, viral gastroenteritis, otitis media, and oral candidiasis[2]. The known risks of AS are similarly well-described and include paradoxical bronchospasm, cardiovascular events, hypersensitivity, and hypokalemia. Most of these are associated with excessive SABA use. The most common adverse reactions are throat irritation, viral respiratory infections, cough, and musculoskeletal pain[3].

MANDALA

Overall, AEs were balanced across treatment arms in MANDALA (Table 15). Since all trials were conducted primarily from 2019 to 2021, with onset of the COVID-19 pandemic in early 2020, disease from SARS-CoV-2 infection (COVID-19) accounts for a significant proportion of AEs, serious adverse events (SAEs), and deaths.

Table 15. MANDALA, Number of Subjects With Any Category of Adverse Event in the Randomized Treatment Period (Safety Analysis Set)

AE	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)	53 (5.2%)	40 (3.8%)	48 (4.5%)
Any AE leading to discontinuation of IP	10 (1.0%)	9 (0.9%)	9 (0.9%)

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

In MANDALA, approximately half of all subjects reported an AE during the study period across all treatment arms. The rate of AEs related to IP and of AEs associated with IP leading to treatment discontinuation (Table 15) were low and balanced across arms. Most of the AEs accounting for the former were oral candidiasis and dyphonia, and for the latter, COVID-19, asthma, and dysphonia. 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. None of these deaths was attributed by investigators as causally related to IP. We reviewed narratives and case report forms (CRFs) for all subjects with an outcome of death. There was a higher number of deaths in the BDA 160/180 arm (4), compared to BDA 80/180 (2) and AS (2) arms. Three deaths were from COVID-19, two in BDA 160/180 and one in AS. 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 if this was related to IP. No deaths

[2] See Pulmicort Flexhaler at https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021949s003lbl.pdf
[3] See Ventolin HFA at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020983s032lbl.pdf

occurred in pediatric subjects. Based on these data, no new safety signals were identified that were unexpected or inconsistent with the known risk profiles of ICS and SABA.

The most common AEs are summarized in Table 16 and include nasopharyngitis, upper respiratory tract infections, COVID-19, asthma exacerbations (not meeting criteria for the primary endpoint), rhinitis, arthralgia, and hypertension. Most AEs were balanced across arms, although asthma-related AEs were higher in the AS arm. We analyzed the most common AEs stratified by background ICS dose to provide the most information on the possible additive effects of ICS, and we did not observe concerning patterns. The highest total incidence of infections and infestations was in the BDA 80/180 receiving high dose background ICS group (30.2%), although the magnitude of difference compared to other arms was small. The highest total incidence of asthma-related AEs was in the AS receiving high dose background ICS group (4.1%).

Table 16. MANDALA, 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		
System Organ Class, Preferred Term	**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)**
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%)	5 (1.6%)	6 (2.3%)	8 (1.6%)	7 (2.4%)	7 (2.9%)	6 (1.2%)	5 (1.6%)
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: Clinical Reviewer. OCS Analysis Studio, Custom Table Tool, adexsum.xpt, adae.xpt.

The most common SAEs are summarized in Table 15. In total, 141 subjects experienced 190 SAEs. Narratives for all SAEs were reviewed. SAEs were generally balanced across treatment arms with on-treatment incidences of: 53 subjects (5.3%) in BDA 160/180, 40 subjects (3.8%) in BDA 80/180, and 48 subjects (4.5%) in AS. Most SAEs were isolated events. The only SAEs occurring in >1% of the population were COVID-19, pneumonia, and asthma. In our review, we did not find an association with worse outcomes or longer hospitalizations among subjects with COVID-19 or pneumonia in any particular subgroup. More asthma events occurred in AS compared to both BDA 160/180 and BDA 80/180 (1.9% vs 0.7%, 0.8%). We present SAEs stratified by background ICS dose, which does not demonstrate significant patterns other than more asthma-related AEs in the AS receiving medium or high dose ICS group. These data were not unexpected given the population, drug classes, and conduct of the trial during the COVID-19 pandemic.

Table 17. MANDALA, Number of Subjects with Common (>1%) Serious 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		
Preferred Term	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)
Asthma	2 (0.9%)	2 (0.4%)	2 (0.6%)	1 (0.4%)	4 (0.8%)	3 (1.0%)	1 (0.4%)	10 (2.0%)	9 (2.8%)
COVID-19	6 (2.6%)	4 (0.9%)	1 (0.3%)	0	2 (0.4%)	3 (1.0%)	1 (0.4%)	5 (1.0%)	2 (0.6%)
COVID-19 pneumonia	2 (0.9%)	0	1 (0.3%)	2 (0.8%)	1 (0.2%)	1 (0.3%)	3 (1.3%)	1 (0.2%)	1 (0.3%)
Pneumonia	0	5 (1.1%)	0	0	2 (0.4%)	2 (0.7%)	0	2 (0.4%)	0

Source: Clinical Reviewer. OCS Analysis Studio, Custom Table Tool, adexsum.xpt, adae.xpt.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', AVALCAT1 = 'Low' or 'Medium' or 'High'.
Table Section 1 - Dataset: Adverse Events; Filter: APHASE = 'Randomized Treatment', AAE003FL = 'Y'; Percent Threshold: ≥1%.

DENALI

Table 18 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 (1%) 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. SAEs were also rare and balanced across treatment arms. All SAEs were isolated events, with the exception of asthma (1 subject in BDA 60/180 and placebo arms, each) and COVID-19 (1 subject in BDA 160 and placebo arms, each). Most AEs were mild in severity. There was a slightly higher incidence of nasopharyngitis (a known risk of ICS) in the BDA arms. Among pediatric subjects, AEs were infrequent, with only 2 subjects 4 to <12 yo experiencing mild AEs in the AS arm. There was only one SAE among pediatric subjects, which was asthma-related in an adolescent subject randomized to BDA 80/180. Refer to Section 6.5 for more details. Based on these data, no new safety signals were identified.

Table 18. 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.

TYREE

In TYREE, there was a total of three AEs throughout both treatment periods, all of which were mild and self-limited.

3.2.3 Safety Issues in Detail

In this section, we present a summary of safety findings in pediatric subjects, as well as findings related to known ICS risks.

