PULMONARY AND ALLERGY DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

BUDESONIDE/ALBUTEROL SULFATE METERED DOSE INHALER

INDICATION: 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

MEETING DATE: NOVEMBER 8, 2022

ADVISORY COMMITTEE MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Definition
ACQ-5	Asthma Control Questionnaire 5-item
ACQ-7	Asthma Control Questionnaire 7-item
AE	adverse event
AQLQ+12	Asthma Quality of Life Questionnaire for 12 years and older
AS	albuterol sulfate
$AUC_{0\text{-}6\ hours}$	area under the curve from time 0 to 6 hours
BD	budesonide
BDA	budesonide/albuterol sulfate
BID	twice daily
CI	confidence interval
COVID-19	coronavirus disease 2019
ECT	exercise challenge test
ED	emergency department
EIB	exercise-induced bronchoconstriction
EOP2	end of Phase 2
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
HFA	hydrofluoroalkane
HR	hazard ratio
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IL	interleukin
IND	Investigational New Drug
IP	investigational product
iPSP	initial Pediatric Safety Plan
IQR	interquartile range
LABA	long-acting β2 agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
LTRA	leukotriene receptor antagonist
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MCID	minimal clinically import difference

Abbreviation or Special Term	Definition
MDI	metered dose inhaler
Min	minimum
NAEPP	National Asthma Education and Prevention Program
NDA	New Drug Application
OCS	oral corticosteroid
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PK	pharmacokinetic(s)
PRN	as needed
PT	preferred term
pt-yrs	patient-years
QID	4 times daily
R	randomization
RLD	reference listed drug
RR	rate ratio
SABA	short-acting β2 agonist
SAE	serious adverse event
SCS	systemic corticosteroid
SD	standard deviation
SE	standard error
SEE	severe exacerbation event
US	United States

1.0 EXECUTIVE SUMMARY

1.1 Introduction

Bond Avillion 2 Development LP (hereafter Sponsor) and AstraZeneca (co-development partner) are seeking marketing approval of budesonide/albuterol sulfate (BDA) metered dose inhaler (MDI). BDA MDI is a first-in-class, fixed-dose combination of 2 active components: albuterol, a short-acting β2 agonist (SABA) that provides rapid relief of asthma symptoms, and budesonide, an inhaled corticosteroid (ICS) that treats airway inflammation, the underlying cause of asthma worsening. In the United States (US), both albuterol and budesonide have been approved and used in patients with asthma for >25 years.

Severe asthma exacerbations are associated with significant morbidity and mortality, occur in patients across the disease severity spectrum, and continue to be a substantial unmet need in many asthma patients.[1] The totality of data summarized in this briefing document demonstrates the efficacy and safety of BDA MDI used as needed, resulting in a favorable benefit-risk assessment.

1.2 Proposed Indication and Dose

Indication and usage	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.
Recommended dosage and administration	• *Adults and adolescent patients 12 years of age and older:* The recommended dose of [TRADENAME] is albuterol 180 µg and budesonide 160 µg (administered as 2 inhalations of [TRADENAME] [albuterol/budesonide 90 µg/80 µg]) as needed by oral inhalation. The proposed maximum daily dose frequency is 6 doses (12 inhalations) in a 24-hour period. • *Pediatric patients 4 to 11 years of age:* The recommended dose of [TRADENAME] is albuterol 180 µg and budesonide 80 µg (administered as 2 inhalations of [TRADENAME] [albuterol/budesonide 90 µg/40 µg]) as needed by oral inhalation. The proposed maximum daily dose frequency is 6 doses (12 inhalations) in a 24-hour period.

1.3 Disease Background and Unmet Need

Asthma is a common, heterogeneous disease with significant prevalence and imposes a considerable burden on patients and the healthcare system. Despite significant therapeutic advances in asthma treatment in recent years, exacerbations are present across the disease severity spectrum, and more than 50% of patients have uncontrolled asthma.[2] In fact, more patients with mild asthma have ≥1 severe exacerbation annually than patients with moderate to severe asthma.[2] This corresponds to a high rate of emergency department (ED) visits for asthma in the US, particularly in the pediatric population, that has remained relatively stable over the past decade.[3,4] Consistent with these data, asthma deaths in the US have remained constant since 2007: on average, 3000 to 4000 deaths per year.[5,6] Nearly all asthma-related deaths are avoidable with appropriate treatment and care.

Exacerbations also lead to increased use of systemic corticosteroids (SCS), which is associated with significant side effects, including adverse cardiovascular outcomes, type 2 diabetes, cataracts, glaucoma, osteoporosis, pneumonia, depression and anxiety, and renal impairment.[7-9] The risk of

these adverse outcomes has been shown to increase in a dose-dependent manner, with increasing cumulative exposure, with thresholds for harm being quite low at 500 to <1000 mg cumulative SCS exposure, equivalent to 4 short SCS courses over a lifetime.[8] This is an unacceptable level of exposure and risk, and there is a call to action regarding increased oral corticosteroid (OCS) stewardship in asthma care.[10]

SABAs remain the most commonly prescribed asthma medications and were first used for asthma care nearly 70 years ago. At the time, asthma was thought to be a disease of bronchoconstriction. However, it is now recognized that asthma is associated with both inflammation and bronchoconstriction.[11] ICSs were first approved in 1981 and are highly effective at preventing asthma deaths. Yet, these medications are underutilized.

In 2019, a fundamental change occurred in the Global Initiative for Asthma (GINA) strategy and treatment of asthma with SABAs alone was no longer recommended for adults and adolescents.[12] The most recent versions of GINA and National Asthma Education and Prevention Program (NAEPP; US guidelines) for all patients ≥12 years of age reflect the data on ICS-containing reliever approaches and recommend the addition of ICSs to rescue treatment.[1,13] Numerous published studies have demonstrated the use of fast-acting bronchodilators (such as formoterol) with ICSs as rescue to be superior to SABAs alone in reducing exacerbation risk.[14-20] This has been observed across the asthma severity spectrum regardless of background maintenance therapy.

In the US, there are several monotherapy products that contain either a SABA or ICS, the latter of which is only approved for maintenance use; however, there is currently no product that combines both components in a single inhaler.

1.4 BDA MDI Development Rationale

The use of a fixed-dose combination of the ICS budesonide and albuterol (BDA) in an MDI would be consistent with the clinical guidelines and is intended to replace current SABA rescue use in clinical practice. The rationale for BDA MDI is based on the provision of rapid relief of asthma symptoms by albuterol while simultaneously treating underlying inflammation with budesonide, working together to improve asthma symptoms. The SABA binds to β2-adrenergic receptors and relaxes airway smooth muscle,[21] while the ICS has relatively rapid nongenomic effects (eg, amplifies β2-agonist-induced bronchodilation, decreases bronchial vascular blood flow, suppresses immune mediators)[22-24] together with genomic effects (eg, increases anti-inflammatory gene transcription, decreases proinflammatory gene transcription, increases β2-receptor gene transcription).[22,25] BDA MDI would provide an important new option for treating and managing asthma. At a population level, the opportunity exists to reduce the considerable burden of asthma exacerbations evident across the spectrum of asthma severity today.

1.5 BDA MDI Clinical Development Program

The BDA MDI clinical development program includes 9 clinical studies: 3 Phase 1 studies, 3 Phase 2 studies, and 3 Phase 3 studies. The Phase 1 and Phase 2 studies:

- Established scientific bridging for BDA MDI to the reference listed drugs (both of which have been approved for >25 years in the US) for the 505(b)(2) application.
- Supported dose selection of the mono-components budesonide and albuterol.

- Provided the required pharmacokinetic (PK) and pharmacodynamic data for albuterol in the MDI device.

The Phase 3 studies, AV003 (MANDALA), AV004 (DENALI), and AV005 (TYREE), met their primary endpoints and therefore support the New Drug Application.

- MANDALA was designed to evaluate the reduction of severe asthma exacerbations reflecting the intended as-needed use of BDA MDI.
- DENALI was designed to demonstrate the contribution of both budesonide and albuterol mono-components to the lung function efficacy of BDA MDI in order to satisfy the US Food and Drug Administration (FDA) Combination Rule (21 CFR 300.50).[26]
- TYREE was designed to evaluate whether prophylactic use of BDA MDI before exercise could prevent bronchoconstriction in patients with asthma and exercise-induced bronchoconstriction (EIB).

1.5.1 Summary of Clinical Efficacy

1.5.1.1 Phase 3 Study: MANDALA

Study Design and Methods

MANDALA was an event-driven exacerbation study in which each patient was treated for ≥24 weeks. A total of 3132 patients ≥4 years of age were randomized. Patients ≥12 years of age were randomized (1:1:1) to receive BDA MDI with 160 µg budesonide and 180 µg albuterol (BDA MDI 160/180), BDA MDI with 80 µg budesonide and 180 µg albuterol (BDA MDI 80/180), or 180 µg albuterol (AS MDI 180), while children 4 to 11 years of age were randomized (1:1) to BDA MDI 80/180 or AS MDI 180. All treatments were administered as needed and the maximum allowed number of inhalations was 12 per 24 hours. Patients were required to be receiving medium- to high-dose ICS or low- to high-dose ICS/long-acting β2 agonists (LABAs), with or without another controller medicine as maintenance therapy. All patients continued their own maintenance therapy throughout the study. MANDALA was conducted in symptomatic patients with moderate to severe asthma, a history of ≥1 severe asthma exacerbation in the year prior to screening, prebronchodilator forced expiratory volume in 1 second (FEV_1) 40% to <90% of predicted normal, and confirmed reversibility to albuterol. See Section 6.1.1 for details.

Demographics and Baseline Characteristics

In MANDALA, approximately two-thirds of the study population was female, and the mean age was 49 years. The mean prebronchodilator percent predicted FEV_1 was 64% (range, 33% to 112%). See Section 6.1.3 for details.

Efficacy Results

Exacerbation Endpoint Results

The primary efficacy endpoint of MANDALA was the time to first severe asthma exacerbation (defined as worsening or onset of asthma symptoms that required SCSs for ≥3 days or ED visit that led to SCS use for ≥3 days or hospitalization for ≥24 hours due to asthma). Treatment comparisons for BDA 160/180 versus AS MDI 180 were made in the ≥12 years subpopulation of the Full Analysis Set (FAS), and treatment comparisons for BDA MDI 80/180 versus AS MDI 180 were made in the FAS all ages population.

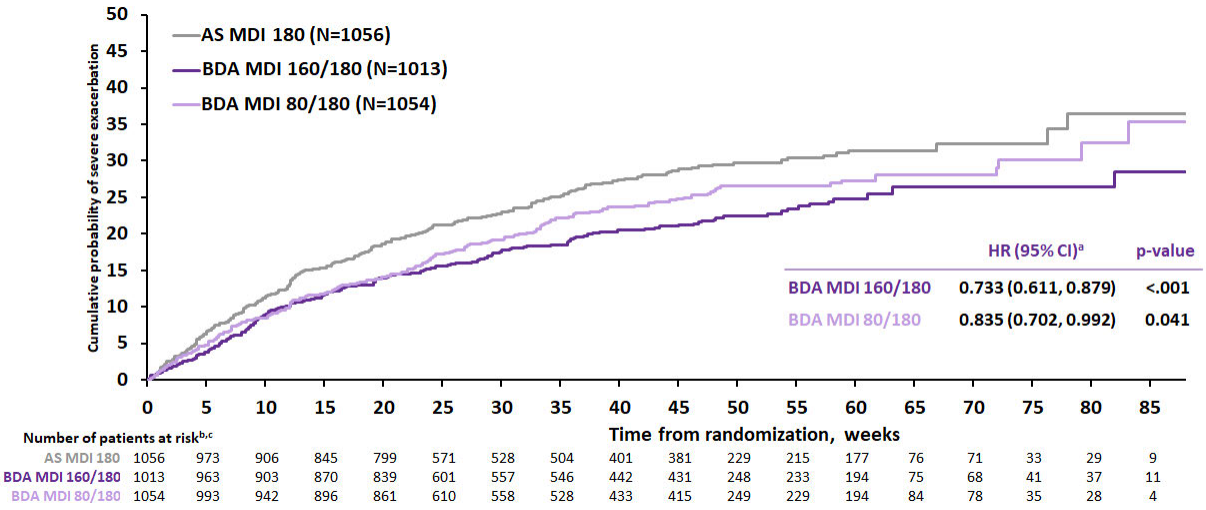
MANDALA met its primary endpoint for both BDA MDI doses. In patients ≥12 years of age, BDA MDI 160/180 demonstrated a statistically significant reduction of 27% in the risk of severe asthma exacerbations, compared with AS MDI 180 (hazard ratio [HR] 0.733; 95% confidence interval [CI], 0.61, 0.88; *P*<0.001). This was supported by a statistically significant and clinically meaningful 24% reduction in the annualized rate of severe asthma exacerbations (rate ratio 0.76 [95% CI, 0.62, 0.93; *P*=0.008]). There was also a statistically significant difference in annualized total SCS exposure compared with AS MDI, with a 33% reduction in mean annualized total SCS dose (mg/patient) relative to AS MDI (*P*=0.002).

In patients of all ages, BDA MDI 80/180 demonstrated a statistically significant reduction of 17% in the risk of severe asthma exacerbations, compared with AS MDI 180 (HR 0.835; 95% CI, 0.70, 0.99; *P*=0.041). This was supported by a statistically significant 20% reduction in the annualized rate of severe asthma exacerbations (risk ratio 0.80 [95% CI, 0.66, 0.98; *P*=0.028]) and a reduction of 25% in mean annualized total SCS dose (mg/patient) compared with AS MDI, although the comparison between treatments was not statistically significant (*P*=0.060).

The reverse Kaplan-Meier plot of time to first severe exacerbation shows an early onset of treatment effect with both doses of BDA MDI, which was maintained over time (**Figure A**). See Section 6.1.4.1 for details.

See Section 6.1.4.2 for details on all secondary endpoints.

Figure A Time to First Severe Asthma Exacerbation During the Randomized Treatment Period (Full Analysis Set; All Ages) – MANDALA



Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; HR = hazard ratio; MDI = metered dose inhaler.

[a] Comparisons of AS MDI 180: vs BDA MDI 160/180 is in patients ≥12 years of age; vs BDA MDI 80/180 is in patients ≥4 years of age.

[b] Curve truncated when <1% of patient population remained at risk.

[c] The number of patients at risk includes all ages, 4 years of age and older.

Reductions in severe asthma exacerbation risk were consistent with the BDA MDI treatment effect regardless of sex, adult age group, race (not prespecified), severe exacerbation history, smoking history, region, maintenance therapy, and baseline lung function (Figure 9).

Pattern of Use

Patients did not use treatments on a regular daily basis, but varied use in response to symptoms. On the majority of study days, patients used ≤2 inhalations; ≥8 inhalations were used on <2% of study days (Figure 10).

1.5.1.2 Phase 3 Study: DENALI

Study Design and Methods

DENALI was a 12-week lung function study including a total of 1000 patients with mild to moderate asthma. Patients ≥12 years of age were randomized 1:1:1:1:1 to receive BDA MDI 160/180, BDA/MDI 80/180, 160 µg budesonide (BD MDI 160), AS MDI 180, or placebo MDI, all administered 4 times daily (QID). Children 4 to 11 years of age were randomized 1:1:1 to receive BDA MDI 80/180, AS MDI 180, or placebo MDI, all administered QID. Patients were previously being treated with as-needed SABA alone or with low-dose ICS maintenance therapy plus as-needed SABA. Patients did not continue their previous background treatment during the study. At screening, patients had a prebronchodilator FEV_1 of ≥50% to <85% predicted normal value for patients ≥18 years of age and ≥50% predicted normal value for patients 4 to 17 years of age. All patients were required to demonstrate reversibility to albuterol. The results of the endpoints are presented for patients ≥12 years of age. See Section 6.2.1 for details.

Demographics and Baseline Characteristics

In DENALI, 62% of the study population was female, and the mean age was 49 years. The mean prebronchodilator percent predicted FEV_1 was 69% (range, 26% to 132%). See Section 6.2.3 for details.

Key Efficacy Results

The dual primary endpoints (change from baseline in FEV_1 area under the curve from time 0 to 6 hours [$AUC_{0\text{-}6\ hours}$] over the 12-week treatment period and change from baseline in trough FEV_1 at Week 12) were met, demonstrating the contribution of both mono-components to BDA MDI efficacy and thereby satisfying the FDA Combination Rule (21 CFR 300.50).[26]

For FEV_1 $AUC_{0\text{-}6\ hours}$, BDA MDI 160/180 showed significantly greater improvement compared with BD MDI 160 (81 mL; 95% CI, 28, 133; P=0.003; Table 13). For trough FEV_1, both doses of BDA MDI showed significantly greater improvements compared with AS MDI 180 (BDA MDI 160/180: 133 mL; 95% CI, 64, 202; P<0.001 and BDA MDI 80/180: 121 mL; 95% CI, 52, 190; P<0.001). See Section 6.2.4 for details.

1.5.1.3 Phase 3 Study: TYREE

Study Design and Methods

TYREE was a single-dose, crossover study of BDA MDI 160/180 versus placebo MDI. Sixty patients aged ≥12 years with asthma and EIB (defined by a ≥20% decrease from pre-exercise challenge best FEV_1 observed within 60 minutes after an exercise challenge) were enrolled, of whom 30 patients received SABA alone as needed (non-ICS arm) and 30 patients received SABA as needed plus low to medium doses of ICS (ICS arm). Patients underwent exercise challenge tests at 2 separate visits. See Section 6.3.1 for details.

Key Efficacy Results

When BDA MDI 160/180 or placebo MDI was taken 30 minutes prior to exercise, the mean maximum percent reduction from postdose, pre-exercise challenge FEV_1 in the overall population was 5.5% and 19.0%, respectively (Figure 16). Additionally, 78.3% of patients were fully protected from EIB when dosed with BDA MDI 160/180 versus 28.3% of patients treated with placebo MDI. Similar effects were seen in the subgroups of patients on SABA alone and ICS maintenance with as-needed SABA. See Section 6.3.4 for details.

1.5.1.4 Efficacy Conclusions

In MANDALA, both doses of BDA MDI used as needed resulted in statistically significant and clinically meaningful reductions in severe exacerbation risk and rate in the overall population. BDA MDI 160/180 resulted in a statistically significant reduction in annualized SCS exposure compared with AS MDI 180. In DENALI, both budesonide and albuterol components demonstrated contribution to BDA MDI efficacy. In TYREE, BDA MDI taken before an exercise challenge test was shown to be effective in protecting patients with asthma and EIB from bronchoconstriction.