Clinical Pharmacology Considerations

For a locally acting drug product, such as BDA, the drug's systemic exposure is correlated with its systemic safety profile; therefore, we first summarize data on both observed and simulated systemic exposures of BDA. The Applicant conducted two PK studies comparing BD systemic exposure between BDA and the RLDs: BDA and Pulmicort Flexhaler in adult healthy subjects (Study ELBRUS, N=67), BDA and Pulmicort Respules in pediatric asthmatics aged 4 to 8 years (Study BLANC, N=12). A cross-study PK comparison indicated that, following the same single dose of BDA 160/180, the BD systemic exposure (C_{max} and AUC_{0-t}) in children is about half the value of that in adults (Table 19).

Table 19. 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} (pg*h/mL)	916 (36.9)	1235 (37.3)	398 (46.3)	985 (78.7)
AUC_{0-inf} (pg*h/mL)	968 (34.8)	1279 (36.7)	NA	NA

Source: Clinical Pharmacology Reviewer.
AUC, area under the concentration-time curve; BDA, budesonide; C_{max}, maximum concentration; n, number of subjects in the PK analysis; NA, not applicable

We conducted additional simulations to mimic the 'worst-case scenario' daily use: i.e., 12 inhalations of high dose BDA (6 doses of BDA 160/180) plus the maximum BD controller dose (Table 20). In this situation, the total systemic exposure ($AUC_{0-24hours}$) of BD in adolescents and children aged 4 to 11 years is still expected to be lower than the value in adults. 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

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 20. 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

Pediatric Safety Results

In MANDALA, the overall incidence of AEs among subjects <18 yo was low and generally balanced across treatment arms (Table 21). Slightly more AEs occurred in the AS arm (42% vs 38% in each BDA arm), a difference driven by asthma-related events. There were no deaths among subjects <18 yo. There were two cases of AEs attributed to IP, both in the <12 yo BD 80/180 arm for reasons of cough and oropharyngeal pain. Only one pediatric subject experienced an AE leading to treatment discontinuation, a subject <12 randomized to BDA 80/180 who reported oropharyngeal pain and cough. An overview of AEs in subjects <18 yo is provided stratified by background ICS to provide the most information on cumulative effects of ICS. When stratified by age cohort, the total number of AEs were balanced between groups (34 or 41% among ≥4 to <12 yo; 39 or 39% among ≥12 to <18 yo).

Table 21. MANDALA, 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		
AE	**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.

Table 22 summarizes the most common AEs in subjects <18 yo, stratified by background ICS dose. Among all subjects ≥4 to <18 yo, 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 randomized treatment arms. As with adults, across all arms, the rates of some infections (e.g., influenza) were slightly higher in the high dose background ICS subgroups compared to others. The only asthma-related AEs occurred in the AS arm. When stratified by age (≥4 to <12 yo, ≥12 to <18 yo), there were no significant imbalances between groups (e.g., influenza reported in 5 subjects (6%) <12 and 4 subjects (4%) ≥12; rhinitis in 2 subjects (2.4%) <12 and 4 subjects (4%) ≥12). Based on these data, we did not identify new safety signals in this population, although the numbers were small.

Table 22. MANDALA, Most Common (Occurring >1 Subject per Arm) Adverse Events During the Randomized Treatment Period, Subjects ≥4 to <18, Stratified by Background ICS, by Preferred Term (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)
Preferred Term									
Influenza	1 (12.5%)	1 (5.0%)	0	0	0	3 (20.0%)	0	2 (4.8%)	2 (10.0%)
Rhinitis allergic	0	1 (5.0%)	1 (16.7%)	0	1 (2.3%)	1 (6.7%)	1 (7.1%)	1 (2.4%)	0
Bronchitis	1 (12.5%)	0	0	0	3 (6.8%)	0	0	0	1 (5.0%)
Cough	0	0	1 (16.7%)	0	1 (2.3%)	1 (6.7%)	1 (7.1%)	1 (2.4%)	0
Suspected COVID-19	0	1 (5.0%)	0	0	2 (4.5%)	1 (6.7%)	1 (7.1%)	0	0
Asthma	0	0	0	0	0	0	0	2 (4.8%)	2 (10.0%)
Headache	0	2 (10.0%)	0	0	0	0	2 (14.3%)	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%)
Ligament sprain	1 (12.5%)	0	0	1 (7.1%)	0	0	0	1 (2.4%)	0
Oropharyngeal pain	0	0	0	0	0	1 (6.7%)	1 (7.1%)	0	1 (5.0%)
Toothache	0	0	0	0	2 (4.5%)	0	0	1 (2.4%)	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
Rhinorrhoea	0	1 (5.0%)	0	0	0	0	0	0	1 (5.0%)
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%)
Urticaria	0	0	0	0	0	1 (6.7%)	0	1 (2.4%)	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%)

Source: Clinical Reviewer. OCS Analysis Studio, adexsum.xpt, adae.xpt.

Table 23 summarizes SAEs among subjects <18 yo. SAEs were rare, and the only event that occurred more than once was asthma in the AS arm (2 subjects ≥12, 1 subject ≤12). The COVID-19 SAE occurred in one subject ≤12 yo, and the anxiety/depressive disorder AE in one subject ≥12 yo. We reviewed narratives and case reports for all SAEs and did not identify any concerning patterns. No SAEs were adjudicated as related to IP. In addition, we examined AEs among subjects <18 yo that were associated with hospitalization, and there were none apart from the SAEs listed below.

Table 23. MANDALA, Number of Subjects ≥4 to <18 with a Serious Adverse Event in the Randomized Treatment Period, by Preferred Term, Stratified by Background ICS (Safety Analysis Set)

	BDA MDI 160/180			BDA MDI 80/180			AS MDI 180		
Preferred Term	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)
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: Clinical Reviewer. OCS Analysis Studio, Custom Table Tool, adae.xpt, adexsum.xpt.

ICS-Related Adverse Events

According to prior agreements with the Agency, the Applicant provided and analyzed AEs related to both systemic and local known toxicities of ICS. Our review is presented in Table 24.

Table 24. MANDALA, Subjects With ICS-Related Adverse Events During the Randomized Treatment Period, by Preferred Term, Stratified by Age (Safety Analysis Set)

	BDA MDI 160/180		BDA MDI 80/180			AS MDI 180		
AE Type	**≥12 - <18 (N=34)**	**≥18 (N=980)**	**≥4 - <12 (N=41)**	**≥12 - <18 (N=32)**	**≥18 (N=982)**	**≥4 - <12 (N=42)**	**≥12 - <18 (N=34)**	**≥18 (N=981)**
Local ICS-Related AE, preferred term								
Oral candidiasis	0	10 (1.0%)	0	0	9 (0.9%)	1 (2.4)	0	4 (0.4%)
Dysphonia	1 (2.9%)	3 (0.3%)	0	0	6 (0.6%)	0	0	4 (0.4%)
Oropharyngeal candidiasis	0	3 (0.3%)	0	0	3 (0.3%)	0	0	1 (0.1%)
Dysgeusia	0	1 (0.1%)	0	0	1 (0.1%)	0	0	2 (0.2%)
Candida infection	0	1 (0.1%)	0	0	1 (0.1%)	0	0	0
Aphonia	0	1 (0.1%)	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	1 (0.1%)
Esophageal candidiasis	0	0	0	0	0	0	0	1 (0.1%)
Systemic ICS-related AE, preferred term								
Insomnia	0	4 (0.4%)	0	0	9 (0.9%)	0	0	4 (0.4%)
Contusion	0	6 (0.6%)	0	1 (3.1%)	4 (0.4%)	0	0	5 (0.5%)
Diabetes mellitus	0	4 (0.4%)	0	0	2 (0.2%)	0	0	5 (0.5%)
Depression	0	4 (0.4%)	0	0	2 (0.2%)	0	0	3 (0.3%)
Cortisol decreased	0	0	0	0	5 (0.5%)	0	0	2 (0.2%)
Rib fracture	0	1 (0.1%)	0	0	2 (0.2%)	0	0	3 (0.3%)
Hyperglycemia	0	2 (0.2%)	0	0	1 (0.1%)	0	0	2 (0.2%)
Type 2 diabetes mellitus	0	3 (0.3%)	0	0	0	0	0	1 (0.1%)
Wrist fracture	0	0	0	0	1 (0.1%)	1 (2.4)	0	2 (0.2%)
Blood glucose increased	0	1 (0.1%)	0	0	1 (0.1%)	0	0	1 (0.1%)
Cataract	0	2 (0.2%)	0	0	0	0	0	1 (0.1%)
Foot fracture	0	1 (0.1%)	0	0	1 (0.1%)	0	0	1 (0.1%)
Radius fracture	0	1 (0.1%)	0	0	1 (0.1%)	0	0	1 (0.1%)
Adjustment disorder with depressed mood	0	1 (0.1%)	0	0	0	1 (2.4)	0	0
Ankle fracture	0	1 (0.1%)	0	0	0	0	0	1 (0.1%)
Diabetes mellitus inadequate control	0	1 (0.1%)	0	0	1 (0.1%)	0	0	0
Diabetic metabolic decompensation	0	0	0	0	0	0	0	2 (0.2%)

AE Type	BDA MDI 160/180		BDA MDI 80/180			AS MDI 180		
	≥12 - <18 (N=34)	≥18 (N=980)	≥4 - <12 (N=41)	≥12 - <18 (N=32)	≥18 (N=982)	≥4 - <12 (N=42)	≥12 - <18 (N=34)	≥18 (N=981)
Stress fracture	0	0	0	0	0	0	0	2 (0.2%)
Adrenocortical insufficiency acute	0	0	0	0	1 (0.1%)	0	0	0
Femur fracture	0	0	0	0	1 (0.1%)	0	0	0
Fibula fracture	0	0	0	0	1 (0.1%)	0	0	0
Glaucoma	0	0	0	0	0	0	0	1 (0.1%)
Grief reaction	0	0	0	0	0	0	0	1 (0.1%)
Lumbar vertebral fracture	0	0	0	0	1 (0.1%)	0	0	0
Mixed anxiety and depressive disorder	1 (2.9%)	0	0	0	0	0	0	0
Osteopenia	0	1 (0.1%)	0	0	0	0	0	0
Scapula fracture	0	0	0	0	0	0	0	1 (0.1%)
Secondary adrenocortical insufficiency	0	0	0	0	1 (0.1%)	0	0	0

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

In general, ICS-related AEs were mild in severity and rarely associated with discontinuation of IP. Only 6 events occurred in subjects <18 yo, 3 in each age cohort: 2 in the AS arm, and 1 in each BDA arm. The only severe AE was the mixed anxiety and depressive disorder SAE in an adolescent previously described. Within the whole SAS, any imbalances between treatment arms (e.g., oral candidiasis more frequent in BDA vs AS) were small and not unexpected. Based on these data, we did not identify new safety concerns regarding the potential use of BDA as an add-on to background ICS.

Pneumonia-Related Adverse Events

Although not specified as an adverse event of special interest (AESI) nor as an ICS-related AE, both the Applicant and Agency identified pneumonia as a potential important safety issue. In MANDALA, 50 subjects reported a pneumonia AE, 33 (55%) of which were attributed to COVID-19 and 24 (48%) of which were classified as SAEs. We reviewed narrative data for all subjects with pneumonia AEs. Although the most pneumonia AEs occurred in the BDA 160/180 arm (2.3% vs 1.3% in BDA 80/180 and 1.2% in AS), this difference was driven by non-serious events; pneumonia SAEs were balanced across arms: 0.9%, 0.8%, and 0.7% in BDA 160/180, BDA 80/180, and AS, respectively. There were no pneumonia events in subjects 4 to 11 yo, and 2 non-serious cases in subjects ≥12 to <18 yo (1 in BDA 160/180 and 1 in AS). When stratified by background ICS, the highest total incidence of pneumonia occurred in subjects on high dose background ICS and BDA 160/180, although the magnitude of difference was small (e.g., 9 subjects or 2.8% on high dose ICS + BDA 160/180 vs 5 subjects or 2.1% on low dose ICS + AS). These findings are not unexpected given the known risks of ICS and conduct of the trial during the COVID-19 pandemic and did not raise new safety concerns.

Growth Velocity

The Applicant also collected height measurements on all subjects <18 yo at screening and 24 weeks. Two subjects from the ≥4 to <12 yo group were excluded because of unreliable measurements. In a *post hoc* analysis in subjects ≥4 to <12 yo 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 yo, 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 size, it is difficult to assess whether these differences are meaningful. 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 for all ICS-containing products.