1.5.2 Summary of Clinical Safety

Both budesonide and albuterol have been approved and used in patients with asthma for >25 years. There were no signals of any new safety issues, both from MANDALA where the drug was used as needed or from DENALI where the drug was administered chronically at a high dose for 12 weeks. The focus of the safety presentation in this executive summary is on MANDALA, which represents the intended as-needed use of BDA MDI. See Section 7.0 for safety data from DENALI and TYREE.

1.5.2.1 Exposure

In MANDALA, the overall mean duration of exposure to randomized treatment was approximately 300 days and comparable across the 3 treatment groups (Table 20). The mean number of inhalations of randomized treatment during the treatment period was comparable across the treatment groups (2.6 to 2.8 inhalations per day).

1.5.2.2 Overview of Adverse Events

In MANDALA, the frequency of adverse events (AEs) and serious AEs (SAEs) were similar across the treatment groups (**Table A**). Less than 50% of patients had a report of any AE. The 3 most commonly reported AEs were nasopharyngitis, headache, and coronavirus disease 2019 (COVID-19). The proportion of patients with an AE causally related to randomized treatment or with an AE leading to discontinuation of investigational product (IP) was low (≤1%) and similar across the groups.

SAEs were reported in 4% to 5% of patients. None of these were considered related to randomized treatment. The most commonly reported SAEs were in the system organ classes of infections and infestations and the majority of these events were COVID-19 related; there were no imbalances across the treatment groups.

Seven fatal events were reported: 4 were COVID-19 related (2 with BDA MDI 160/180 and 1 each with BDA MDI 80/180 and AS MDI 180) and 3 were reported as elevated glucose and cardiac

arrest (both with BDA MDI 160/180) and lung metastases (with BDA MDI 80/180). None of the deaths were considered to be IP-related and none were adjudicated as asthma related.

Table A MANDALA Overview of Adverse Events (Safety Analysis Set)

Category	Number (%) of Patients[a]		
	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[b]	21 (2.1)	20 (1.9)	16 (1.5)
Any AE leading to discontinuation of IP	10 (1.0)	9 (0.9)	9 (0.9)
Any SAE	53 (5.2)	40 (3.8)	48 (4.5)
Any AE with outcome of death	4 (0.4)	2 (0.2)	1 (0.1)

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; IP = investigational product; MDI = metered dose inhaler; SAE = serious adverse event.

[a] Patients with multiple events in the same category were only counted once in that category. Patients with events in more than 1 category were counted once in each of those categories.

[b] As assessed by the investigator.

1.5.2.3 Safety Related to Additional ICS Exposure

Adverse Events by Dose Category of Background Maintenance ICS

In MANDALA, patients were required to continue their asthma background maintenance treatment, and patients were analyzed by 3 different categories of background maintenance ICS according to GINA recommendations: low-, medium-, and high-dose ICS. Exposure to IP was similar across these subgroups (Table 30). There were >200 patients in each subgroup. The percentages of patients with any AE in the different background maintenance ICS categories were similar to the overall population and also similar across the treatment groups in each category.

Adverse Events by Mean Daily IP Use

Patients were also evaluated within different categories of mean daily IP use. The mean daily IP use was low (ie, the majority of patients had mean daily use of >0 to <3 inhalations per day; Table 29). Across the analyzed categories of mean daily IP use, the percentages of patients with AEs in the different treatment groups were similar. A detailed review of these data showed a consistent AE profile across the treatment groups and did not show new safety concerns.

1.5.2.4 Systemic or Local ICS-Associated Adverse Events

In MANDALA, the number of patients with any systemic ICS-associated AE was low and comparable across the treatment groups (range, 3.2% to 3.8%). Selected preferred terms for adrenal disorders, diabetes and glucose disorders, and ocular and skeletal disorders were generally comparable across the treatment groups.

The number of patients with any local ICS-associated AE was low and also generally comparable across the treatment groups (range, 1.3% to 2.0%), with the exception of a slightly higher number of patients with oral and oropharyngeal candidiasis, which are well known local AEs for ICS, in the BDA MDI groups.

1.5.2.5 Safety Conclusions

The overall safety profile of BDA MDI is consistent with the well-established safety profiles of budesonide and albuterol in all age groups with asthma across all severities, and no new safety signals were identified. The safety findings from MANDALA are considered representative of real-world, as-needed use and long-term exposure of ≥24 weeks in asthma patients on maintenance therapy. In MANDALA, the frequency of systemic or local ICS-associated AEs was low and there were similar percentages of patients with AEs irrespective of maintenance ICS or frequent daily use across the treatment groups.

1.5.3 Summary of Clinical Efficacy and Safety in Pediatric Populations

Efficacy in Pediatric Populations

Both the Agency and Sponsor recognize the scientific rationale for extrapolating the overall efficacy findings in MANDALA to the pediatric subgroups to better understand potential effects of BDA MDI compared with albuterol. GINA and NAEPP asthma guidelines use similar principles to guide diagnosis, assessment, and treatment strategies of asthma across the ages.[1] This is based on the broadly similar airway inflammation and bronchoconstriction during exacerbations,[27] immunopathology and disease characteristics,[28] and asthma biology across the age subgroups. Although there are some differences between children and adults with asthma, there is sufficient scientific justification for extrapolation of adult findings to pediatric populations.[29] In addition, the same endpoints are used to measure efficacy in asthma clinical trials across all ages. Furthermore, budesonide/formoterol rescue studies conducted outside of the US demonstrate similar treatment effects across adults, adolescents, and children.[30] Therefore, it is reasonable to expect that the efficacy of BDA MDI is similar across all ages. Finally, when adult data are available in conditions that exist in both adults and children, evidence of clinical benefit from the drug in adults can provide support for the prospect of direct benefit in children,[31] as is the case in asthma.

The FDA requested we include small numbers of children aged 4 to 11 years in the BDA MDI Phase 3 program. The limited number of patients (100 adolescents [≥12 to <17 years of age] and 83 children [≥4 to <11 years of age]) in MANDALA precluded meaningful statistical inference of treatment benefits. However, modeling using a Bayesian approach[32] across age and dose groups indicated a point estimate in favor of BDA MDI for the primary endpoint in pediatric subpopulations (Figure 21). See Section 8.1 for details on clinical efficacy results and refer to Section 8.3 for details on the Bayesian analysis.

Safety in Pediatric Populations

Overall, BDA MDI was well tolerated with no new safety findings, and was consistent with the well-known profiles of budesonide and albuterol. There was no clinically important increase in AEs in pediatric patients with BDA MDI compared with AS MDI. See Section 8.2 for details on clinical safety results.

1.6 Benefit-Risk Assessment

Asthma can impose a significant burden on patients across age groups, and the risk of severe asthma exacerbations is associated with increased use of SCS and significant morbidity and mortality. Asthma exacerbations are caused by increased inflammation, and use of SABA alone does not adequately address the underlying pathophysiologic inflammatory process. Published data led to revisions in clinical practice guidelines to recommend as-needed co-administration of

an ICS with a fast-acting bronchodilator used as rescue to prevent exacerbations. The combination of budesonide and albuterol in BDA MDI administered as needed provides rapid relief of asthma symptoms through bronchodilation while simultaneously treating increasing underlying inflammation. MANDALA demonstrated that as-needed BDA MDI prevents asthma exacerbations and significantly reduces the associated SCS use. The overall safety profile of BDA MDI is consistent with the well-established safety profiles of budesonide and albuterol in all age groups across all asthma severities, and no new safety concerns were identified. The Phase 3 program demonstrated a positive benefit-risk profile for BDA MDI. The totality of the data supports the proposed indication of BDA MDI 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.

2.0 DISEASE BACKGROUND AND UNMET NEED

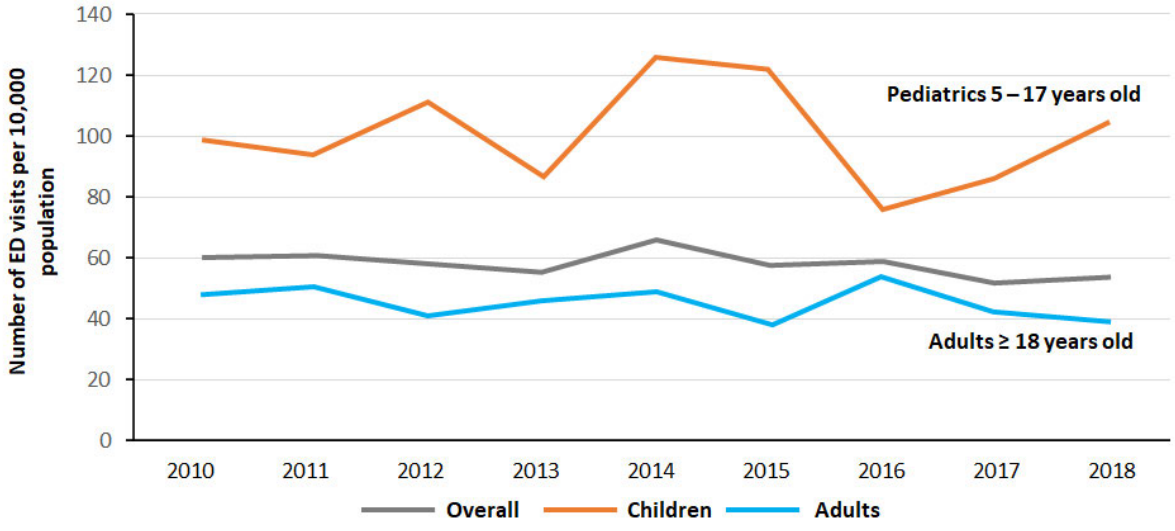
2.1 Overview of Asthma and Exacerbations

Asthma is a chronic disease of the airways and is characterized by underlying inflammation leading to a variety of respiratory symptoms, including shortness of breath, wheezing, chest tightness, and cough, and expiratory airflow limitation, which may later become persistent.[33-36] Symptoms and bronchoconstriction vary over time and in intensity and are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or respiratory infections. These symptoms and airflow limitation may resolve spontaneously or in response to medication, or symptoms may develop into a severe exacerbation, asthma exacerbation, requiring treatment, acute care visits, and hospitalization.

Asthma is a common disease and in the United States (US), approximately 25 million individuals are living with asthma, with 1 in 10 children diagnosed with asthma.[37,38] A significant burden of disease exists across the age spectrum. Asthma is the main reason for missing school, with 13.8 million days missed annually.[38] Adults with asthma miss a similarly staggering number of days of work (14.2 million work days per year), costing the US economy an estimated $80 billion annually.[38] Most people with asthma (3 in 5) limit their physical activity,[38] leading to other related health conditions that can be attributed to a sedentary lifestyle.

Despite significant therapeutic advances in asthma treatment in recent years, asthma exacerbations occur across the spectrum of disease severity, and more than half of patients in the US have uncontrolled asthma.[2] In fact, annually, more patients with mild asthma have ≥1 severe exacerbation than those with moderate or severe asthma.[2] This corresponds with a high rate of emergency department (ED) visits for asthma in the US, which has remained relatively stable over the past 10 years (Figure 1).[3,39] As illustrated, the number of ED visits is highest in the pediatric population.[3,4]

Figure 1 Asthma Emergency Department Visit Rate by Age Group



Abbreviation: ED = emergency department.
ED visit rate: Crude ED visit rate per 10,000 population.
Age group: Child, persons aged 17 years and younger; adult, persons aged 18 years and older.
Sources: CDC. National health care use. 2018[39] and CDC. Asthma attacks. 2021.[3]

Consistent with these data, asthma deaths in the US have remained constant since 2007: on average, 3000 to 4000 deaths per year. In 2020, 4145 people died from asthma.[5,6] Nearly all asthma-related deaths are avoidable with appropriate treatment and care. A medical need exists to improve asthma morbidity and mortality rates.

2.2 Burden of Systemic Corticosteroids

Systemic corticosteroids (SCSs) became available in 1956, and their introduction provided effective treatment for control of asthma symptoms and exacerbations.[22,40] However, their common use led to the recognition that SCSs are associated with significant side effects, including adverse cardiovascular outcomes, type 2 diabetes, cataracts, glaucoma, osteoporosis, pneumonia, depression and anxiety, and renal impairment in adults.[7-9] A study by Price and colleagues[8] has changed the thinking about the safety of SCSs. This study showed that the risk of these adverse outcomes increases in a dose-dependent fashion with increasing cumulative exposure, with thresholds for harm being quite low at 500 to <1000 mg cumulative SCS exposure, equivalent to 4 short SCS courses over a lifetime.[8]

SCSs are also associated with significant adverse effects in both adolescents and children. A recent retrospective population study evaluating patients younger than 18 years of age found that one course of SCSs used for up to 14 days was associated with a 1.4- to 2.2-fold increase risk of gastrointestinal bleeding, sepsis, and pneumonia within the first month after dosing.[41] In a metanalysis, vomiting and mood swings/behavioral issues/sleep disturbance were most common adverse drug reactions after short course SCS.[42]

2.3 Current Treatment of Asthma and Unmet Need

Short-acting β2 agonists (SABAs) remain the most commonly prescribed medications for asthma, and were discovered and first used for asthma care nearly 70 years ago, with the advent of isoproterenol and epinephrine. It is notable that at the time asthma was thought to be a disease of bronchoconstriction. The understanding of asthma pathogenesis has advanced significantly, and it is now recognized that asthma is associated with both inflammation and bronchoconstriction.[11] Inhaled corticosteroids (ICSs) were first approved in 1981 and are highly effective at reducing asthma mortality,[43] with a 21% reduction in the rate of death from asthma with each additional canister used.[44] Yet, these medications are underutilized.

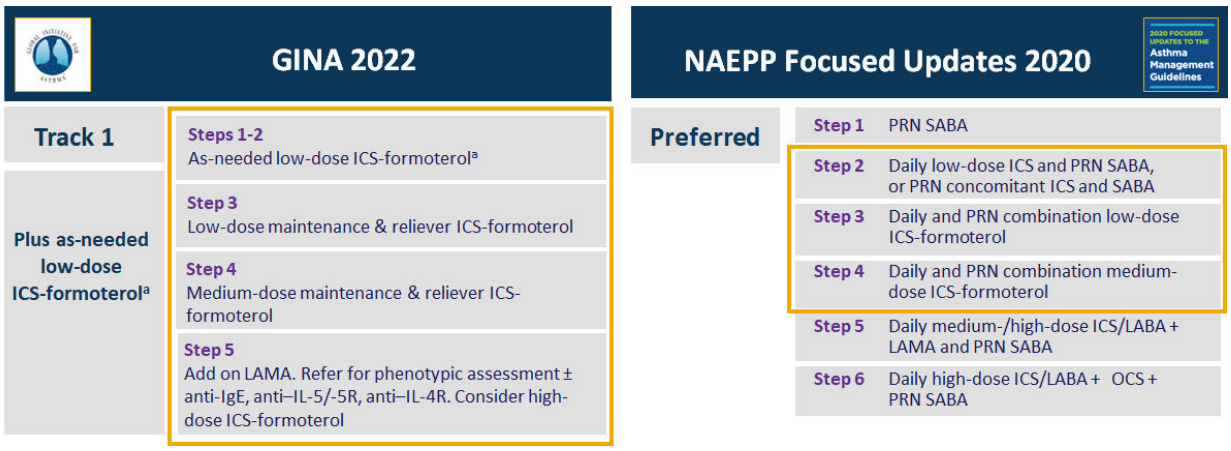
To help understand why ICS therapies are underutilized, it may be important to consider how patients with asthma view their inhalers. Data from the global INSPIRE study, which examined the attitudes and actions of 3415 patients aged ≥16 years with physician-confirmed asthma prescribed regular maintenance therapy with ICSs or ICSs + long-acting β2 agonists (LABAs), showed that 38% of patients believed there is no need to take medication daily when they felt well, whereas 90% of patients prioritized treatments that provide immediate relief.[45] These data suggest patient behavior prioritizes quick relief from SABAs when needed. The immediate relief reinforces potentially harmful approaches to acute asthma symptoms. However, regular use of SABAs without accompanying ICSs results in poor asthma control, loss of functional antagonism, enhanced exercise-induced bronchoconstriction (EIB), and increased airway inflammation. This ultimately leads to increased exacerbation frequency and higher mortality rates.

2.4 Paradigm Shift in Asthma Care and Current Guidelines

In 2019, a fundamental change occurred in the Global Initiative for Asthma (GINA) strategy and treatment of asthma, and SABAs alone were no longer recommended for adults and adolescents.[12]

The most recent versions of GINA and National Asthma Education and Prevention Program (NAEPP; US guidelines) for all patients ≥12 years of age reflect the data on ICS-containing reliever approaches and recommend the addition of ICSs to rescue treatment (Figure 2).[1,13] Numerous published studies demonstrate the use of fast-acting bronchodilators (such as formoterol) with ICS to be superior to SABA alone in reducing exacerbation risk.[14-20] This has been observed across the asthma severity spectrum regardless of background maintenance therapy.

Figure 2 Current GINA and NAEPP Recommendations



Abbreviations: GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; LABA = long-acting β2 agonist; NAEPP = National Asthma Education and Prevention Program; OCS = oral corticosteroid; PRN = as needed; SABA = short-acting β2 agonist.

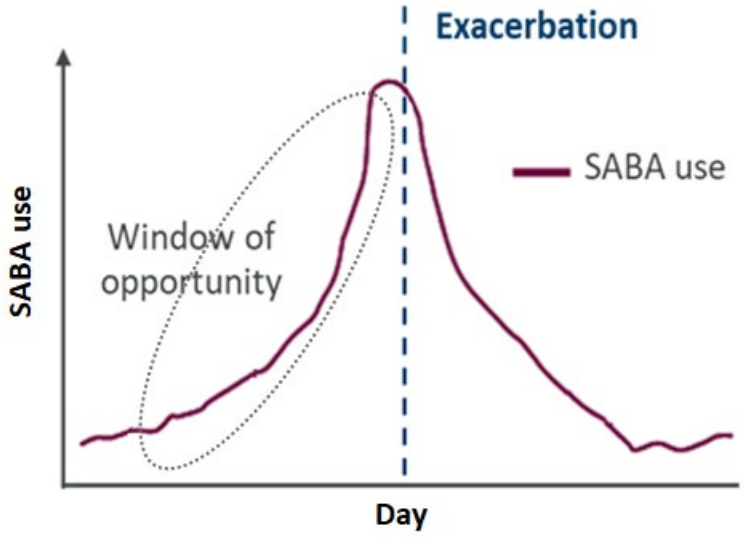
[a] ICS-formoterol should not be used as the rescue therapy by patients who are taking a different maintenance ICS-LABA; for these patients, the appropriate rescue therapy is SABA.

In the US, there are several monotherapy products that contain either a SABA or ICS, the latter of which is only approved for maintenance use; however, there is currently no product that combines both components in a single inhaler.

2.5 Development Rationale for Budesonide/Albuterol Sulfate Metered Dose Inhaler

As described above, a clear rationale exists to change the asthma rescue treatment paradigm. Figure 3 shows that as symptoms increase, SABA use increases in the run-up to an exacerbation.[46] However, there is a period before the exacerbation, a possible "window of opportunity," during which interrupting the rise in inflammation could prevent the peak and resulting exacerbation. As previously described, SABA currently treats the symptoms but does not address the underlying inflammation. The addition of ICS to a fast-acting bronchodilator used as rescue is helpful to treat fluctuating increases in inflammation.

Figure 3 SABA Use Before and After Exacerbations



Abbreviation: SABA = short-acting β2 agonist.
Adapted from Tattersfield AE, et al. *Am J Respir Crit Care Med.* 1999;160:594-599.[46]

The use of a fixed-dose combination of the ICS budesonide and albuterol (BDA) in a metered dose inhaler (MDI) would be consistent with the clinical guidelines and is intended to replace current SABA rescue use in clinical practice. The rationale for BDA MDI is based on the provision of rapid relief of asthma symptoms by albuterol while simultaneously treating increasing underlying inflammation with budesonide, working together to improve asthma symptoms. SABA binds to β2-adrenergic receptors and relaxes airway smooth muscle,[21] while ICS improves lung function within 1 to 4 hours through nongenomic effects (eg, amplifies β2-agonist-induced bronchodilation, decreases bronchial vascular blood flow, suppresses immune mediators)[22-24] together with genomic effects (eg, increases anti-inflammatory gene transcription, decreases proinflammatory gene transcription, increases β2-receptor gene transcription) that occur after about 4 hours and last for up to 24 hours.[22,25] BDA MDI would provide an important new option for treating and managing asthma. At a population level, the opportunity exists to reduce the considerable burden of asthma exacerbations evident across the spectrum of asthma severity today.

3.0 OVERVIEW OF BUDESONIDE/ALBUTEROL SULFATE METERED DOSE INHALER

3.1 Drug Description

Bond Avillion 2 Development LP (hereafter Sponsor) in partnership with AstraZeneca have developed a novel, first-in-class combination drug-device product containing 2 active and previously approved pharmaceutical ingredients, budesonide (40 or 80 µg) and albuterol sulfate (90 µg), in a pressurized MDI (Figure 4).

Budesonide is an anti-inflammatory ICS that exhibits potent glucocorticoid and weak mineralocorticoid activity. First approved by the US Food and Drug Administration (FDA) in 1994, budesonide is indicated for the treatment of asthma, chronic obstructive pulmonary disease, and allergic rhinitis, and as asthma maintenance treatment in patients 12 months of age and older (PULMICORT RESPULES® [budesonide], PULMICORT FLEXHALER® [budesonide]).[47,48] Since launch (in December 1981) to April 30, 2022, the cumulative global postmarketing patient exposure to budesonide (all formulations) has been estimated to be approximately 75.98 million patient-years.[49] Approximately 28,000 patients have been exposed to budesonide in clinical trials, of whom approximately 4000 were aged 4 to 11 years and approximately 1600 were aged 12 to 17 years.[49]

Albuterol is a SABA that induces airway smooth muscle relaxation and reduces or prevents bronchoconstriction. First approved by the FDA in 1981, albuterol is indicated for the treatment and prevention of bronchospasm in patients with reversible obstructive airway disease and for prevention of EIB; both indications are approved in patients 4 years of age and older.[50]

Figure 4 BDA MDI Drug/Device Combination Product

Abbreviations: BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler.

3.2 Proposed Indication and Dose

3.2.1 Indication and Usage

The proposed [TRADENAME] 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.

3.2.2 Recommended Dosage and Administration

Adult and Adolescent Patients 12 Years of Age and Older

The recommended dose of [TRADENAME] is albuterol 180 µg and budesonide 160 µg (administered as 2 inhalations of [TRADENAME] [albuterol/budesonide 90 µg/80 µg]) as needed by oral inhalation. The proposed maximum daily dose allows a frequency of up to 6 doses (12 inhalations) in a 24-hour period.

Pediatric Patients 4 to 11 Years of Age

The recommended dose of [TRADENAME] is albuterol 180 µg and budesonide 80 µg (administered as 2 inhalations of [TRADENAME] [albuterol/budesonide 90 µg/40 µg]) as needed by oral inhalation. The proposed maximum daily dose allows a frequency of up to 6 doses (12 inhalations) in a 24-hour period.

4.0 BDA MDI DEVELOPMENT PROGRAM

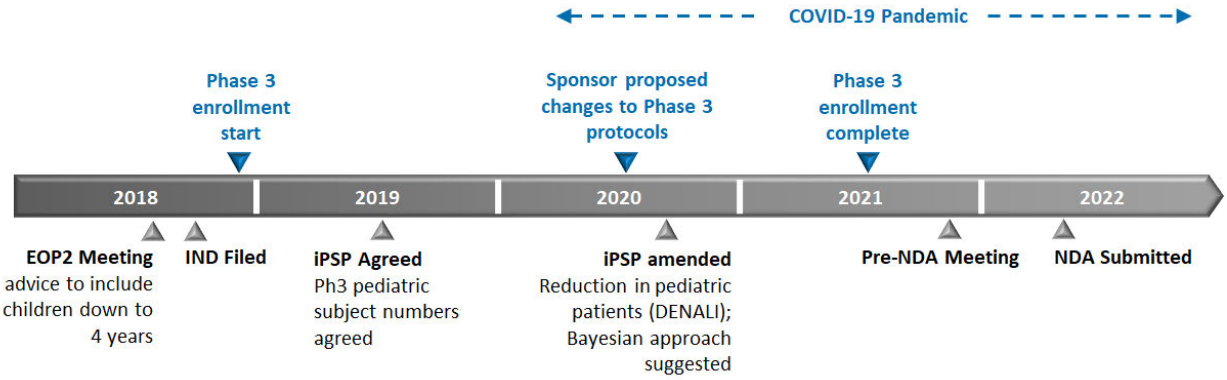
The Sponsor, in discussion with the Agency, designed a comprehensive development program to satisfy the 505(b)(2) requirements (21 CFR 314.54) and the FDA Combination Rule (21 CFR 300.50) for fixed combination dosage form prescription drugs.[26] The 505(b)(2) pathway allows reliance on the FDA's previous findings of safety and efficacy for budesonide and albuterol sulfate, based on pharmacokinetic (PK) assessments in relative bioavailability studies.

4.1 Regulatory History

As a 505(b)(2) application, the Sponsor is relying on information that has been used either for prior approval of the reference listed drugs (RLDs) or is new information obtained by the Sponsor during clinical trials to establish the safety and efficacy of BDA MDI. The FDA required demonstration of bioequivalence to the relevant or corresponding components in the RLDs, as well as Phase 3 studies to demonstrate safety and efficacy.

Regulatory history pertaining to the inclusion of pediatric patients in the Phase 3 program is summarized in Figure 5. The interactions with FDA included guidance in 2018 to include children as young as 4 years of age. The Phase 3 program for BDA MDI started in December 2018 and continued during the coronavirus disease 2019 (COVID-19) pandemic. The initial enrollment targets for adolescents and children were reduced for DENALI, owing to the additional challenges of enrolling pediatric patients during the pandemic. In June 2020, the FDA suggested additional analyses, such as a Bayesian approach based on borrowing efficacy information from the overall population to support efficacy in adolescents. In the pre-New Drug Application (NDA) meeting written response in December 2021, the FDA also suggested that a Bayesian approach[32] could be used to support efficacy determinations in children.

Figure 5 BDA MDI Key FDA Interactions Related to the Pediatric Study Plan



Abbreviations: BDA = budesonide/albuterol sulfate; COVID-19 = coronavirus disease 2019; EOP2 = End of Phase 2; FDA = US Food and Drug Administration; IND = Investigational New Drug; iPSP = initial Pediatric Safety Plan; MDI = metered dose inhaler; NDA = New Drug Application.

4.2 Clinical Development Overview

The primary purpose of the BDA MDI clinical program was to evaluate the safety and efficacy of as-needed administration of BDA MDI, which was expected to reduce symptoms, bronchoconstriction, and airway inflammation, thereby preventing progression to a severe asthma exacerbation requiring treatment with SCS. In addition, the BDA MDI clinical program was to

show the contribution of each component to the overall efficacy of BDA MDI. The global clinical program compared BDA MDI with albuterol in patients with asthma ≥4 years of age.

The BDA MDI asthma clinical development program comprised 9 completed studies, including 3 Phase 3 studies, 3 supportive Phase 2 studies, and 3 Phase 1 PK studies (Table 1).

- The Phase 3 studies MANDALA, DENALI, and TYREE were designed to evaluate the efficacy and safety of BDA MDI in patients with asthma, providing primary support for the proposed indication and satisfying the FDA Combination Rule (21 CFR 300.50).[26] The Phase 3 program included >4000 patients across the asthma disease severity spectrum.
- The supportive Phase 2 ANTORA, ASPEN, and PT008001 studies supported dose selection for the Phase 3 clinical studies (see Section 5.3).
- The Phase 1 LOGAN, ELBRUS, and BLANC studies provided mono-component exposure relative to the dual combination BDA MDI and a bridge to the RLDs.

Table 1 Overview of Clinical Studies in BDA MDI Asthma Development Program

Study Identifier	Design/Purpose	Population	N
Phase 3 Studies			
AV003 (MANDALA; D6930C00005)	Randomized, double-blind, event-driven study of BDA MDI 160/180 µg and BDA MDI 80/180 µg vs AS MDI 180 µg, PRN with minimum of 24-week treatment period	Symptomatic patients with moderate to severe asthma and history of 1 or more severe exacerbations	All ages: 3132 ≥12 years: 3040
AV004 (DENALI; D6930C00004)	Randomized, double-blind, chronic-dosing (12 weeks) study of BDA MDI 160/180 µg and BDA MDI 80/180 µg vs BD BDI 160 µg, AS MDI 180 µg, and placebo MDI, given QID	Patients with mild to moderate asthma	All ages: 1001 ≥12 years: 991
AV005 (TYREE; D6930C00006)	Randomized, double-blind, single-dose, 2-period, crossover study of BDA MDI 160/180 µg vs placebo MDI	Patients with asthma and EIB	60
Phase 2 Studies			
D6930C00001 (ANTORA; PT007001)	Randomized, double-blind, single-dose, placebo-controlled, 5-treatment, 5-period, crossover study of AS MDI vs Proventil HFA	Patients with stable asthma receiving PRN rescue SABA or low- to medium-dose maintenance ICS or ICS/LABA	86
D6930C00002 (ASPEN; PT007002)	Randomized, open-label, 2-period, crossover, cumulative-dose comparison of AS MDI and Proventil HFA	Patients with stable mild to moderate asthma receiving PRN rescue SABA or low- to medium-dose maintenance ICS or ICS/LABA	46
PT008001	Randomized, double-blind, placebo-controlled, chronic-dosing, 4-period, 5-treatment, crossover study of BD MDI	Patients with ≥6 months clinical history of mild to moderate persistent asthma	147

Study Identifier	Design/Purpose	Population	N
Phase 1 PK Studies			
D6930C00003 (LOGAN)	Randomized, open-label, single-dose, 3-period, 3-treatment, 3-way, crossover study to establish scientific bridge between BDA MDI and mono-components (AS MDI and BD MDI)	Healthy volunteers aged 19 to 55 years	91
D6930C00011 (ELBRUS)	Randomized, open-label, single-dose, 2-way, crossover study to establish scientific bridge based on BD exposure between BDA MDI and RLD Pulmicort Flexhaler	Healthy volunteers aged 18 to 55 years	67
AV006 (BLANC)	Randomized, open-label, single-dose, 2-way, crossover study to establish scientific bridge based on BD exposure between BDA MDI and RLD Pulmicort Respules	Children with asthma aged 4 to 8 years	12

Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; EIB = exercise-induced bronchoconstriction; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; MDI = metered dose inhaler; PK = pharmacokinetics; PRN = as needed; QID = 4 times daily; RLD = reference listed drug; SABA = short-acting β2 agonist.

5.0 CLINICAL PHARMACOLOGY

5.1 Scientific Bridging to the Reference Listed Drugs

The scientific bridge between albuterol sulfate (AS) MDI and Proventil HFA was established with the ANTORA and ASPEN studies. ANTORA demonstrated that the bronchodilatory effects of AS MDI were noninferior to those of Proventil HFA. ASPEN demonstrated that the improvement in lung function following AS MDI was equivalent to Proventil HFA, with the systemic exposure to albuterol lower with AS MDI. Additionally, ASPEN demonstrated that AS MDI generally changed extrapulmonary pharmacodynamic parameters less than Proventil HFA. These results showed that AS MDI was therapeutically equivalent to Proventil HFA, and therefore support the use of AS MDI as the comparator in the Phase 3 MANDALA and DENALI studies and the use of Proventil HFA as the RLD for albuterol.

The scientific bridges between the combination product, BDA MDI, and the mono-components, AS MDI and budesonide (BD) MDI, were established with the LOGAN study. This study demonstrated that the systemic exposure to albuterol and budesonide delivered from BDA MDI was equivalent to that from AS MDI and BD MDI, respectively.

The scientific bridge between BDA MDI and Pulmicort Flexhaler was established with the ELBRUS study, which demonstrated that systemic exposure to budesonide delivered from BDA MDI did not exceed that delivered from Pulmicort Flexhaler and supported the use of Pulmicort Flexhaler as the RLD for budesonide in patients 6 years of age and older.

The scientific bridge between BDA MDI and Pulmicort Respules was established in children 4 to 8 years of age with the BLANC study, which demonstrated that systemic exposure to budesonide delivered from BDA MDI did not exceed that from Pulmicort Respules following inhalation of 160/180 µg and 1 mg, respectively, and supported the use of Pulmicort Respules as the RLD for budesonide in patients 4 to 5 years of age.

5.2 Pharmacokinetic Modeling of Maximum Budesonide Exposure

Required PK studies used for maintenance with standard blood sampling do not apply for an as-needed medication. Instead, budesonide systemic exposure during as-needed use of BDA MDI was modeled using dosing data from the Phase 3 MANDALA study and PK data from the Phase 1 LOGAN, ELBRUS, and BLANC studies. This modeling approach was accepted by the FDA.

This analysis was conducted to simulate the PK of budesonide following administration of BDA MDI as follows: BDA MDI alone, BDA MDI with average use (3 inhalations per day), BDA MDI 4 times daily (QID) dosing (as in DENALI), and BDA MDI proposed maximum daily use (12 inhalations per day) with rapid-use simulation in an asthma action plan.

Adolescents were grouped with adults as almost all ICS dosing recommendations include adolescents with adults. Budesonide systemic exposure in all modeled BDA MDI 160/180 dosing scenarios was lower or comparable to that with the maximum approved dose of Pulmicort Flexhaler for adults (720 µg twice daily [BID]).

In children 6 to 11 years of age receiving maintenance treatment with Pulmicort Flexhaler 180 µg BID, budesonide systemic exposure in all permitted BDA MDI 80/180 dosing scenarios was lower or comparable to that with the maximum approved dose of Pulmicort Flexhaler (360 µg BID). Budesonide systemic exposure with the mean daily usage of BDA MDI 80/180 observed in

MANDALA (3 inhalations per day) was 15% higher than with maintenance alone. During the maximum permitted daily usage (12 inhalations per day), budesonide systemic exposure was 59% higher than with maintenance alone.

In children 4 to 8 years of age receiving the maximum approved maintenance treatment with Pulmicort Respules 1 mg, budesonide systemic exposure using the mean daily usage of BDA MDI 80/180 observed in MANDALA (3 inhalations per day) was 28% higher than with maintenance alone. During the maximum permitted daily usage, budesonide exposure was 111% higher than with maintenance alone.

Overall, the modeling results concluded that the systemic exposure to budesonide in children following administration of BDA MDI alone does not exceed that in adult and adolescents. In the maximum dosing scenarios on top of maximum maintenance dosing, the systemic exposure in children was substantially lower than that in adults and adolescents due to lower administered doses and lower budesonide bioavailability in children (Table 2).

Table 2 Budesonide Systemic Exposure at Steady-State Following Maximum Allowed BDA MDI Dosing in Addition to Maximum Approved Maintenance Dosing Across Age Groups

Population	Maintenance Treatment (Labeled Doses)	BDA MDI Treatment	$AUC_{24\ hours}$ (pg/mL*h)
Adults and adolescents ≥12 years	Pulmicort Flexhaler (720 µg BID)	12×80/90 µg	17500
Children 6-11 years	Pulmicort Flexhaler (360 µg BID)	12×40/90 µg	8800
Children 4-8 years	Pulmicort Respules (0.5 mg BID)	12×40/90 µg	2780

Abbreviations: $AUC_{24\ hours}$ = area under the concentration-time curve in 24 hours; BDA = budesonide/albuterol sulfate; BID = twice daily; MDI = metered dose inhaler.
For Pulmicort Flexhaler, the labeled dose is 90 µg, while the dose delivered from the mouthpiece is 80 µg per inhalation.

5.3 Dose Selection for Phase 3 Clinical Studies

Two dose levels of budesonide (80 and 160 µg) added to albuterol 180 µg were evaluated in the BDA MDI clinical development program.

Budesonide

The Phase 3 program was designed to evaluate 2 as-needed doses of budesonide (80 and 160 µg) in BDA MDI. Dose selection was based on previous experience with as-needed dosing with SYMBICORT® (budesonide/formoterol) in asthma, the Phase 2 PT008001 dose-ranging study, and advice from FDA at the pre-Investigational New Drug meeting. As children may be more responsive to ICS,[51] and to minimize exposure, patients younger than 12 years of age were only randomized to receive the 80 µg dose.