Follow Up Safety Data

The event-driven design of MANDALA resulted in the primary database lock occurring while 38 subjects <18 yo were still under observation and 37 had not yet met the 24-week minimum study period. These subjects were included in the FAS and SAS for primary efficacy and safety analyses, and the Applicant submitted an addendum with additional outcomes and AEs, which we reviewed separately. Among these subjects, 3 additional non-severe AEs occurred: 1 in BDA 80/180 of arthralgia and 2 in AS of asthma and sinusitis. These data did not have a meaningful impact on the efficacy or safety analyses.

3.3 Risk Mitigation

Since we did not identify any new or unique safety signals, we do not anticipate risk mitigation strategies beyond clear, accurate labeling and routine pharmacovigilance.

4 Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

While we typically present one overall benefit-risk framework, given the varying uncertainties in the pediatric data, we provided separate benefit-risk frameworks for the relevant subgroups.

Table 25. Benefit-Risk Framework 1, Subjects ≥18 Years of Age

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Airway inflammation is a central component of asthma. • Most asthma exacerbations may be managed in the outpatient setting with PRN SABA or, for severe exacerbations, with systemic corticosteroids, which may themselves be associated with morbidity and effects on quality of life. • Severe exacerbations may require hospitalization, higher or prolonged doses of corticosteroids, and may result in death.	• Most patients with asthma do not have severe disease, but all patients are vulnerable to severe exacerbations, which may be life-threatening.
Current Treatment Options	• There is only one class of inhaled therapy (SABA) approved in the US as reliever treatment. • Although treatment guidelines recommend ICS/formoterol, it is not currently approved for this indication. • There are no approved reliever therapies that carry the indication to prevent severe acute exacerbations.	• There is a need for safe and effective therapies to prevent severe exacerbations.

	Evidence and Uncertainties	Comments to the Advisory Committee
Benefits	• 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. • Supportive evidence of benefit comes from DENALI. • 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. Descriptive analyses of secondary endpoints, including ACQ-7, a validated PRO, and rate of exacerbations also demonstrated a numerical trend in favor of BDA 160/180.	• In subjects ≥18 (and in subjects ≥12, combining adolescents and adults), both pivotal trials met the FDA-agreed upon primary endpoints. BDA 160/180 demonstrated benefit in reducing severe asthma exacerbations and reducing systemic corticosteroid use.
Risks 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. • Should BDA be approved for patients ≥18, accurate labeling and routine pharmacovigilance should be appropriate risk mitigation strategies.	• For patients ≥18, labeling and routine pharmacovigilance would constitute an adequate risk mitigation strategy.

Source: Clinical reviewer.

Point(s) to Consider

- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥18 years of age with asthma? If not, what additional data are needed?

Table 26. Benefit Risk Framework 2, Subjects ≥12 to <18 Years of Age

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Airway inflammation is a central component of asthma. • Most asthma exacerbations may be managed in the outpatient setting with PRN SABA or, for severe exacerbations, with systemic corticosteroids, which may themselves be associated with morbidity and effects on quality of life. • Severe exacerbations may require hospitalization, higher or prolonged doses of corticosteroids, and may result in death. • Historically, when appropriate, clinical trials, including large trial networks, and drug development programs have grouped adolescents with adults. International guidelines (NAEPP, GINA) also group subjects ≥12 with adults.	• Like adults, adolescents with asthma are vulnerable to severe exacerbations.
Current Treatment Options	• There is only one class of inhaled therapy (SABA) approved in the US as reliever treatment. • Although treatment guidelines recommend ICS/formoterol, it is not currently approved for this indication. • There are no approved reliever therapies that carry the indication to prevent severe acute exacerbations. • Most inhaled asthma therapies approved for adults are approved down to at least age 12.	• The need for a safe and effective therapy to prevent severe exacerbations also applies to adolescents. •

	Evidence and Uncertainties	Comments to the Advisory Committee
Benefits	• 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 BD 80/180. • 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. • In DENALI, in exploratory sub-group analyses of FEV1, trends suggested benefit of BDA 160/180 compared to AS for this age group.	• Although the study results for BDA 160/180 in subjects ≥12 to <18 are inconclusive, given the expected similarity between adolescents and adults, extrapolation of adult efficacy data may be appropriate and could support efficacy in this age group and address residual uncertainty.
Risks and Risk Management	• 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. • Should BDA be approved for patients ≥12 to <18, accurate labeling and routine pharmacovigilance should be appropriate risk mitigation strategies.	• The safety profile demonstrated in the BDA development program did not uncover unexpected or concerning safety signals in this population. 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).

Source: Clinical reviewer.

Point(s) to Consider

- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥12 to <18 years of age with asthma? If not, what additional data are needed?

Table 27. Benefit Risk Framework 3, Subjects 4 to <12 Years of Age

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Airway inflammation is a central component of asthma. • Most asthma exacerbations may be managed in the outpatient setting with PRN SABA or, for severe exacerbations, with systemic corticosteroids, which may themselves be associated with morbidity and effects on quality of life. • Severe exacerbations may require hospitalization, higher or prolonged doses of corticosteroids, and may result in death. • Children with all severities of asthma are vulnerable to severe acute exacerbations.	• There are differences—and uncertainties about these differences—between pediatric and adult disease; however, the basic pathophysiology of acute airway inflammation leading to exacerbations is likely similar in both adults and children.
Current Treatment Options	• The current reliever treatment considerations are similar for children to those for adolescents and adults. • Most inhaled asthma therapies approved for adolescents and adults are approved for children as young as 4-6 year, including albuterol and budesonide. • The basis for these approvals has been dedicated pediatric efficacy trials, and extrapolation has supported approval in a few instances.	• The need for a safe and effective therapy to prevent severe exacerbations also applies to children.
Benefits	• 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.	• Although the study results for BDA in subjects ≥4 to <12 are inconclusive, extrapolation of efficacy from adult data may be appropriate; however, there is residual uncertainty regarding the benefits of BDA for children in this age group.