Albuterol

Based on the Phase 2 AS MDI studies demonstrating AS MDI noninferiority (ANTORA) and equivalency (ASPEN) to Proventil HFA, 180 µg was selected as the albuterol dose for use in the Phase 3 program. This is the labeled recommended dose of Proventil HFA administered for the treatment or prevention of bronchospasm in patients with reversible obstructive airway disease 4 years of age and older.[52]

6.0 CLINICAL EFFICACY

Data from 3 positive Phase 3 studies support the efficacy of BDA MDI. MANDALA evaluated the intended as-needed use of BDA MDI in patients with moderate to severe asthma and demonstrated statistically significant and clinically meaningful reductions in asthma exacerbation risk and rate and annualized SCS exposure. Data from the overall population are presented in this section (refer to Section 8.1 for efficacy data from the individual pediatric subgroups). DENALI, a lung function study conducted in patients with mild to moderate asthma administered BDA MDI with scheduled QID dosing, demonstrated the individual contributions of budesonide and albuterol in BDA MDI, satisfying the FDA Combination Rule (21 CFR 300.50).[26] TYREE, which evaluated single doses of BDA MDI in the prevention of EIB in a crossover study design, showed that BDA MDI was effective in preventing bronchoconstriction induced by an exercise challenge test in patients with asthma and EIB.

6.1 Phase 3 Study: MANDALA

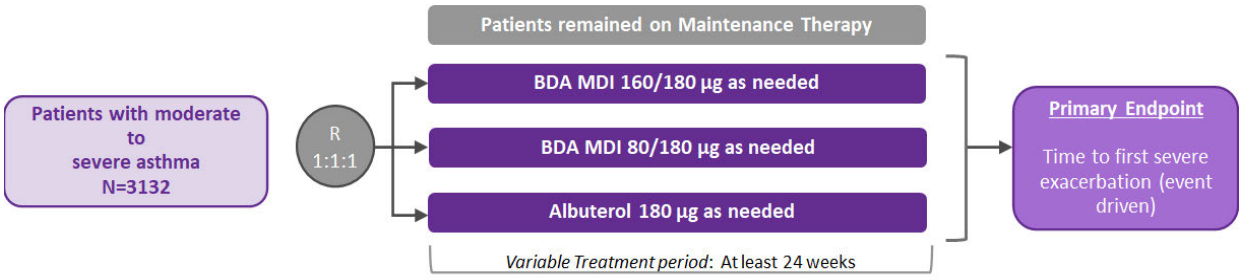
6.1.1 Study Design and Methods

MANDALA was a Phase 3, global, randomized, double-blind, parallel-group, multicenter, event-driven study of BDA MDI 160/180 and BDA MDI 80/180 compared with 180 µg albuterol (AS MDI 180), all administered as needed, with a minimum 24-week treatment period in patients aged ≥4 years with moderate to severe asthma (Figure 6). Patients remained on their background ICS-containing asthma maintenance medications throughout the study and blinded investigational product (IP) was provided to be used as patients normally used their rescue medication. The study was designed to evaluate the reduction of severe asthma exacerbations reflecting the intended as-needed use of BDA MDI.

Patients ≥12 years of age were randomized in a 1:1:1 ratio to BDA MDI 160/180 (given as 2 inhalations of BDA MDI 80/90), BDA MDI 80/180 (given as 2 inhalations of BDA MDI 40/90), or AS MDI 180 (given as 2 inhalations of AS MDI 90). Randomization for patients ≥12 years of age was stratified by age group (12 to 17 years, ≥18 years); 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 screening plus any severe exacerbation event experienced during the screening period. Children 4 to 11 years of age were randomized in a 1:1 ratio to BDA MDI 80/180 or AS MDI 180. Randomization for children was not stratified.

Patients were instructed not to take >8 inhalations per day and advised to contact the investigator if their symptoms necessitated >8 inhalations. The maximum daily dosage was not to exceed 12 inhalations or 6 doses per day.

Figure 6 MANDALA Study Design



Abbreviations: BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler; R = randomization.

The primary objective was to evaluate the efficacy of BDA MDI 160/180 and BDA MDI 80/180 administered as needed compared with AS MDI 180 on reducing severe asthma exacerbation risk and associated SCS use and improving asthma control and quality of life; 2 BDA MDI treatment doses were included to support final dose selection for approval. The primary endpoint was time to first severe asthma exacerbation, defined as worsening or onset of asthma symptoms that required SCSs for at least 3 days or an ED visit that led to the use of SCSs for at least 3 days or a hospitalization for at least 24 hours due to asthma. The secondary endpoints were annualized severe exacerbation rate, annualized total SCS exposure over the treatment period, and Asthma Control Questionnaire 5-item (ACQ-5) and Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) change from baseline and responder analyses.

6.1.1.1 Key Eligibility Criteria

Eligible patients were male or female aged ≥4 years with a diagnosis of moderate to severe asthma and ≥1 severe asthma exacerbation within the previous 12 months prior to screening. Prebronchodilator forced expiratory volume in 1 second (FEV_1) of ≥40% to <90% predicted normal value for patients ≥18 years of age, and ≥60% predicted normal for patients 4 to 17 years of age. Patients must have been regularly taking ICS-containing asthma maintenance therapy for ≥3 months with stable dosing for ≥4 weeks prior to the screening visit. ICSs with or without a long-acting β2 agonist (LABA) and a third controller (leukotriene receptor antagonists [LTRAs], theophylline, and long-acting muscarinic antagonists [LAMAs]) were permitted as maintenance therapy. Patients had to be symptomatic (defined as ACQ-5 ≥1.5) and have used SABA as needed regularly due to asthma symptoms.

6.1.1.2 Statistical Considerations

Analysis Sets

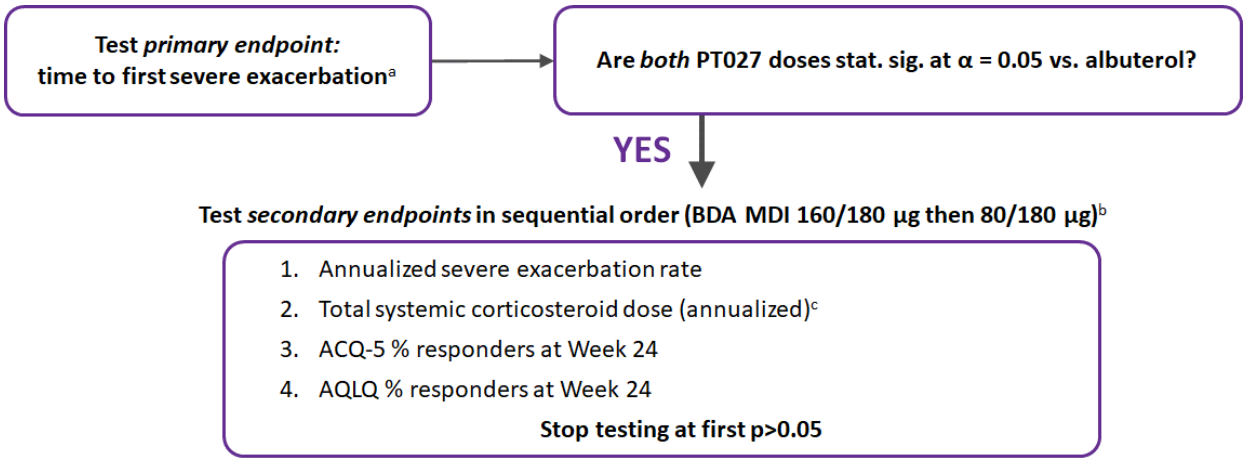
All efficacy analyses were conducted on the Full Analysis Set (FAS) all ages, defined as all patients who were randomly assigned and took ≥1 inhalation of randomly assigned treatment. For all efficacy analyses, the comparison between BDA MDI 160/180 (which excluded children) and AS MDI 180 was made in a subpopulation of the FAS that included patients 12 years of age and older (FAS ≥12 years), and the comparison between BDA MDI 80/180 and AS MDI 180 was made in the FAS all ages population.

Hierarchical Testing Strategy

Figure 7 illustrates the hierarchical testing procedure. The analysis in the hierarchical testing are based on the efficacy estimand that included all data obtained prior to changes in maintenance

therapy or discontinuation of treatment. First, both BDA MDI doses were assessed using the Hochberg method[53] at an alpha of 0.05; once that was confirmed, the secondary endpoints were tested in a prespecified hierarchical order, first for BDA MDI 160/180 and then for BDA MDI 80/180. Once any comparison failed to meet $P<0.05$, formal testing was stopped and any subsequent endpoints could only be assessed with a nominal P value.

Figure 7 MANDALA Hierarchical Testing Strategy



Abbreviations: ACQ-5 = Asthma Control Questionnaire 5-item; AQLQ+12 = Asthma Quality of Life Questionnaire for 12 years and older; BDA = budesonide/albuterol sulfate; MCID = minimal clinically import difference; MDI = metered dose inhaler; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; SCS = systemic corticosteroid.
Note: ACQ-5 is scored on a scale from 0 to 6 (lower numbers indicating better asthma control; MCID, 0.5 points); AQLQ+12 is scored on a scale from 1 to 7 (higher scores indicating better asthma-related quality of life; MCID, 0.5 points). Responders were defined as patients with a decrease (ACQ-5) or increase (AQLQ+12/PAQLQ) of ≥0.5 from baseline score.
[a] Severe exacerbation defined as deterioration of asthma requiring use of SCS for ≥3 days or inpatient hospitalization or emergency department visit that required SCS.
[b] Hochberg step-up procedure; type 1 error no longer controlled at first $P>0.05$.
[c] Calculated as annualized total SCS dose (mg/year).

Sample Size and Power Calculation

A sample size of 1000 adult and adolescent patients per treatment group and 570 first severe exacerbation events would provide 87% power to observe a 25% reduction in the risk of severe exacerbation with at least 1 dose of BDA MDI versus AS MDI. In addition, up to 100 children 4 to 11 years of age with moderate to severe asthma were to be randomly assigned 1:1 to either BDA MDI 80/180 or AS MDI 180.

6.1.2 Patient Disposition

Of the 3132 patients randomized to treatment in MANDALA, 3127 received ≥1 dose of randomized treatment: 1015 were in the BDA MDI 160/180 treatment group, 1055 in the BDA MDI 80/180 treatment group, and 1057 in the AS MDI 180 treatment group (Table 3). All 3127 patients were included in the Safety Analysis Set and 3123 patients were included in the FAS. In total, 92.3% remained on study treatment for at least 24 weeks. Randomized treatment was discontinued by 100 (9.8%) patients in the BDA MDI 160/180 group, 122 (11.5%) in the BDA MDI 80/180, and 141 (13.3%) in the AS MDI 180 group. The most common reasons for treatment discontinuation were patient decision (6.0%) and lost to follow-up (2.1%).

Table 3 Patient Disposition (All Patients Screened) – MANDALA

	Number (%) of Patients			
	BDA MDI 160/180	BDA MDI 80/180	AS MDI 180	Total
Patients screened[a]				5620
Patients who were randomized	1016 (100.0)	1057 (100.0)	1059 (100.0)	3132 (100.0)
Patients who were not randomized[b]				2488
Screen failure				2456
Withdrawal by patient				18
Lost to follow-up				2
Death				1
Withdrawal by parent/guardian				1
Other				10
Patients who received randomized treatment	1015 (99.9)	1055 (99.8)	1057 (99.8)	3127 (99.8)
Patients who did not receive randomized treatment	1 (0.1)	2 (0.2)	2 (0.2)	5 (0.2)
Patient discontinued study prior to dosing randomized treatment	1 (0.1)	2 (0.2)	2 (0.2)	5 (0.2)
Patient who remained on randomized treatment up to Week 24	960 (94.5)	975 (92.2)	956 (90.3)	2891 (92.3)
Patient who attended the end of study visit on randomized treatment	909 (89.5)	919 (86.9)	898 (84.8)	2726 (87.0)
Patients who were ongoing in the study at the primary database lock	6 (0.6)	14 (1.3)	18 (1.7)	38 (1.2)
Patient who discontinued randomized treatment[c]	100 (9.8)	122 (11.5)	141 (13.3)	363 (11.6)
Patient decision	52 (5.1)	62 (5.9)	74 (7.0)	188 (6.0)
Patient lost to follow-up	19 (1.9)	25 (2.4)	21 (2.0)	65 (2.1)
Adverse event	11 (1.1)	9 (0.9)	9 (0.8)	29 (0.9)
Severe nonadherence to protocol	5 (0.5)	6 (0.6)	8 (0.8)	19 (0.6)
Development of study-specific discontinuation criteria	2 (0.2)	6 (0.6)	10 (0.9)	18 (0.6)
≥3 severe exacerbations within a 3-month period	1 (0.1)	4 (0.4)	4 (0.4)	9 (0.3)
≥5 total severe exacerbation events	0	1 (0.1)	1 (0.1)	2 (0.1)
A single severe exacerbation event longer than 20 days in duration	0	1 (0.1)	2 (0.2)	3 (0.1)
Pregnancy	1 (0.1)	0	3 (0.3)	4 (0.1)
Lack of therapeutic response	1 (0.1)	2 (0.2)	2 (0.2)	5 (0.2)
Condition under investigation worsened	2 (0.2)	0	1 (0.1)	3 (0.1)
Other	8 (0.8)	12 (1.1)	16 (1.5)	36 (1.1)
Patients who remained in study until Week 24[c]	968 (95.3)	978 (92.5)	963 (90.9)	2909 (92.9)
Patients withdrew from study[c]	93 (9.2)	122 (11.5)	137 (12.9)	352 (11.2)
Withdrawal by patient	48 (4.7)	56 (5.3)	68 (6.4)	172 (5.5)
Lost to follow-up	19 (1.9)	26 (2.5)	22 (2.1)	67 (2.1)
Protocol deviation	4 (0.4)	7 (0.7)	8 (0.8)	19 (0.6)
Adverse event	4 (0.4)	7 (0.7)	7 (0.7)	18 (0.6)
Development of study-specific discontinuation criteria	2 (0.2)	5 (0.5)	10 (0.9)	17 (0.5)
Withdrawal by parent/guardian	1 (0.1)	3 (0.3)	6 (0.6)	10 (0.3)

	Number (%) of Patients			
	BDA MDI 160/180	BDA MDI 80/180	AS MDI 180	Total
Death	4 (0.4)	2 (0.2)	1 (0.1)	7 (0.2)
Screen failure	0	1 (0.1)	2 (0.2)	3 (0.1)
Other	11 (1.1)	15 (1.4)	13 (1.2)	39 (1.2)

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler.
Note: The percentages are calculated using the number of patients who were randomized. Patients who were not randomized to study treatment were not assessed for withdrawal from study.
[a] Informed consent received.
[b] Patients not randomized summary only includes patients who have successfully enrolled (provided informed consent).
[c] Includes patients who discontinued randomized treatment/study during the extension phase, post Week 24. Only includes patients who were randomized to study treatment.

6.1.3 Demographic and Other Baseline Characteristics

Overall, demographic and disease-related baseline characteristics were generally well balanced across the treatment groups in MANDALA.

Patients had a mean age of 49.4 years and were predominantly female (64.8%; Table 4). In total, 2.7% of patients were 4 to 11 years of age, 3.2% of patients were 12 to 17 years of age, 76.0% of patients were 18 to 64 years of age, and 18.1% of patients were ≥65 years of age.

The median time since asthma diagnosis was 19.9 years (Table 5). The most common asthma triggers were allergens (47.6%) and exercise (35.2%).

Lung function as assessed by spirometry was similar across the treatment groups. The mean prebronchodilator FEV_1 was 2.016 L (68.6% predicted; Table 6) and mean FEV_1 reversibility (assessed at the screening visit) was 27.6%.

Table 4 Demographic and Baseline Characteristics (Full Analysis Set; All Ages) – MANDALA

Characteristic	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
Age, years				
n	1013	1054	1056	3123
Mean	50.6	48.5	49.1	49.4
SD	15.06	16.71	17.23	16.40
Median	52.0	51.0	52.0	52.0
Min, Max	12, 84	5, 83	4, 84	4, 84
Age groups (years), n (%)				
≥4 to <12	0	41 (3.9)	42 (4.0)	83 (2.7)
≥12 to <18	34 (3.4)	32 (3.0)	34 (3.2)	100 (3.2)
≥18 to <65	787 (77.7)	804 (76.3)	783 (74.1)	2374 (76.0)
≥65	192 (19.0)	177 (16.8)	197 (18.7)	566 (18.1)
Sex, n (%)				
Male	368 (36.3)	369 (35.0)	362 (34.3)	1099 (35.2)
Female	645 (63.7)	685 (65.0)	694 (65.7)	2024 (64.8)
Race, n (%)				

Characteristic	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
White	818 (80.8)	847 (80.4)	868 (82.2)	2533 (81.1)
Black or African American	139 (13.7)	141 (13.4)	137 (13.0)	417 (13.4)
Asian	29 (2.9)	33 (3.1)	23 (2.2)	85 (2.7)
American Indian or Alaska Native	1 (0.1)	1 (0.1)	0	2 (0.1)
Other	26 (2.6)	32 (3.0)	28 (2.7)	86 (2.8)
Ethnicity, n (%)				
Hispanic or Latinx	233 (23.0)	260 (24.7)	315 (29.8)	808 (25.9)
Not Hispanic or Latinx	780 (77.0)	794 (75.3)	741 (70.2)	2315 (74.1)
Region[a]				
North America, Western Europe, and South Africa	536 (52.9)	556 (52.8)	563 (53.3)	1655 (53.0)
Rest of world	477 (47.1)	498 (47.2)	493 (46.7)	1468 (47.0)

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.
Note: Percentages are based on the number of patients with data.
[a] Collected at randomization.