	Evidence and Uncertainties	Comments to the Advisory Committee
Risks and Risk Management	• 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. • Should BDA be approved for patients ≥4 to <12, accurate labeling and routine pharmacovigilance should be appropriate risk mitigation strategies, pending new information from any additional trials.	• Although the safety profile demonstrated in the BDA development program did not uncover unexpected or concerning signal, there is uncertainty regarding potential risks from long-term exposure to higher doses of ICS (e.g. growth restriction, hypercorticisim) that were not captured by the small sample size and short duration of the trials.

Source: Clinical reviewer.

Point(s) to Consider

- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥4 to <12 years of age with asthma? If not, what additional data are needed?

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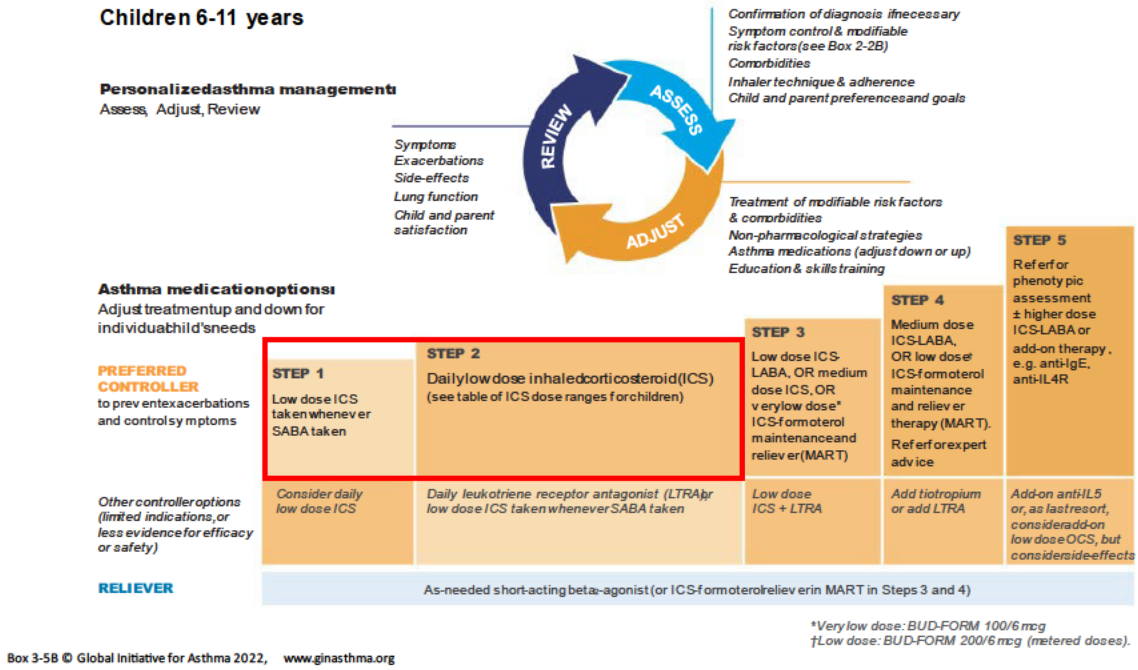
6 Appendix

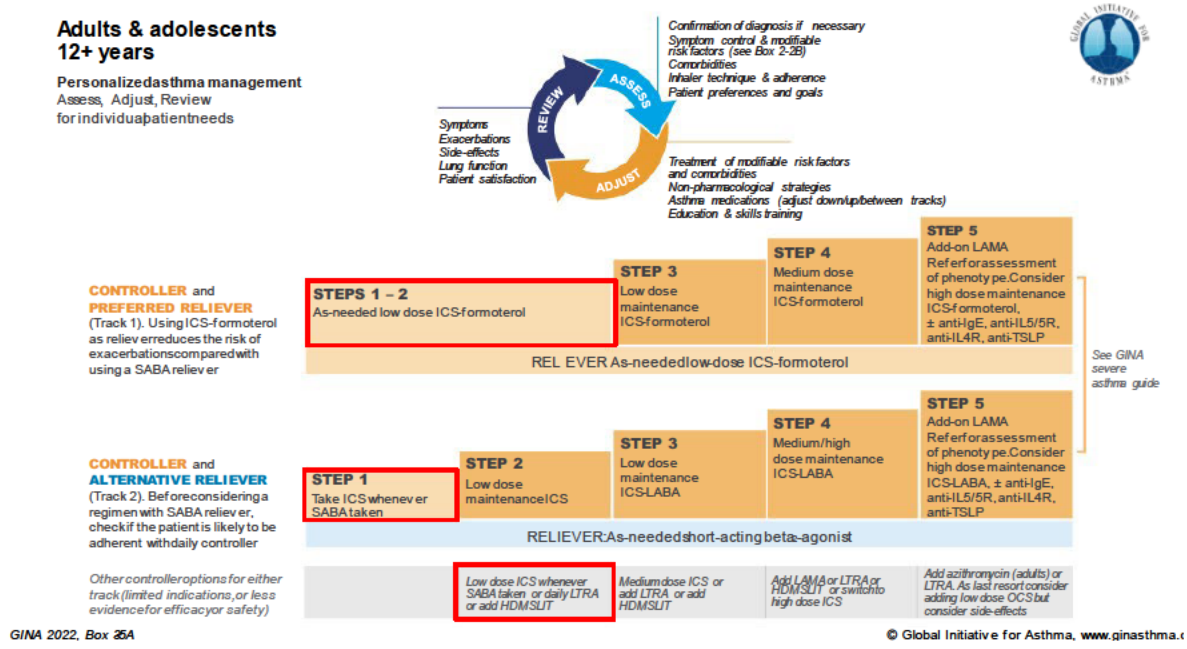
6.1 Appendix: Asthma Treatment Guidelines

Figure A. GINA 2022 Asthma Management Guidelines, Children 6 to 11 Years



Source: GINA Science Committee (2022)

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



Source: GINA Science Committee (2022)

Figure C. NAEPP Asthma Management Guidelines 2020, Ages ≥12 Years

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	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)

6.2 Appendix: ICS Dose Definitions

The following tables are reproduced from the Applicant's Clinical Study Protocol for MANDALA (AV003) Version 2.0. These tables are, themselves, adapted from GINA guidelines published in 2018.