Table 5 Asthma Characteristics at Study Entry (Full Analysis Set; All Ages) – MANDALA

Characteristic	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
Time since diagnosis of asthma, years				
n	1013	1054	1056	3123
Median	20.20	19.05	19.88	19.87
Min, Max	1.1, 74.0	1.0, 80.1	1.1, 74.3	1.0, 80.1
Time since last severe exacerbation, days				
n	1013	1054	1056	3123
Median	182.00	176.00	171.00	178.00
Min, Max	26.0, 516.0	36.0, 388.0	40.0, 391.0	26.0, 516.0
Number of severe exacerbations per patient within 12 months prior to screening, n (%)				
1	788 (77.8)	822 (78.0)	840 (79.5)	2450 (78.5)
2	185 (18.3)	185 (17.6)	164 (15.5)	534 (17.1)
3	27 (2.7)	38 (3.6)	45 (4.3)	110 (3.5)
4	7 (0.7)	7 (0.7)	6 (0.6)	20 (0.6)
5	5 (0.5)	2 (0.2)	1 (0.1)	8 (0.3)
9	1 (0.1)	0	0	1 (0.0)
Associated conditions, triggers, or allergies, n (%)				
Seasonal conjunctivitis	172 (17.0)	180 (17.1)	175 (16.6)	527 (16.9)
Atopic dermatitis or eczema	88 (8.7)	92 (8.7)	99 (9.4)	279 (8.9)
Allergens asthma trigger	491 (48.5)	511 (48.5)	484 (45.8)	1486 (47.6)
Aspirin asthma trigger	33 (3.3)	39 (3.7)	32 (3.0)	104 (3.3)
Exercise asthma trigger	350 (34.6)	395 (37.5)	353 (33.4)	1098 (35.2)
Other asthma trigger	299 (29.5)	314 (29.8)	312 (29.5)	925 (29.6)

Characteristic	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
Nasal polyps	74 (7.3)	58 (5.5)	58 (5.5)	190 (6.1)
Eczema	73 (7.2)	86 (8.2)	84 (8.0)	243 (7.8)
Chronic sinusitis	131 (12.9)	116 (11.0)	115 (10.9)	362 (11.6)
History of sinus surgery	62 (6.1)	51 (4.8)	53 (5.0)	166 (5.3)
History of positive allergy tests	342 (33.8)	355 (33.7)	341 (32.3)	1038 (33.2)

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum.
Note: Asthma history was collected at the screening visit for all patients.

Table 6 Lung Function at Baseline (Full Analysis Set; All Ages) – MANDALA

Lung Function Variable	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)	Total (N=3123)
FEV_1 prebronchodilator, L				
N	1013	1054	1056	3123
Mean	2.048	1.993	2.008	2.016
SD	0.7113	0.6926	0.7226	0.7091
Median	1.918	1.906	1.885	1.904
Min, Max	0.57, 5.30	0.56, 4.89	0.60, 5.36	0.56, 5.36
FEV_1 prebronchodilator, % predicted normal				
n	1013	1054	1056	3123
Mean	68.21	68.29	69.38	68.63
SD	15.958	16.503	15.961	16.149
Median	67.88	67.83	68.78	68.04
Min, Max	21.6, 121.8	23.5, 126.2	32.4, 123.1	21.6, 126.2

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; FEV_1 = forced expiratory volume in 1 second; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.
Note: Baseline is defined as the most recent nonmissing measurement prior to and including the date of randomization.

Overall, 23% of patients were on low-, 47% on medium-, and 30% on high-dose ICS-containing maintenance asthma therapy. Approximately 83% of patients were on LABA-ICS and 17% were on mono-ICS. Additional controller medications were used by approximately 15% of patients, with approximately 10% on LTRAs, 4% on LAMAs, and 2.2% on xanthines.

6.1.4 Efficacy Results

6.1.4.1 Primary Endpoint: Time to First Severe Exacerbation

MANDALA met its primary endpoint for both doses, with BDA MDI demonstrating a statistically significant and clinically meaningful reduction in the risk of a severe exacerbation (Table 7). The hazard ratio (HR) for severe exacerbation risk for BDA MDI 160/180 versus AS MDI 180 in patients ≥12 years of age was 0.733 (95% confidence interval [CI], 0.611, 0.879), corresponding to a 27% risk reduction (P<0.001). For BDA MDI 80/180 versus AS MDI 180 across all ages, the HR for severe exacerbation risk was 0.835 (95% CI, 0.702, 0.992), corresponding to a 17% risk reduction (P=0.041).

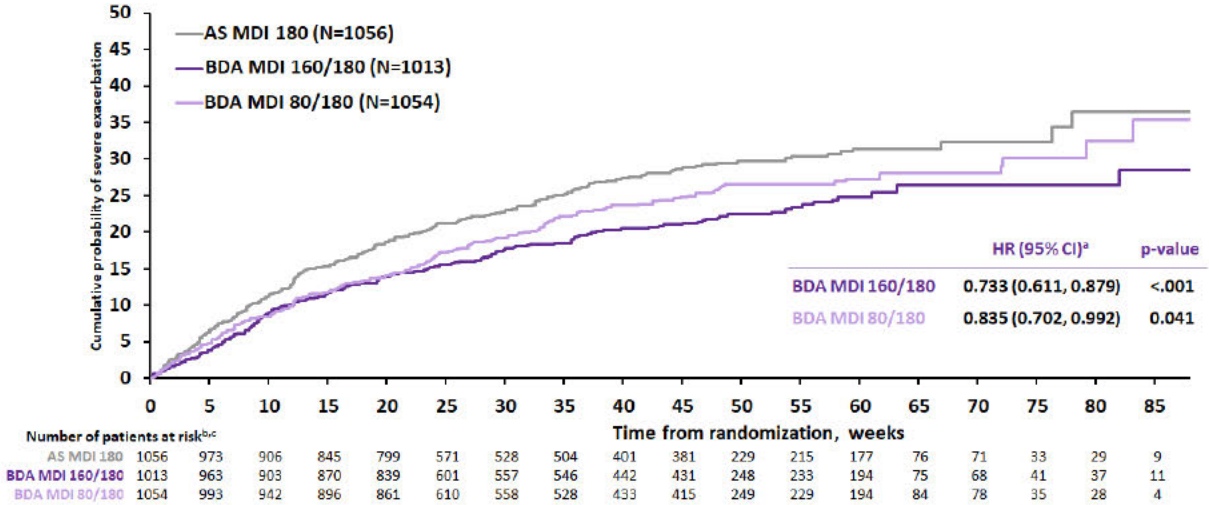
Table 7 Primary Analysis of Time to First Severe Exacerbation During the Randomized Treatment Period, Cox Regression, Efficacy Estimand (Full Analysis Set) – MANDALA

Treatment Group	N	Number (%) of Patients With Severe Exacerbation[a,b]	Time at Risk (person-years)	Hazard Ratio	95% CI	*P* Value (2-sided)
≥12 years						
BDA MDI 160/180	1013	207 (20.4)	729.7	0.733	0.611, 0.879	<0.001
AS MDI 180	1014	266 (26.2)	679.4		--	
All ages						
BDA MDI 80/180	1054	241 (22.9)	736.6	0.835	0.702, 0.992	0.041
AS MDI 180	1056	276 (26.1)	700.1		--	

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; MDI = metered dose inhaler; SCS = systemic corticosteroid.
Note: 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] Deterioration of asthma requiring use of SCS for at least 3 days or inpatient hospitalization or emergency department visit that required SCSs.
[b] Before discontinuation of randomized treatment or change in maintenance therapy.

The reverse Kaplan-Meier plot of time to first severe exacerbation shows an early separation of curves between the BDA MDI and AS MDI treatment groups, demonstrating an early onset of treatment effect with both doses of BDA (Figure 8).

Figure 8 Time to First Severe Asthma Exacerbation During the Randomized Treatment Period, Reverse Kaplan-Meier Plot, Efficacy Estimand (Full Analysis Set; All Ages) – MANDALA



Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; HR = hazard ratio; MDI = metered dose inhaler.
[a] Comparisons of AS MDI 180: vs BDA MDI 160/180 is in patients ≥12 years of age; vs BDA MDI 80/180 is in patients ≥4 years of age.
[b] Curve truncated when <1% of patient population remained at risk.
[c] The number of patients at risk includes all ages, 4 years of age and older.

Table 8 summarizes all severe exacerbation events during the randomized treatment period. All but 3 patients with a severe exacerbation had documented SCS treatment for ≥3 days, whereas 1.2% of all patients had a severe exacerbation requiring hospitalization and 5.3% required an ED or urgent care facility visit. The number of patients with severe asthma exacerbations requiring ED or urgent care visits or hospitalizations were numerically lower in the BDA MDI treatment groups compared with the AS MDI group.

Table 8 Severe Asthma Exacerbations During the Randomized Treatment Period, Exacerbation Rate Descriptive Statistics, Efficacy Estimand (Full Analysis Set) – MANDALA

	≥12 Years		All Ages		
Parameter	**BDA MDI 160/180 (N=1013)**	**AS MDI 180 (N=1014)[a]**	**BDA MDI 80/180 (N=1054)**	**AS MDI 180 (N=1056)**	**Total (N=3123)**
Total time at risk (pt-yrs)	848.7	824.6	870.3	850.2	2569.2
All severe exacerbations					
Patients with ≥1 severe exacerbation, n (%)	207 (20.4)	266 (26.2)	241 (22.9)	276 (26.1)	724 (23.2)
Total number of severe exacerbations	334	413	354	426	1114
Total number of severe exacerbations/time at risk (pt-yrs)	0.39	0.50	0.41	0.50	0.43
Severe exacerbations requiring SCS use					
Patients with ≥1 severe exacerbation, n (%)	206 (20.3)	265 (26.1)	240 (22.8)	275 (26.0)	721 (23.1)
Total number of severe exacerbations	332	441	352	424	1108
Total number of severe exacerbations/time at risk (pt-yrs)	0.39	0.50	0.40	0.50	0.43
Severe exacerbations requiring hospitalization					
Patients with ≥1 severe exacerbation, n (%)	9 (0.9)	16 (1.6)	10 (0.9)	17 (1.6)	36 (1.2)
Total number of severe exacerbations	9	17	11	18	38
Total number of severe exacerbations/time at risk (pt-yrs)	0.01	0.02	0.01	0.02	0.01
Severe exacerbations requiring ED or urgent care visit					
Patients with ≥1 severe exacerbation, n (%)	49 (4.8)	64 (6.3)	50 (4.7)	66 (6.3)	165 (5.3)
Total number of severe exacerbations	62	79	62	81	205
Total number of severe exacerbations/time at risk (pt-yrs)	0.07	0.10	0.07	0.10	0.08

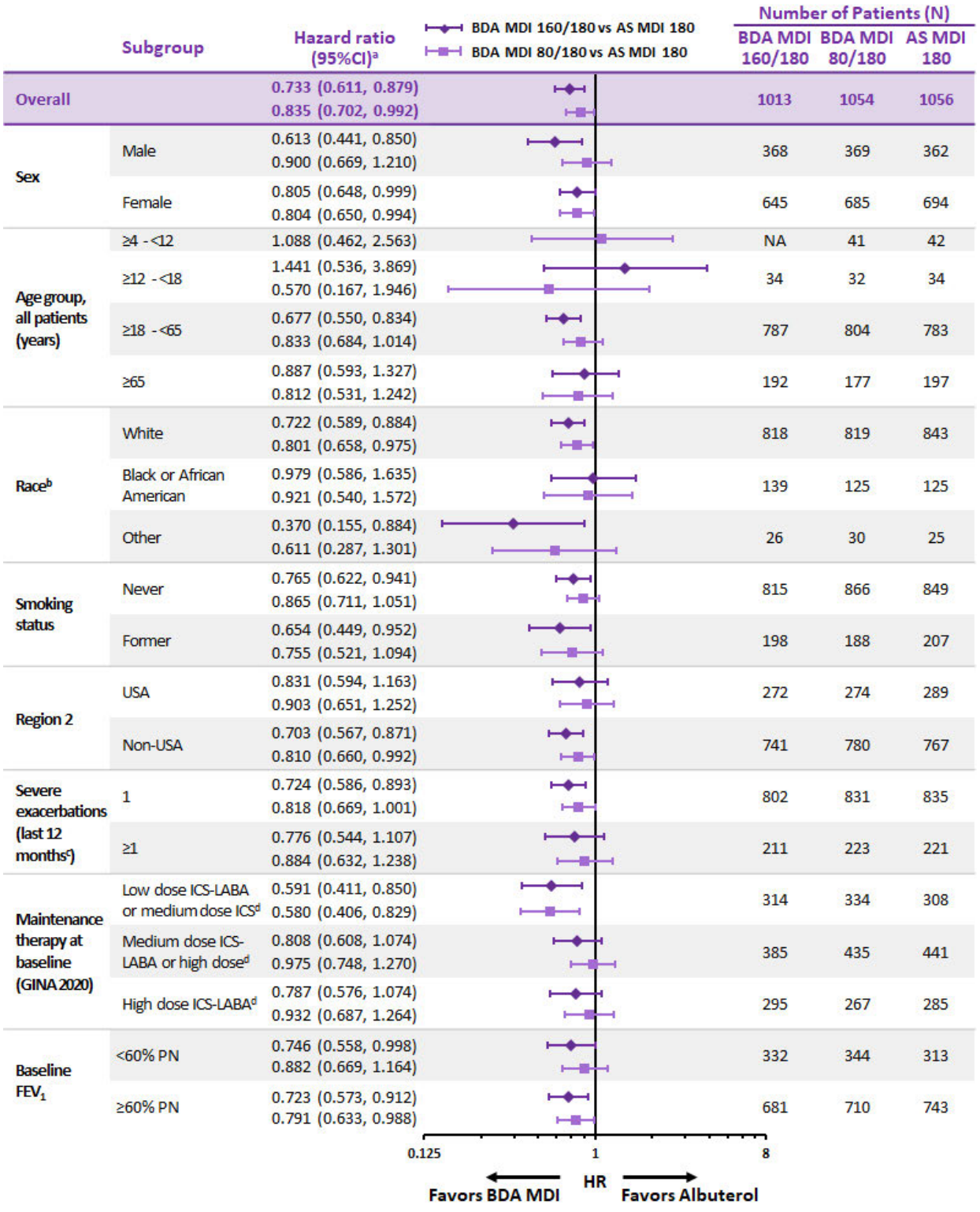
Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; ED = emergency department; pt-yrs = patient-years; SCS = systemic corticosteroids.
Note: Severe asthma exacerbation was defined as a deterioration of asthma requiring SCSs for ≥3 days or inpatient hospitalization or ED visit that required SCSs. Time at risk was defined as the cumulative number of days in the randomized treatment period across all patients in the treatment group, excluding the days during a severe exacerbation event and the 7 days following it resolving. Only excludes exacerbations that occurred prior to discontinuation of randomized investigational product and/or a change in maintenance therapy.
[a] Note that the AS MDI (≥12 years) is a subset of AS MDI (all ages) and did thus not contribute to the Total column.

Overall, sensitivity and supporting analyses for the primary endpoint yielded results consistent with the primary analysis. The results for BDA MDI 160/180 versus AS MDI 180 comparisons conducted for each supportive estimand, including the de facto estimand (treatment policy), were consistent estimates of treatment effect with the efficacy estimand. However, the results for BDA MDI 80/180 versus AS MDI 180 were less robust to small changes under all the supportive estimand analyses.

6.1.4.1.1 Subgroup Analyses of Primary Endpoint

Across the subgroups based on sex, adult age group, severe exacerbation history, smoking history, region, baseline maintenance therapy and baseline FEV_1, and race (not prespecified), reductions in severe exacerbation risk favored BDA MDI 160/180 compared with AS MDI 180 (Figure 9). For patients treated with BDA MDI 80/180, reductions in severe exacerbation risk favored BDA MDI 80/180 compared with AS MDI 180, the observed subgroup treatment effects were generally smaller than those observed with BDA MDI 160/180. The consistently large interaction *P* values (>0.10) do not suggest the treatment effect varies with subgroups. It is important to note the study was not powered to assess efficacy within any predefined subgroup; as such, these analyses are considered exploratory. However, the subgroup analysis suggests efficacy of BDA MDI versus AS MDI across the various subgroups for the key patient demographics and characteristics evaluated.

Figure 9 **Subgroup Analysis of Time to First Severe Asthma Exacerbation During the Randomized Treatment Period, Cox Regression Forest Plot, Efficacy Estimand (Full Analysis Set; All Ages) – MANDALA**



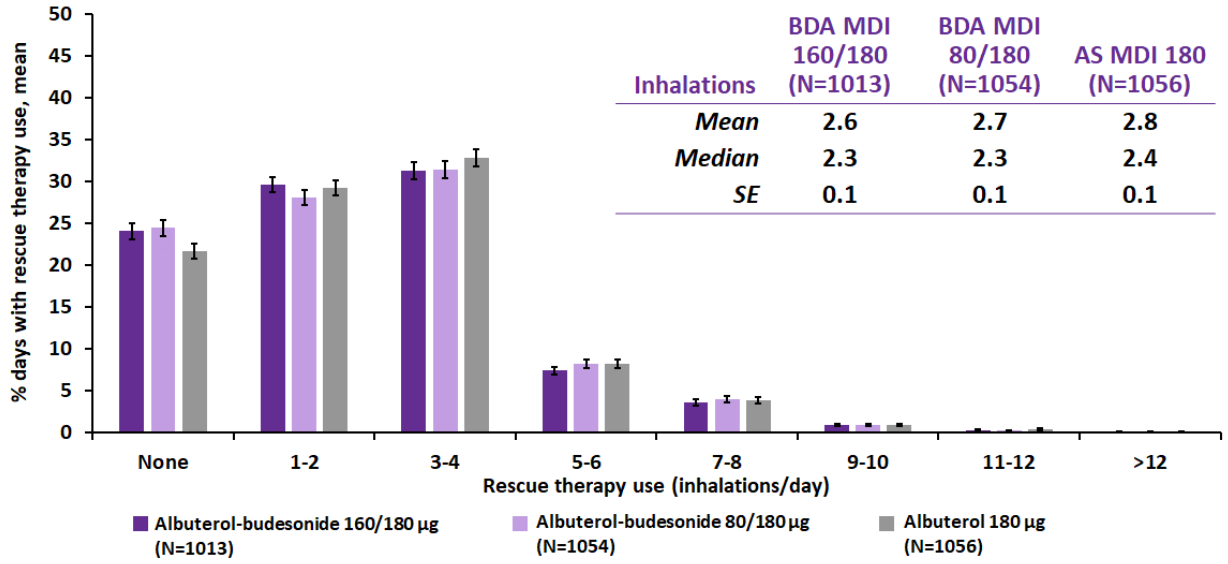
	Subgroup	Hazard ratio (95%CI)[a]	Number of Patients (N) BDA MDI 160/180	BDA MDI 80/180	AS MDI 180
Overall		0.733 (0.611, 0.879) 0.835 (0.702, 0.992)	1013	1054	1056
Sex	Male	0.613 (0.441, 0.850) 0.900 (0.669, 1.210)	368	369	362
	Female	0.805 (0.648, 0.999) 0.804 (0.650, 0.994)	645	685	694
Age group, all patients (years)	≥4 - <12	1.088 (0.462, 2.563)	NA	41	42
	≥12 - <18	1.441 (0.536, 3.869) 0.570 (0.167, 1.946)	34	32	34
	≥18 - <65	0.677 (0.550, 0.834) 0.833 (0.684, 1.014)	787	804	783
	≥65	0.887 (0.593, 1.327) 0.812 (0.531, 1.242)	192	177	197
Race[b]	White	0.722 (0.589, 0.884) 0.801 (0.658, 0.975)	818	819	843
	Black or African American	0.979 (0.586, 1.635) 0.921 (0.540, 1.572)	139	125	125
	Other	0.370 (0.155, 0.884) 0.611 (0.287, 1.301)	26	30	25
Smoking status	Never	0.765 (0.622, 0.941) 0.865 (0.711, 1.051)	815	866	849
	Former	0.654 (0.449, 0.952) 0.755 (0.521, 1.094)	198	188	207
Region 2	USA	0.831 (0.594, 1.163) 0.903 (0.651, 1.252)	272	274	289
	Non-USA	0.703 (0.567, 0.871) 0.810 (0.660, 0.992)	741	780	767
Severe exacerbations (last 12 months[c])	1	0.724 (0.586, 0.893) 0.818 (0.669, 1.001)	802	831	835
	≥1	0.776 (0.544, 1.107) 0.884 (0.632, 1.238)	211	223	221
Maintenance therapy at baseline (GINA 2020)	Low dose ICS-LABA or medium dose ICS[d]	0.591 (0.411, 0.850) 0.580 (0.406, 0.829)	314	334	308
	Medium dose ICS-LABA or high dose[d]	0.808 (0.608, 1.074) 0.975 (0.748, 1.270)	385	435	441
	High dose ICS-LABA[d]	0.787 (0.576, 1.074) 0.932 (0.687, 1.264)	295	267	285
Baseline FEV_1	<60% PN	0.746 (0.558, 0.998) 0.882 (0.669, 1.164)	332	344	313
	≥60% PN	0.723 (0.573, 0.912) 0.791 (0.633, 0.988)	681	710	743

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; HR = hazard ratio; FEV_1 = forced expiratory volume in 1 second; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; MDI = metered dose inhaler; USA = United States of America.
Note that subgroup analysis by race was not prespecified.
[a] Comparison for BDA 160/180 vs AS MDI 180 is in patients ≥12 years of age.
[b] Subgroup analysis by race was not prespecified.
[c] Prior to randomization.
[d] With or without an additional LTRA, LAMA, or theophylline.