Low, Medium, and High Doses of Inhaled Corticosteroids

Adults and adolescents (12 years and older)			
	Daily dosage (µg)		
DRUG	**LOW**	**MEDIUM**	**HIGH**
Beclometasone dipropionate (CFC)[a]	200-500	>500-1000	>1000
Beclometasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	NA	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000

Source: Applicant, Clinical Study Protocol Version 2.0 MANDALA (AV003)

Children 6-11 years			
Beclometasone dipropionate (CFC)[a]	100-200	>200-400	>400
Beclometasone dipropionate (HFA)	50-100	>100-200	>200
Budesonide (DPI)	100-200	>200-400	>400
Budesonide (nebules)	250-500	>500-1000	>1000
Ciclesonide	80	>80-160	>160
Fluticasone furoate (DPI)	NA	NA	NA
Fluticasone propionate (DPI)	100-200	>200-400	>400
Fluticasone propionate (HFA)	100-200	>200-500	>500
Mometasone furoate	110	≥220-<440	≥440
Triamcinolone acetonide	400-800	>800-1200	>1200

Abbreviations: CFC=chlorofluorocarbon propellant; DPI=dry powder inhaler; HFA=hydrofluoroalkane propellant; NA=not applicable

[a] Beclometasone dipropionate CFC is included for comparison with other literature.

Low Daily Doses of Inhaled Corticosteroids for Children 5 Years and Younger

DRUG	Low daily dosage (µg)[a] (age group with adequate safety and effective data)
Beclometasone dipropionate (HFA)	100 (ages ≥5 years)
Budesonide nebulized	500 (ages ≥1 year)
Fluticasone propionate (HFA)	100 (ages ≥4 years)
Mometasone furoate	110 (ages ≥4 years)
Budesonide pMDI + spacer	Not sufficiently studied in this age group
Ciclesonide	Not sufficiently studied in this age group
Triamcinolone acetonide	Not sufficiently studied in this age group

Abbreviations: HFA=hydrofluoroalkane propellant; pMDI=pressurized metered-dose inhaler

[a] Subjects 5 years and younger meeting GINA step 3 eligibility should be treated with double low-dose ICS or Low dose ICS + LTRA (Global Initiative for Asthma [GINA] 2018).

Source: Applicant, Clinical Study Protocol Version 2.0 MANDALA (AV003)

6.3 Appendix: MANDALA Statistical Analysis Plan (SAP)

Analysis Population and Estimand

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 primary estimand was an efficacy estimand which 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.

Primary Endpoint Analysis Method

The primary endpoint, 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. 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.

Sensitivity/Robustness Analyses

Multiple imputation tipping point analysis under an informative censoring assumption (Censored not at random; CNAR) was conducted for the primary endpoint of time to first severe exacerbation using the full analysis set. For subjects in the BDA MDI treatment groups, this method imputed unobserved event times post early IP discontinuation/ change in maintenance therapy for lack of asthma control, assuming they were more likely to have a severe asthma exacerbation event than was implied under the censoring at random (CAR) assumption. For subjects in the AS MDI treatment group, event times were imputed using multiple imputation but assumed non-informative CAR. The multiple imputation process was conducted using bootstrapped samples with replacement within each treatment group to create 100 bootstrap samples, one for each imputed dataset. Each fully imputed dataset was individually analysed using a Cox proportional hazards model as specified in the primary analysis. The estimates of the treatment effect, confidence intervals and p-values were combined using Rubin's rules (Rubin 1987). As the time to event data are not normally distributed, results were combined on the log-scale and were back-transformed for reporting in displays. Then clinical plausibility of penalty imposed to the missing data at the tipping point where statistical significance is lost is evaluated for robustness of data.

Key Secondary Endpoints Analysis Methods

Annualized severe exacerbation rate ratios and p-values were estimated from a negative binomial model with treatment, age group region, and number of severe exacerbations in the last 12 months prior to randomization as categorical covariates. The logarithm of the time at risk is included as an offset variable.

Total annualized SCS dose was calculated by summing the cumulative dose of SCS during the randomized treatment period and dividing by duration (years) of the randomized treatment period. Only SCS use following a severe exacerbation is included. SCS are normalized to prednisone equivalents when

calculating total dose. The differences in predicted means were estimated from a log-normal hurdle model adjusted for randomized treatment. The p-values were calculated via a Wilcoxon rank sum test separately for BDA MDI 160/180 vs AS MDI 180 and BDA 80/180 vs AS MDI 180.

ACQ-5 responder was defined as a subject with a change from baseline to Week 24 overall ACQ-5 score ≤-0.5. The overall ACQ-5 score is the averaged score across the 5 domains. Odds ratios and p-values were estimated from a logistic regression model with baseline ACQ-5 as a continuous covariate and age group, region and number of severe exacerbations in the past 12 months prior to randomization (Visit 2) as categorical covariates. All subjects who discontinued treatment or had a change in maintenance therapy prior to Week 24 were classified as non-responders.

AQLQ+12 responder was defined as a subject with an increase from baseline to week 24 AQLQ+12 score of at least 0.5. The overall AQLQ+12 score is the average score of the 32 questions. Odds ratios and p-values were estimated from a logistic regression model with baseline AQLQ+12 as a continuous covariate and age group, region and number of severe exacerbations in the past 12 months prior to randomization (Visit 2) as categorical covariates. All subjects who discontinued treatment or had a change in maintenance therapy prior to Week 24 were classified as non-responders.

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 secondary endpoints were tested only if the primary endpoint was significant for both comparisons of the high dose BDA vs AS and the low dose BDA vs AS. 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 vs AS MDI 180 µg
2. BDA MDI 80/180 µg vs AS MDI 180 µg

Total annualized dose of systemic corticosteroid

3. BDA MDI 160/180 µg vs AS MDI 180 µg
4. BDA MDI 80/180 µg vs AS MDI 180 µg

Asthma Control Questionnaire-5 (ACQ-5) change from baseline responder analysis at Week 24

5. BDA MDI 160/180 µg vs AS MDI 180 µg
6. BDA MDI 80/180 µg vs 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 vs AS MDI 180 µg
8. BDA MDI 80/180 µg AS MDI 180 µg

6.4 Appendix: MANDALA Sensitivity Analysis

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 . 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 a 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.

Table A. Tipping Point Analysis p-Values for BDA 160/180 MDI Severe Asthma Exacerbations (MANDALA)

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).

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 B). 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.

Table B. Tipping Point Analysis p-Values for BDA 80/180 MDI Severe Asthma Exacerbations (MANDALA)

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

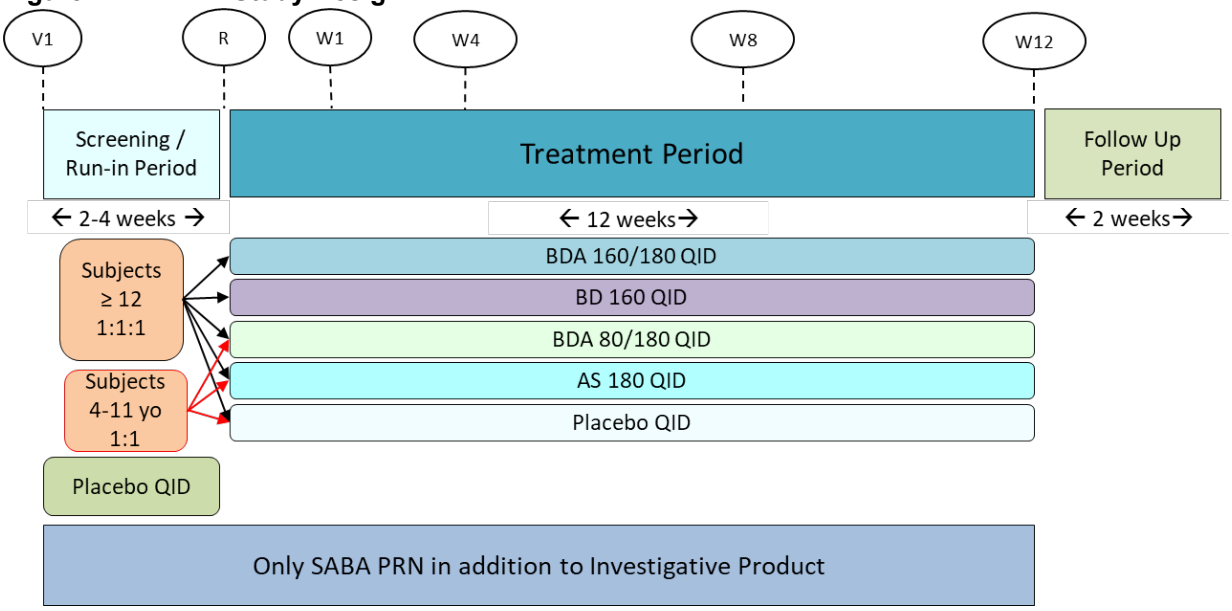
Source: The Applicant's response to Information Request, dated September 9, 2022 (Clinical Information Amendment, Table 1.11.3-1). Gray background and bold text represent the p-value for the penalties at which the tipping point occurs.

6.5 Appendix: DENALI Overview

1. DENALI Study Design

The DENALI study schema is shown in Figure D. As previously described, DENALI was a 12-week, randomized, double-blind, placebo- and active comparator-controlled trial. As in MANDALA, subjects ≥12 were randomized to all treatment arms, and a small cohort of subjects ≥4 to <12 were randomized only to low dose BDA, AS, and placebo.

Figure D. DENALI Study Design



Source: Clinical Reviewer.
QID, four times daily; v1, visit 1; R, randomization; w1, week 1; w4, week 4; w8, week 8; w12, week 12
During the screening/run-in period, all subjects were given placebo MDI to use QID; those with inadequate compliance by the randomization visit were counted as screen failures. At visit 1, all subjects were given Ventolin HFA to use PRN for symptoms, in place of pre-enrollment SABA. During the screening and treatment periods only IP and Applicant-provided Ventolin were permitted.

2. Denali Results

DENALI Efficacy Results

Table C summarizes the dual primary endpoints from DENALI, stratified by age cohort. 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.

As previously mentioned, subjects <12 were enrolled in DENALI for the purpose of exploratory analyses and collection of safety data only. Keeping that in mind, and the extremely small sample sizes, it is not possible to draw clear conclusions about the pharmacodynamic (PD) effects of BDA in this age group. The numeric trends, however, demonstrate no benefit for BDA 80/180 in subjects <12, while both doses resulted in numeric benefit for subjects ≥12 to <18. Given the limitations, this data does not add information beyond what is known from the approved monocomponent drug products.

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

				Comparison Between Groups		
Dual Primary Endpoints	Visit	Comparison	Least Squares (LS) Mean	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) vsBD 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 Denali AV004 Table 14; results reproduced by Statistical Reviewer and Statistical Analyst using adre.xpt.
AS, A buterol 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

Table D. Subgroup Analysis by Age—FEV1 $AUC_{0\text{-}6hours}$ Over the 12-Week Period and Trough FEV1 at Week 12 (DENALI, Full Analysis Set)

				Comparison Between Groups		
Dual Primary Endpoints	Subgroup	Comparison	Least Squares (LS) Mean	Diff in LS Means	95% CI	P-value
Change from baseline in FEV1 $AUC_{0\text{-}6hours}$ (mL) over 12 weeks	≥4 - <12	AS MDI 180 (N=4) vs Placebo MDI (N=3)	128.1 vs 114.2	13.9	-429.5, 457.4	0.93
	≥12 - <18	AS MDI 180 (N=5) vs Placebo MDI (N=4)	225.9 vs -135.9	361.8	-395.7, 1119.2	0.35
		BDA MDI 160/180 (N=4) vs Placebo MDI (N=4)	567.0 vs -135.9	702.8	-415.3, 1821.0	0.21
		BDA MDI 160/180 (N=4) vs BD MDI 160 (N=5)	567.0 vs 199.4	367.6	-249.0, 984.1	0.24