6.1.4.1.2 Pattern of Use

An integral aspect of understanding the effect of BDA is to consider usage patterns. The pattern of use for BDA MDI was similar to albuterol. The overall mean daily use ranged from 2.6 to 2.8 inhalations, which is slightly >1 dose (Figure 10). On the majority of study days, patients used ≤2 inhalations; >8 inhalations were used on <2% of study days.

Figure 10 Investigational Therapy, Days (%) Absolute Values, Descriptive Statistics, Efficacy Estimand (Full Analysis Set; All Ages) – MANDALA



Inhalations	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)
Mean	2.6	2.7	2.8
Median	2.3	2.3	2.4
SE	0.1	0.1	0.1

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; ICS = inhaled corticosteroid; MDI = metered dose inhaler; SE = standard error.
Note: 1 dose equates to 2 inhalations; mean additive ICS exposure from study medication was 209 and 106 µg/day for albuterol 180/160 and 180/80, respectively.

6.1.4.2 Secondary Endpoints

Secondary endpoints demonstrated further benefits of BDA MDI as-needed treatment and favored BDA MDI 160/180 (Table 9).

Treatment with BDA MDI showed a statistically significant reduction in the annualized rate of severe asthma exacerbations compared with AS MDI (Figure 11). The rate reduction was 24% for BDA MDI 160/180 versus AS MDI 180 (rate ratio [RR] 0.76; 95% CI, 0.62, 0.93; *P*=0.008) and 20% for BDA MDI 80/180 versus AS MDI 180 (RR 0.80; 95% CI, 0.66, 0.98; *P*=0.028).

Treatment with BDA MDI 160/180 led to a statistically significant difference in annualized total SCS dose (*P*=0.002), compared with AS MDI 180, with a reduction in arithmetic means of 33.4%

in patients 12 years of age and older. A numerical reduction in total SCS dose of 24.8% was observed with BDA MDI 80/180 compared with AS MDI 180, but the treatment difference was not statistically significant (*P*=0.060). Given that the SCS reduction with BDA 80/180 did not have a *P* value <0.05, the testing procedure stopped. Hence, the differences observed for quality of life were only nominally significant.

A numerically higher percentage of patients treated with BDA MDI had a clinically meaningful improvement in asthma control based on ACQ-5 (defined as a reduction in ACQ-5 total score of ≥0.5 from baseline to Week 24) versus AS MDI 180. The odds ratio for BDA MDI 160/180 versus AS MDI 180 was nominally significant (1.22 [95% CI, 1.02, 1.47; *P*=0.033]).

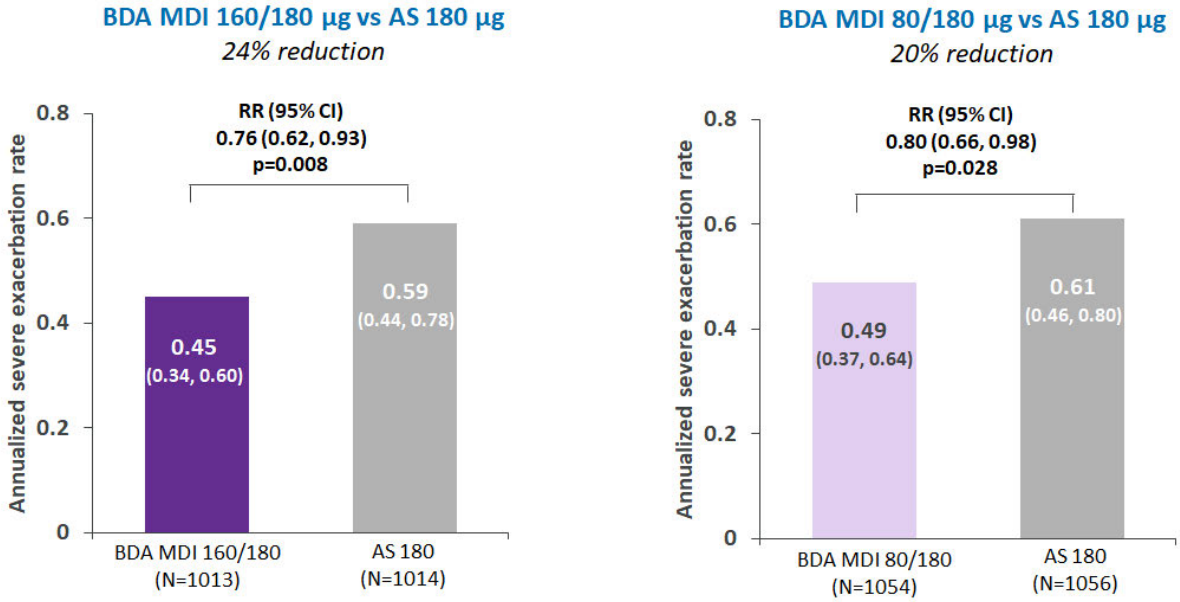
A numerically higher percentage of patients treated with BDA MDI 160/180, compared with AS MDI 180, had a clinically meaningful improvement in asthma quality of life, based on AQLQ+12 (defined as an increase in AQLQ+12 overall score of ≥0.5 from baseline to Week 24). The AQLQ odds ratio was nominally significant for BDA MDI 160/180 versus AS MDI 180 (1.23 [95% CI, 1.02, 1.48; *P*=0.028]) The odds ratio for BDA MDI 80/180 versus AS MDI 180 was 1.11 (95% CI, 0.93, 1.34; *P*=0.260).

Table 9 Overview of Secondary Analyses With Type-I Error Controlled Comparisons, Efficacy Estimand (Full Analysis Set; All Ages) – MANDALA

Secondary Endpoint (BDA MDI vs AS MDI 180)	BDA MDI Estimate (n)	AS MDI Estimate (n)	Treatment Comparison (95% CI)	*P* Value
BDA MDI 160/180 (N=1013) vs AS MDI (N=1056)				
Annualized total SCS dose, % difference in arithmetic means	86.2 mg/patient (1012)	127.1 mg/patient (1052)	-33.4%	0.002
ACQ-5 MCID at Week 24, responder analysis (odds ratio)	66.8% (1013)	62.1% (1014)	1.22 (1.02, 1.47)	0.033
AQLQ+12 MCID at Week 24, responder analysis (odds ratio)	51.1% (994)	46.4% (993)	1.23 (1.02, 1.48)	0.028
BDA MDI 80/180 (N=1054) vs AS MDI (N=1056)				
Annualized total SCS dose, % difference in arithmetic means	95.5 mg/patient (1052)	127.1 mg/patient (1052)	-24.8%	0.060
ACQ-5 MCID at Week 24, responder analysis (odds ratio)	64.7% (1052)	61.6% (1055)	1.13 (0.95, 1.35)	0.175
AQLQ+12 MCID at Week 24, responder analysis (odds ratio)	49.5% (987)	46.4% (993)	1.11 (0.93, 1.34)	0.260

Abbreviations: ACQ-5 = Asthma Control Questionnaire 5-item; AQLQ+12 = Asthma Quality of Life Questionnaire for 12 years and older; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; MCID = minimal clinically import difference; MDI = metered dose inhaler; SCS = systemic corticosteroid.

Figure 11 Annualized Severe Exacerbation Rate With Type-I Error Controlled Comparisons, Efficacy Estimand (Full Analysis Set) – MANDALA



Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; MDI = metered dose inhaler; RR = rate ratio.

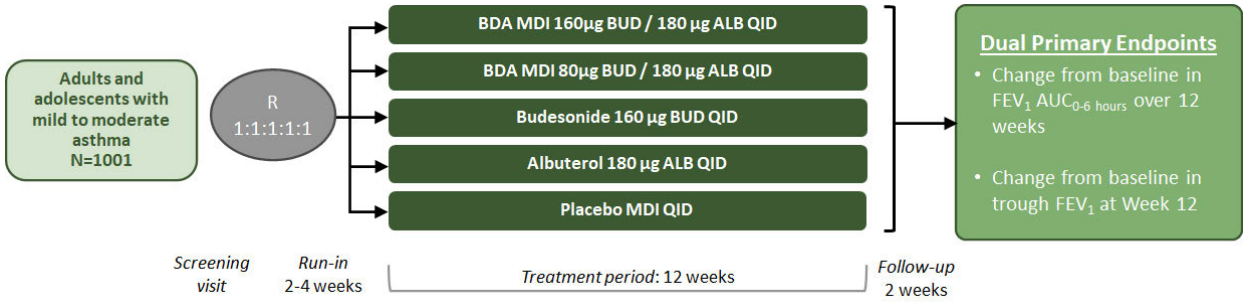
6.2 Phase 3 Study: DENALI

6.2.1 Study Design and Methods

DENALI was a 12-week, randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate 2 dose levels of BDA MDI compared with its mono-components, budesonide and albuterol, and placebo on improvement on lung function and symptoms in patients ≥4 years of age with mild to moderate asthma (Figure 12). All treatments were administered QID.

Adult and adolescent patients (≥12 years of age) who met the eligibility criteria were randomly assigned to 1 of the following 5 treatment groups in a 1:1:1:1:1 ratio: BDA MDI 80/180 QID, BDA MDI 160/180 QID, BD MDI 160 QID, AS MDI 180 QID, or placebo MDI QID. In addition, eligible children (4 to 11 years of age) were randomly assigned (1:1:1) to receive BDA MDI 80/180 QID, AS MDI 180 QID, or placebo MDI.

Figure 12 DENALI Study Design



Abbreviations: ALB = albuterol sulfate; AUC = area under the curve; BDA = budesonide/albuterol sulfate; BUD = budesonide; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler; QID = 4 times daily; R = randomization.

The primary objective was to demonstrate the contribution of budesonide and albuterol in BDA MDI 80/180 and 160/180 administered QID by comparing with the mono-components (BD MDI 160, AS MDI 180) and placebo on lung function. The dual primary endpoints were:

- Change from baseline in FEV_1 area under the curve from time 0 to 6 hours ($AUC_{0\text{-}6\ hours}$) over 12 weeks.
- Change from baseline in trough FEV_1 at Week 12.

Secondary efficacy measures were time to onset and duration of effect on Day 1, Asthma Control Questionnaire-7 (ACQ-7) responder analysis at Week 12, and trough FEV_1 at Week 1.

6.2.1.1 Key Eligibility Criteria

Eligible patients were male and female ≥4 years of age with a diagnosis of asthma as defined by GINA criteria with prebronchodilator FEV_1 of ≥50 to <85% predicted normal value (patients ≥18 years of age) and ≥50 predicted normal value (patients 4 to 17 years of age) with demonstrated in-clinic FEV_1 bronchodilator responsiveness (reversibility of airflow defined as ≥15% increase in FEV_1 relative to baseline) after administration of Sponsor-provided SABA. Patients must have taken Ventolin on ≥2 of 7 days prior to Visit 2.

6.2.1.2 Statistical Considerations

All efficacy analyses were conducted on the FAS, which was defined as all patients who took at least 1 inhalation of randomly assigned treatment and had at least 1 efficacy assessment. For all efficacy analyses, a subpopulation of the FAS, including patients aged 12 years and older (FAS ≥12 years), was used for comparisons between treatment groups, which excluded children (BDA MDI 160/180 and BD MDI 160). The primary analyses of the dual primary endpoints were on the FAS ≥12 years and Type-I error controlled. These analyses were evaluated for the efficacy estimand.

The dual primary endpoints were analyzed using a repeated-measures linear model to compare treatment groups.

6.2.2 Patient Disposition

Of the 1001 patients randomized to treatment in DENALI, 197 were in the BDA MDI 160/180 group, 204 in the BDA MDI 80/180 group, 200 in the BD MDI 160 group, 201 in the AS MDI 180 group, and 199 in the placebo MDI group. A total of 72 (7.2%) patients prematurely discontinued IP and were withdrawn from the study. The most common reasons for treatment discontinuation were patient decision (3.5%) and adverse events (AEs; 1.2%).

6.2.3 Demographic and Other Baseline Characteristics

Overall, demographic and disease-related baseline characteristics were generally well balanced across the treatment groups in DENALI.

The mean age was 48.9 years and 62.2% of patients were female (Table 10). Most patients were White (89.0%), followed by Black or African American (9.2%). The 12 to 17 years of age group included 25 patients (2.5%), the 18 to 64 years of age group included 789 patients (79.8%), and the 65 years of age and older group included 175 patients (17.7%).

The median time since asthma diagnosis was 21 years and the most common asthma triggers were allergens and exercise (Table 11).

The overall mean prebronchodilator FEV_1 at baseline was 2.137 L (69.11% predicted; Table 12). At screening, the overall mean FEV_1 reversibility was 28.65% after 4 inhalations of albuterol.

At study entry, 47.8% were on low-dose ICS and 52.2% were on non-ICS asthma therapy.

Table 10 Demographic and Baseline Characteristics (Full Analysis Set ≥12 Years) – DENALI

Characteristic	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=201)	BD MDI 160 (N=199)	AS MDI 180 (N=196)	Placebo MDI (N=196)	Total (N=989)
Age, years						
n	197	201	199	196	196	989
Mean	50.0	49.2	48.3	47.8	49.2	48.9
SD	15.80	16.21	15.80	16.13	15.13	15.81
Median	51.0	52.0	49.0	49.0	51.0	50.0
Min, Max	13, 81	12, 80	13, 90	14, 81	12, 85	12, 90
Age groups (years), n (%)						
≥12 to <18	4 (2.0)	7 (3.5)	5 (2.5)	5 (2.6)	4 (2.0)	25 (2.5)
≥18 to <65	154 (78.2)	155 (77.1)	161 (80.9)	158 (80.6)	161 (82.1)	789 (79.8)
≥65	39 (19.8)	39 (19.4)	33 (16.6)	33 (16.8)	31 (15.8)	175 (17.7)
Sex, n (%)						
Male	72 (36.5)	74 (36.8)	79 (39.7)	77 (39.3)	72 (36.7)	374 (37.8)
Female	125 (63.5)	127 (63.2)	120 (60.3)	119 (60.7)	124 (63.3)	615 (62.2)
Race, n (%)						
White	179 (90.9)	185 (92.0)	180 (90.5)	164 (83.7)	172 (87.8)	880 (89.0)
Black or African American	14 (7.1)	12 (6.0)	18 (9.0)	29 (14.8)	18 (9.2)	91 (9.2)
Asian	1 (0.5)	0	0	0	1 (0.5)	2 (0.2)
American Indian or Alaska Native	1 (0.5)	0	0	0	1 (0.5)	2 (0.2)
Other	2 (1.0)	4 (2.0)	1 (0.5)	3 (1.5)	4 (2.0)	14 (1.4)
Ethnicity, n (%)						
Hispanic or Latinx	61 (31.0)	62 (30.8)	50 (25.1)	45 (23.0)	61 (31.1)	279 (28.2)
Not Hispanic or Latinx	136 (69.0)	139 (69.2)	149 (74.9)	151 (77.0)	135 (68.9)	710 (71.8)

Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.
Note: Percentages are based on the number of patients with data.