Dual Primary Endpoints	Subgroup	Comparison	Least Squares (LS) Mean	Comparison Between Groups		
				Diff in LS Means	95% CI	P-value
	≥18	AS MDI 180 (N=191) vs Placebo MDI (N=192)	152.5 vs 97.8	54.7	1.6, 107.7	0.04
		BDA MDI 160/180 (N=193) vs Placebo MDI (N=192)	251.8 vs 97.8	154.0	101.3, 206.6	<0.01
		BDA MDI 160/180 (N=193) vs BD MDI 160 (N=194)	251.8 vs 174.6	77.2	24.8, 129.6	<0.01
Change from baseline in trough FEV1 (mL) at Week 12	≥4 - <12	BDA MDI 80/180 (N=3) vs Placebo MDI (N=3)	85.9 vs 209.2	-123.3	-1942.6, 1695.9	0.82
		BDA MDI 80/180 (N=3) vs AS MDI 180 (N=4)	85.9 vs 273.4	-187.5	-2410.9, 2035.9	0.79
	≥12 - <18	BD MDI 160 (N=5) vs Placebo MDI (N=4)	178.5 vs -24.7	203.2	-534.4, 940.8	0.58
		BDA MDI 160/180 (N=4) vs Placebo MDI (N=4)	511.6 vs -24.6	536.2	-236.9, 1309.3	0.17
		BDA MDI 160/180 (N=4) vs AS MDI 180 (N=5)	511.6 vs 112.8	398.8	-220.8, 1018.3	0.19
		BDA MDI 80/180 (N=7) vs Placebo MDI (N=4)	98.6 vs -24.6	123.2	-506.5, 752.9	0.69
		BDA MDI 80/180 (N=7) vs AS MDI 180 (N=5)	98.6 vs 112.8	-14.3	-548.2, 519.7	0.96
	≥18	BD MDI 160 (N=194) vs Placebo MDI (N=192)	105.2 vs 35.8	69.5	0.2, 138.8	0.049
		BDA MDI 160/180 (N=193) vs Placebo MDI (N=192)	126.1 vs 35.8	90.4	21.0, 159.7	0.01
		BDA MDI 160/180 (N=193) vs AS MDI 180 (N=191)	126.1 vs -2.7	128.8	59.1, 198.5	<0.01
		BDA MDI 80/180 (N=194) vs Placebo MDI (N=192)	127.8 vs 35.8	92.0	22.3, 161.8	0.01
		BDA MDI 80/180 (N=194) vs AS MDI 180 (N=191)	127.8 vs -2.7	130.5	60.4, 200.6	<0.01

Source: Statistical Reviewer, adre.xpt.
AS, A buterol 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
In each age subgroup, the dual-primary endpoints were modelled separately using a repeated measures model with baseline FEV1, percentage revers bility 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. If the procedure did not converge, then a compound symmetric variance covariance matrix was used instead.

3. DENALI SAP

Analysis Population and Estimand

The full analysis set (FAS) was defined as all subjects who are randomized, take at least one inhalation of randomized treatment and have at least one efficacy assessment. Subjects were analyzed according to the treatment they were assigned at randomization. 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. The primary analyses of the dual-primary endpoints were on the FAS ≥12 years.

Primary Endpoint Analysis Methods

The primary efficacy analysis comprised dual-primary endpoints of change from baseline in FEV1 $AUC_{0\text{-}6hours}$ over 12 weeks and change from baseline in trough FEV1 at Week 12. Baseline FEV1 was taken as the average of the 60- and 30-minute pre-dose spirometry measures on or before randomization. FEV1 $AUC_{0\text{-}6\ hours}$ was calculated for the changes from the baseline using the trapezoidal rule and was normalized by dividing by the time from dosing to the last measurement included (typically 360 minutes; 10 post-dose FEV1 measures 5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes in each visit) . At each of the post-randomization visits, trough FEV1 was taken as the average of the 60-and 30-minute predose spirometry measures prior to dosing of randomized treatment.

The dual-primary endpoints 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.

Sensitivity/Robustness Analyses

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). Then clinical plausibility of penalty imposed to the missing data at the tipping point where statistical significance is lost is evaluated for robustness of data.

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:

4. BD MDI 160 µg QID vs Placebo MDI QID
5. BDA MDI 160/180 µg QID vs Placebo MDI QID
6. 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 mcg, as shown below:

Change from baseline in trough FEV1 at Week 12:

7. BDA MDI 80/180 µg QID vs Placebo MDI QID
8. 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).

4. DENALI Safety

The most common AEs in DENALI are summarized in Table , and included nasopharyngitis, headache, gastrointestinal symptoms, and upper respiratory tract infection, all of which are known risks associated with ICS or SABA. The incidences of AEs were relatively balanced between treatment arms, with the biggest difference occurring between nasopharyngitis in BDA 160/180 compared to other arms. No new safety concerns were identified based on these results.

Table E. DENALI, Most Common (>2%) Adverse Events During the Randomized Treatment Period, by Preferred Term (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)
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, adae.xpt, adsl.xpt.

Table F summarizes AEs in pediatric subjects during the randomized treatment period of DENALI. As previously mentioned, the total incidence was low. Most AEs were mild to moderate in intensity and none were associated with treatment discontinuation. The only SAE (an asthma exacerbation) was also the AE attributed to randomized treatment. Based on these data, no new safety signals were identified.

Table F. 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
AE	≥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

Source: Clinical Reviewer. OCS Analysis Studio. Custom table tool, adsl.xpt, adae.xpt

6.6 Appendix: Bayesian Analysis

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[4] 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

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

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 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

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

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

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

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

Schmidli et al.[5] provide formulas proportional to the likelihoods in equation [A.2] to calculate $p\left(M_{inform}|y\right)$.

(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.

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

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.,[6] 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. 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

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

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

[5] Schmidli H, Gsteiger S, Roychoudhury R, O'Hagan A, Spiegelhalter D, Neunschwander B. Robust meta analytic predictive priors in clinical trials with historical control information. Biometrics 2014;70:1023-1032. DOI: 10.1111/biom.12242

[6] Best N, Price RG, Pouliquen IJ, Keene ON. Assessing efficacy in important subgroups in confirmatory trials: An example using Bayesian dynamic borrowing. Pharmaceutical Statistics 2021;20:551-562. DOI: 10.1002/pst.2093

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.[7] 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.[8]

[7] Neunschwander B, Weber S, Schmidli H, O'Hagan A. Predictively consistent prior effective sample sizes. Biometrics 2020:76:578-587. https://doi.org/10.1111/biom.13252

[8] Weber, S, Li Y, Seaman III JW, Kakizume T, Schmidli H. Applying meta-analytic-predictive priors with the R Bayesian evidence synthesis tools. Journal Statistical Software. 2021:100;1-32. https://doi.org/10.18637/jss.v100.i19