Table 11 Asthma Disease Baseline Characteristics (Full Analysis Set ≥12 Years) – DENALI

Characteristic	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=201)	BD MDI 160 (N=199)	AS MDI 180 (N=196)	Placebo MDI (N=196)	Total (N=989)
Time since diagnosis of asthma, years						
n	197	201	199	196	196	989
Median	22.10	19.87	20.25	21.49	23.18	21.12
Min, Max	1.1, 74.8	0.6, 74.9	0.0, 70.8	0.7, 72.0	0.6, 76.0	0.0, 76.0
Associated conditions, triggers, or allergies, n (%)						
Seasonal conjunctivitis	35 (17.8)	43 (21.4)	36 (18.1)	44 (22.4)	34 (17.3)	192 (19.4)
Atopic dermatitis or eczema	18 (9.1)	16 (8.0)	24 (12.1)	18 (9.2)	15 (7.7)	91 (9.2)
Allergens asthma trigger	91 (46.2)	86 (42.8)	96 (48.2)	98 (50.0)	87 (44.4)	458 (46.3)
Aspirin asthma trigger	4 (2.0)	2 (1.0)	2 (1.0)	2 (1.0)	5 (2.6)	15 (1.5)
Exercise asthma trigger	72 (36.5)	81 (40.3)	90 (45.2)	92 (46.9)	67 (34.2)	402 (40.6)
Other asthma trigger	58 (29.4)	62 (30.8)	63 (31.7)	59 (30.1)	45 (23.0)	287 (29.0)
Nasal polyps	12 (6.1)	8 (4.0)	10 (5.0)	14 (7.1)	10 (5.1)	54 (5.5)
Eczema	16 (8.1)	11 (5.5)	20 (10.1)	12 (6.1)	15 (7.7)	74 (7.5)
Chronic sinusitis	16 (8.1)	15 (7.5)	11 (5.5)	7 (3.6)	14 (7.1)	63 (6.4)
History of sinus surgery	10 (5.1)	7 (3.5)	5 (2.5)	12 (6.1)	6 (3.1)	40 (4.0)
History of positive allergy tests	78 (39.6)	70 (34.8)	70 (35.2)	87 (44.4)	71 (36.2)	376 (38.0)

Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum.
Note: Asthma history was collected at the screening visit for all patients.

Table 12 Lung Function at Baseline (Full Analysis Set ≥12 Years) – DENALI

Lung Function Variable	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=201)	BD MDI 160 (N=199)	AS MDI 180 (N=196)	Placebo MDI (N=196)	Total (N=989)
FEV_1 prebronchodilator, L						
n	197	200	199	196	196	988
Mean	2.102	2.133	2.146	2.200	2.106	2.137
SD	0.6313	0.7128	0.6780	0.6900	0.6686	0.6763
Median	2.033	1.969	2.021	2.081	1.998	2.017
Min, Max	0.89, 4.06	0.87, 4.73	0.77, 4.15	0.86, 4.11	0.90, 4.27	0.77, 4.73
FEV_1 prebronchodilator, % predicted normal						
n	197	200	199	196	196	988
Mean	68.81	70.00	68.88	69.54	68.31	69.11
SD	13.112	14.634	13.820	12.934	14.501	13.805
Median	68.27	69.46	67.95	69.31	67.07	68.45
Min, Max	25.9, 112.3	28.6, 105.8	33.6, 132.4	35.0, 112.0	28.2, 110.4	25.9, 132.4

Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; FEV_1 = forced expiratory volume in 1 second; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.
Note: Baseline derived as the average of the 60- and 30-minute predose assessments at randomization (Visit 2).

6.2.4 Efficacy Results

6.2.4.1 Primary Endpoint

BDA MDI 160/180 and BDA MDI 80/180 demonstrated statistically significant improvement in the dual primary endpoints of change from baseline in postdose FEV_1 $AUC_{0\text{-}6\ hours}$ over 12 weeks compared with BD MDI 160 (BDA MDI 160/180: 81 mL; 95% CI, 28, 133; P=0.003) and change from baseline in trough FEV_1 at Week 12 compared with AS MDI 180 (BDA MDI 160/180: 133 mL; 95% CI, 64, 202; P<0.001 and BDA MDI 80/180: 121 mL; 95% CI, 52, 190; P<0.001, respectively; Table 13). The results showed that each mono-component of BDA MDI contributes to lung function efficacy, satisfying the FDA Combination Rule (21 CFR 300.50).[26]

Table 13 Summary of Dual Primary Endpoint Results (Full Analysis Set ≥12 Years) – DENALI

Variable	Visit	Comparison of Interest	LS Mean	Difference in LS Mean	95% CI	*P* Value
Change from baseline FEV_1 $AUC_{0\text{-}6\ hours}$ (mL)	Treatment average	BDA MDI 160/180 (N=197) vs BD MDI 160 (N=199)	259 vs 178	81	(28, 133)	0.003
Change from baseline in trough FEV_1 (mL)	Week 12	BDA MDI 160/180 (N=197) vs AS MDI 180 (N=196)	136 vs 3	133	(64, 202)	<0.001
		BDA MDI 80/180 (N=201) vs AS MDI 180 (N=196)	124 vs 3	121	(52, 190)	<0.001

Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LS = least squares; MDI = metered dose inhaler.
Note: The dual primary endpoints were modeled separately using a repeated-measures model with baseline FEV_1, percentage reversibility to Ventolin and age as continuous covariate, and visit, treatment, treatment-by-visit interaction and prior ICS use (Yes/No) as categorical covariates. An unstructured covariance matrix structure was used. A sequential testing strategy was used such that the hypothesis tests were listed in the table in ascending 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. Includes data from the date of first dose up to the date of last dose of randomized treatment.

6.2.4.2 Secondary Endpoints

The number of patients achieving a response (defined as ≥15% improvement over the pretreatment value in FEV_1 within 30 minutes after the first dose on Day 1) was similar for both BDA MDI groups and AS MDI 180. The percentage of patients who responded within 30 minutes was 49.7% for BDA MDI 160/180 and 44.0% for BDA MDI 80/180 compared with 42.9% for AS MDI 180 (Table 14). Both BDA MDI and AS MDI had similar fast onset and duration of bronchodilation. Following a single dose on Day 1, the median time to onset and mean duration of bronchodilation were 7.5 and 186.9 minutes with BDA MDI 160/180, 7.0 and 191.4 minutes with BDA MDI 80/180, and 9.5 and 168.2 minutes with AS MDI 180, respectively (Table 14 and Table 15). No diminution in the 6-hour bronchodilator effect was observed with either BDA MDI 160/180 or BDA MDI 80/180 during the 12 weeks of QID therapy (Figure 13 and Figure 14).

Table 14 Time to 15% Increase in FEV_1 Over the Pretreatment Value, for Patients With a 15% Increase in FEV_1 on Day 1 (Full Analysis Set ≥12 Years) – DENALI

Comparison of Interest	Number (%) of Responders	Median Time to Onset (Minutes)	Comparison Between Groups	
			Median Difference	95% CI
BDA MDI 80/180 (N=201) vs AS MDI 180 (N=196)	88 (44.0) vs 84 (42.9)	7.0 vs 9.5	-1.5	(-3.0, 0.0)
BDA MDI 160/180 (N=197) vs AS MDI 180 (N=196)	98 (49.7) vs 84 (42.9)	7.5 vs 9.5	-1.0	(-2.0, 0.0)

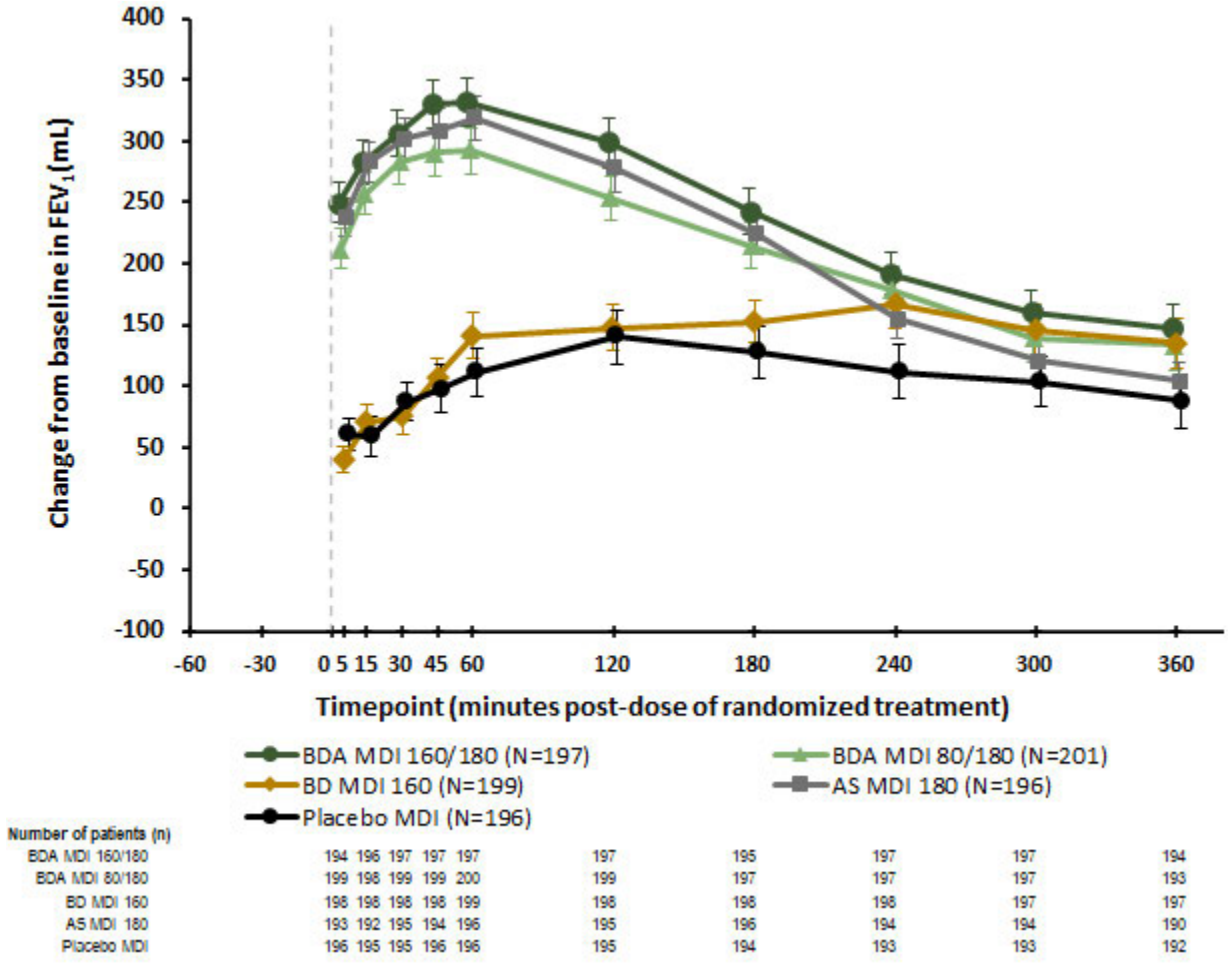
Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler.
Note: The time to onset was defined as the time (minutes) from the first inhalation of randomized treatment (Day 1) to the first instance where a percentage change from baseline in FEV_1 of at least 15% is observed. Patients were only included in the analyses if a percent change from baseline of at least 15% is observed within 30 minutes post dose. Baseline FEV_1 was defined as the average of the 60- and 30-minute predose spirometry measures taken at randomization. The estimated median difference and 95% CIs were calculated using the Hodges-Lehmann method.

Table 15 Duration of 15% Increase in FEV_1 Over the Pretreatment Value on Day 1 (Full Analysis Set ≥12 Years) – DENALI

Parameter	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=201)	BD MDI 160 (N=199)	AS MDI 180 (N=196)	Placebo MDI (N=196)
n	98	88	27	84	26
Mean (minutes)	186.9	191.4	163.9	168.2	191.5
SD	122.54	127.31	153.02	127.95	152.77
Median	185.5	174.0	98.0	158.5	229.5
Min, Max	4, 363	10, 362	14, 354	9, 363	8, 356

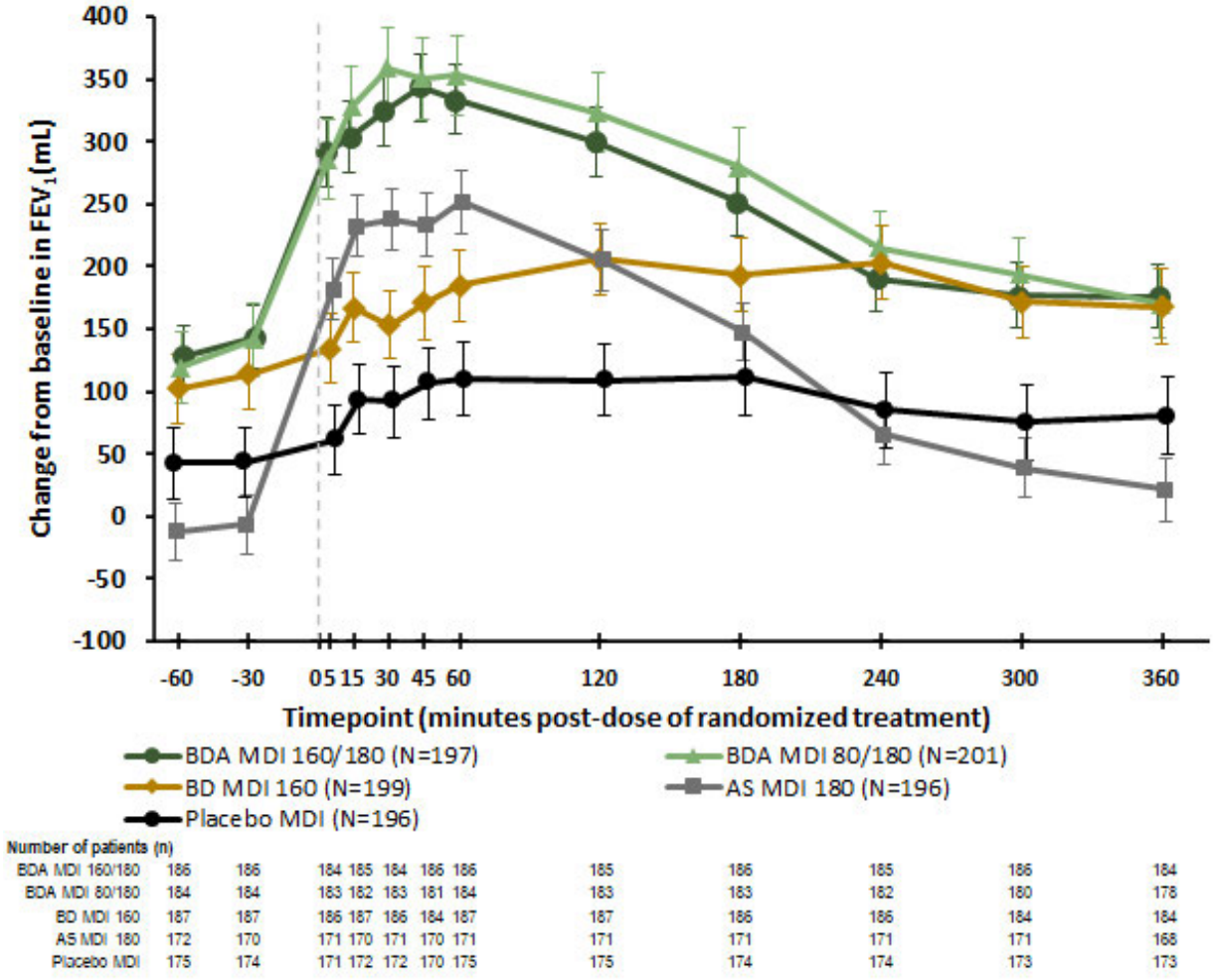
Abbreviations: BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.
Note: Percentages are based on the number of patients with data.

Figure 13 Serial Spirometry Mean Change From Baseline FEV_1 on Day 1 (Full Analysis Set ≥12 Years) – DENALI



Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler.

Figure 14 Serial Spirometry Mean Change From Baseline FEV_1 at Week 12 (Full Analysis Set ≥12 Years) – DENALI



Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler.

Both BDA MDI 160/180 and BDA MDI 80/180 increased the odds of patients responding (ie, having a clinically meaningful improvement in asthma control) as measured by ACQ-7 compared with AS MDI 180 at Week 12. Patients in the BDA MDI treatment groups had nominally higher odds of a response in ACQ-7 compared with AS MDI. The odds ratio was 2.33 (95% CI, 1.47, 3.69) for BDA MDI 160/180 versus AS MDI 180 and 2.30 (95% CI, 1.46, 3.63) for BDA MDI 80/180 versus AS MDI 180 (P<0.001 and P<0.001, respectively).

Both BDA MDI 160/180 and BDA MDI 80/180 increased the percentage of patients who responded (ie, having a clinically meaningful improvement in quality of life) as measured by AQLQ+12 compared with AS MDI 180 at Week 12. The percentage of responders was 45.2% with BDA MDI 160/180, 49.5% with BDA MDI 80/180, and 36.2% with AS MDI 180 at Week 12, with an odds ratio of 1.55 (95% CI, 1.00, 2.40; P=0.050) for BDA MDI 160/180 versus AS MDI 180 and 1.86 (95% CI, 1.20, 2.88; P=0.005) for BDA MDI 80/180 compared with AS MDI 180.

6.3 Phase 3 Study: TYREE

6.3.1 Study Design and Methods

TYREE was a multicenter, randomized, double-blind, single-dose, placebo-controlled, 2-period, crossover study (Figure 15). The purpose of the study was to evaluate the efficacy and safety of BDA MDI compared with placebo MDI on the prevention of EIB in adults and adolescents, 12 to 70 years of age, with asthma.

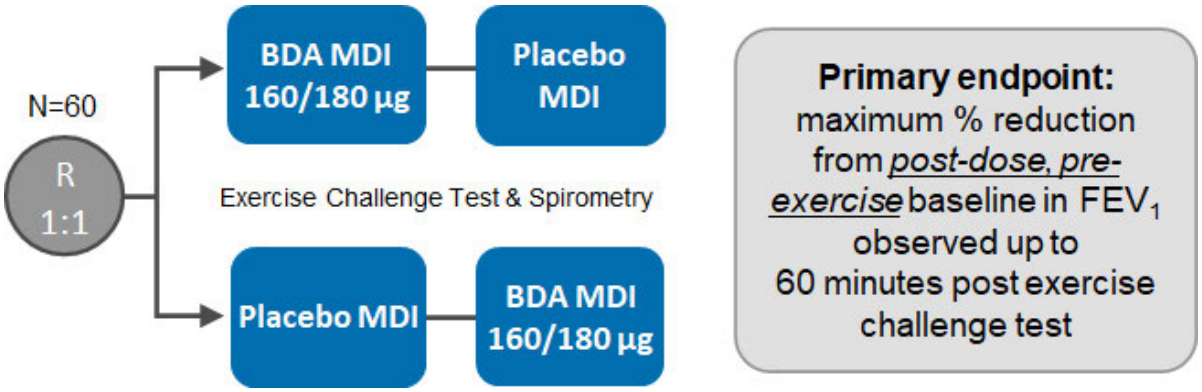
During the study, standardized exercise challenge tests were conducted. At each visit, standard FEV_1 spirometry assessments were performed relative to exercise challenge test and dosing, (before and after) as applicable.

To be eligible for the treatment phase of the study, patients with asthma were required to meet spirometry criteria and demonstrate EIB through standardized exercise challenge test.

Patients who met all eligibility criteria at the screening visits (Visits 1 and 2) were randomized 1:1 to 1 of 2 treatment sequences (ie, A/B or B/A) as specified below:

- A/B: BDA MDI 160/180 (given as 2 actuations of BDA MDI 80/90) at Visit 3 (Period 1) and placebo MDI (given as 2 actuations) at Visit 4 (Period 2).
- B/A: Placebo MDI (given as 2 actuations) at Visit 3 (Period 1) and BDA MDI 160/180 (given as 2 actuations of BDA MDI 80/90) at Visit 4 (Period 2).

Figure 15 TYREE Study Design



Abbreviations: BDA = budesonide/albuterol sulfate; FEV_1 = forced expiratory volume in 1 second; MDI = metered dose inhaler; R = randomization.

The primary endpoint was the maximum percentage fall from postdose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge, and the secondary endpoint was the percentage of patients with a maximum percentage fall in FEV_1 post-exercise challenge of <10%.

6.3.1.1 Key Eligibility Criteria

Patients included in the study were male and female adults and adolescents 12 to 70 years of age with a diagnosis of asthma as defined by GINA criteria and EIB as defined by a ≥20% decrease from pre-exercise challenge best FEV_1 observed within 60 minutes after an exercise challenge at both screening visits.

6.3.2 Patient Disposition

Of the 60 patients randomized in TYREE, 59 (98.3%) completed both treatment periods and the safety follow-up phone call. One patient was discontinued prior to taking randomized placebo MDI at Visit 4 (crossover period 2) due to failing to meet the predose FEV_1 of >70% of the predicted normal value.

6.3.3 Demographic and Other Baseline Characteristics

Overall, the 2 treatment groups in TYREE were balanced in terms of demographic and disease-related baseline characteristics.

The mean patient age was 40.5 years, 63.3% were female, and most patients were White (65.0%) (Table 16). The median time since asthma diagnosis was 27.4 years and in addition to EIB, the most common asthma trigger was allergens.

There were fewer patients in the BDA MDI 160/180/placebo MDI group who had a history of positive allergy tests (55.2%) compared with the placebo MDI/BDA MDI 160/180 group (80.6%) (Table 17).

The mean prebronchodilator FEV_1 was 2.658 L (81.44% predicted; Table 18).

Table 16 Demographic and Baseline Characteristics (Full Analysis Set All Patients) – TYREE

Characteristic	BDA MDI 160/180/ Placebo MDI (N=29)	Placebo MDI/ BDA MDI 160/180 (N=31)	Total (N=60)
Age, years[a]			
n	29	31	60
Mean	39.1	41.8	40.5
SD	12.28	11.31	11.76
Median	39.0	41.0	40.5
Min, Max	17, 67	15, 61	15, 67
Age groups (years), n (%)			
≥12 to <18	1 (3.4)	1 (3.2)	2 (3.3)
≥18 to <65	27 (93.1)	30 (96.8)	57 (95.0)
≥65	1 (3.4)	0	1 (1.7)
Sex, n (%)			
Male	8 (27.6)	14 (45.2)	22 (36.7)
Female	21 (72.4)	17 (54.8)	38 (63.3)
Race, n (%)			
White	21 (72.4)	18 (58.1)	39 (65.0)
Black or African American	5 (17.2)	13 (41.9)	18 (30.0)
Asian	1 (3.4)	0	1 (1.7)
Native Hawaiian or Other Pacific Islander	1 (3.4)	0	1 (1.7)
Other	1 (3.4)	0	1 (1.7)

Characteristic	BDA MDI 160/180/ Placebo MDI (N=29)	Placebo MDI/ BDA MDI 160/180 (N=31)	Total (N=60)
Ethnicity, n (%)			
Hispanic or Latinx	0	3 (9.7)	3 (5.0)
Not Hispanic or Latinx	29 (100.0)	28 (90.3)	57 (95.0)

Abbreviations: BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.
Note: Percentages are based on the number of patients with data.
[a] Age at randomization.

Table 17 Asthma Characteristics at Study Entry (Full Analysis Set All Patients) – TYREE

Characteristic	BDA MDI 160/180 µg/ Placebo MDI (N=29)	Placebo MDI/ BDA MDI 160/180 µg (N=31)	Total (N=60)
Time since diagnosis of asthma to randomization, years			
n	29	31	60
Median	25.19	28.59	27.36
Min, Max	2.5, 54.6	3.4, 56.1	2.5, 56.1
Associated conditions, triggers, or allergies, n (%)			
Seasonal conjunctivitis	8 (27.6)	11 (35.5)	19 (31.7)
Atopic dermatitis or eczema	6 (20.7)	3 (9.7)	9 (15.0)
Allergens asthma trigger	15 (51.7)	23 (74.2)	38 (63.3)
Aspirin asthma trigger	0	1 (3.2)	1 (1.7)
Exercise asthma trigger	29 (100.0)	31 (100.0)	60 (100.0)
Other asthma trigger	8 (27.6)	12 (38.7)	20 (33.3)
Nasal polyps	0	2 (6.5)	2 (3.3)
Eczema	7 (24.1)	4 (12.9)	11 (18.3)
Chronic sinusitis	1 (3.4)	2 (6.5)	3 (5.0)
History of sinus surgery	1 (3.4)	3 (9.7)	4 (6.7)
History of positive allergy tests	16 (55.2)	25 (80.6)	41 (68.3)

Abbreviations: BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum.
Note: Asthma history was collected at screening and defined as preexisting asthma history within 1 year of Visit 1.

Table 18 Lung Function at Randomization (Full Analysis Set All Patients) – TYREE

Lung Function Variable	BDA MDI 160/180/ Placebo MDI (N=29)	Placebo MDI/ BDA MDI 160/180 (N=31)	Total (N=60)
Predose pre-ECT FEV_1, L			
n	29	31	60
Mean	2.712	2.608	2.658
SD	0.5895	0.6409	0.6137
Median	2.570	2.540	2.555

Lung Function Variable	BDA MDI 160/180/ Placebo MDI (N=29)	Placebo MDI/ BDA MDI 160/180 (N=31)	Total (N=60)
Min, Max	1.96, 4.09	1.61, 4.30	1.61, 4.30
Predose pre-ECT FEV_1, % predicted normal			
n	29	31	60
Mean	84.86	78.24	81.44
SD	12.914	6.567	10.593
Median	79.81	76.72	77.60
Min, Max	71.3, 128.6	70.7, 95.6	70.7, 128.6

Abbreviations: BDA = budesonide/albuterol sulfate; ECT = exercise challenge test; FEV_1 = forced expiratory volume in 1 second; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.

6.3.4 Efficacy Results

6.3.4.1 Primary Endpoint

TYREE showed that in patients with asthma and EIB, when taken 30 minutes before exercise, a single dose of BDA MDI 160/180 prevented EIB compared with placebo MDI. Following a single dose of BDA MDI 160/180, the mean maximum percentage fall from postdose, pre-exercise challenge FEV_1 was 5.45% compared with 18.97% for placebo MDI (Table 19 and Figure 16). The maximum percentage fall from postdose, pre-exercise challenge FEV_1 was reduced by 13.51% (95% CI, 10.09%, 16.94%; $P<0.001$). Additionally, 47 (78.3%) of patients were fully protected from EIB (as defined by a maximum percentage fall in FEV_1 post-exercise challenge of <10%) following a single dose of BDA MDI 160/180 versus 17 (28.3%) with placebo MDI, odds ratio 10.548 (95% CI, 4.311, 25.805; $P<0.001$). Effects were similar in patients on as-needed SABA alone at baseline and in patients on low- to medium-dose ICS maintenance treatment at baseline plus as-needed SABA.

While TYREE did not evaluate the contribution of budesonide to this effect, the study demonstrated that BDA MDI was effective in preventing bronchoconstriction in these patients with asthma.

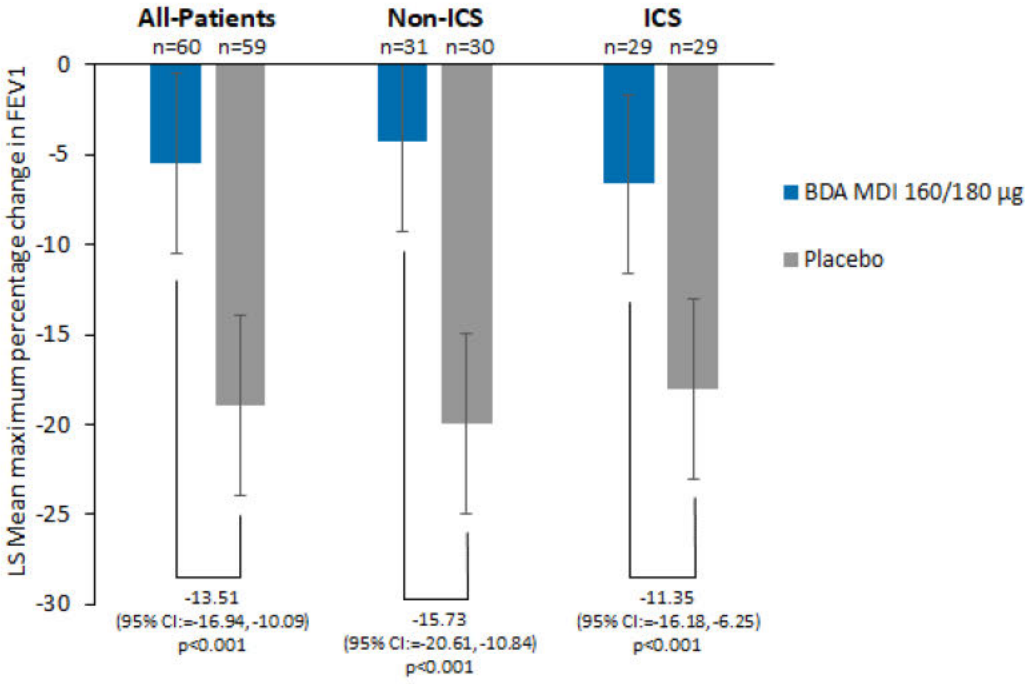
Table 19 Primary Efficacy Analysis: Maximum Percentage Reduction From Postdose, Pre-Exercise Baseline in FEV_1 Up to 60 Minutes Post-Exercise Challenge (Full Analysis Set) – TYREE

Background Therapy	Treatment Group	N	LS Mean (95% CI)	Comparison vs Placebo MDI		
				Difference in LS Mean	95% CI	*P* Value
All patients	BDA MDI 160/180 (N=60)	60	5.45 (2.56, 8.35)	-13.51	-16.94, -10.09	<0.001
	Placebo MDI (N=60)	59	18.97 (16.06, 21.88)			
Non-ICS	BDA MDI 160/180 (N=31)	31	4.27 (0.16, 8.37)	-15.73	-20.61, -10.84	<0.001
	Placebo MDI (N=31)	30	19.99 (15.84, 24.14)			

Background Therapy	Treatment Group	N	LS Mean (95% CI)	Comparison vs Placebo MDI		
				Difference in LS Mean	95% CI	*P* Value
ICS	BDA MDI 160/180 (N=29)	29	6.65 (2.45, 10.84)	-11.35	-16.18, -6.52	<0.001
	Placebo MDI (N=29)	29	18.00 (13.81, 22.19)			

Abbreviations: BDA = budesonide/albuterol sulfate; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LS = least squares; MDI = metered dose inhaler.
Note: Maximum percentage fall in postdose, pre-exercise FEV_1 up to 60 minutes post-exercise challenge was analyzed using a mixed effects model adjusted for treatment, treatment period, treatment sequence as categorical fixed effects, period-specific predose baseline FEV_1 and average predose baseline FEV_1 as continuous covariates, and a random patient within treatment sequence effect. Background therapy estimates were calculated by additionally adjusting for background therapy and background therapy*treatment group interaction in the mixed model.
Note: A sequential testing strategy was used such that the hypothesis tests are listed in the table in descending order of sequence.
Note: Tests are each conducted at the 5% level of significance.

Figure 16 Primary Efficacy Analysis: Maximum Percentage Reduction From Postdose, Pre-Exercise Baseline in FEV_1 Up to 60 Minutes Post-Exercise Challenge (Full Analysis Set) – TYREE



Abbreviations: BDA = budesonide/albuterol sulfate; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LS = least squares; MDI = metered dose inhaler.

6.4 Overall Efficacy Conclusions

Overall, the Phase 3 program demonstrated that BDA MDI is effective for the as-needed treatment or prevention of bronchoconstriction and for the prevention of severe asthma exacerbations. In MANDALA, both doses of BDA MDI used as needed resulted in statistically significant and

clinically meaningful reductions in severe exacerbation risk and rate compared with albuterol monotherapy. BDA MDI 160/180 resulted in statistically and clinically relevant reductions in severe exacerbation rate and annualized mean total SCS exposure, and improvements in asthma control and quality of life measures compared with albuterol. In DENALI, both albuterol and budesonide components contributed to BDA MDI efficacy. The onset and duration of effects on acute lung function improvements were similar to albuterol. In TYREE, BDA MDI taken before an exercise challenge test was effective in protecting patients with asthma and EIB from bronchoconstriction.

7.0 CLINICAL SAFETY

The overall safety profile of BDA MDI is consistent with the well-established safety profiles of the mono-components budesonide and albuterol in all age groups with asthma that have been approved in the US for >30 years. No new safety concerns were identified. This safety section focuses on the Phase 3 MANDALA study, which represents the intended as-needed use of BDA MDI and is therefore of main interest. Data from the overall population are presented in this section (refer to Section 8.2 for safety data from the individual pediatric subgroups). In addition, safety data from the Phase 3 DENALI and TYREE studies are also summarized.

7.1 Overall Extent of Exposure

Phase 3: MANDALA

In MANDALA, a total of 3132 patients were randomized, of whom 3127 received at least 1 dose of IP and were included in the Safety Analysis Set. The mean duration of exposure to randomized study treatment was similar in the BDA MDI 160/180 (310.0 days), BDA MDI 80/180 (305.6 days), and AS MDI 180 (298.9 days) treatment groups (Table 20). On average, patients used 2.6, 2.6, and 2.8 inhalations per day of BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180, respectively. Overall, patients in the BDA MDI treatment groups had similar IP use compared to patients in the AS MDI treatment group.

Table 20 Exposure to Randomized Treatment (Safety Analysis Set) – MANDALA

Parameter	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Duration of exposure to randomized treatment, days			
n	1015	1055	1057
Mean	310.0	305.6	298.9
SD	132.86	133.95	135.77
Median	335.0	334.0	330.0
Min, Max	1, 703	2, 744	1, 757
Total daily number of inhalations of randomized study treatment			
n	1011	1055	1053
Mean	2.6	2.6	2.8
SD	1.86	1.92	1.89
Median	2.3	2.3	2.4
Min, Max	0, 11	0, 10	0, 12

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum.
Note: Study treatment exposure (days) = Date of last dose of randomized study treatment – Date of first dose of randomized study treatment + 1.

Phase 3: DENALI

In DENALI, a total of 1001 patients were randomized, of whom 1 patient did not receive randomized treatment and was excluded from the Safety Analysis Set. The total mean duration of exposure to randomized treatment was 83.1 days with only slight variation across treatment groups (Table 21). Overall, a mean total of 8 daily inhalations of randomized study treatment were administered in alignment with QID dosing of IP per the clinical study protocol.

Table 21 Exposure to Randomized Treatment (Safety Analysis Set) – DENALI

Parameter	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)
Duration of exposure to randomized treatment, days					
n	197	204	199	201	199
Mean	84.9	82.5	84.1	82.5	81.7
SD	8.37	12.99	10.77	15.29	16.41
Median	85.0	85.0	85.0	85.0	85.0
Min, Max	27, 137	3, 111	8, 121	6, 126	1, 124
Total daily number of inhalations of randomized study treatment					
n	197	204	199	201	198
Mean	8.0	8.0	8.0	8.0	8.0
SD	0.04	0.38	0.08	0.03	0.15
Median	8.0	8.0	8.0	8.0	8.0
Min, Max	8, 8	3, 8	7, 8	8, 8	6, 8

Abbreviations: AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.
Note: Study treatment exposure (days) = Date of last dose of randomized study treatment – Date of first dose of randomized study treatment + 1.

Phase 3: TYREE

In TYREE, 60 patients were randomized; all were included in the Safety Analysis Set. Of the randomly assigned patients, 59 (98.3%) completed both treatment periods (ie, received BDA MDI 160/180 or placebo MDI) and the safety follow-up.

7.2 Adverse Events

7.2.1 Overview of Adverse Events

Phase 3: MANDALA

In MANDALA, there were no clinically important differences in the percentage of patients experiencing treatment-emergent AEs or serious AEs (SAEs) between treatment groups during the randomized treatment period (Table 22). Overall, 46.2% of patients in the BDA MDI 160/180 group, 47.1% of patients in the BDA MDI 80/180 group, and 46.4% of patients in the AS MDI 180 group had at least 1 AE. The percentage of patients who experienced at least 1 SAE was low and similar in all 3 treatment groups, ranging from 3.8% to 5.2%. The percentage of patients who experienced an AE leading to IP discontinuation was low (≤1.0% of patients) and similar across treatment groups. There were 7 deaths during the randomized treatment period: 4 in the BDA MDI 160/180 group, 2 in the BDA MDI 80/180 group, and 1 in the AS MDI 180 group.

Table 22 Overview of Adverse Events During the Randomized Treatment Period (Safety Analysis Set) – MANDALA

Patients with	Number (%) of Patients[a]		
	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[b]	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)

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; IP = investigational product; MDI = metered dose inhaler; SAE = serious adverse event.
Note: The randomized treatment period was defined as the date of randomization up to and including completion/discontinuation of randomized study treatment.
[a] Patients with multiple events in the same category were only counted once in that category. Patients with events in more than 1 category were counted once in each of those categories.
[b] As assessed by the investigator.

Phase 3: DENALI

In DENALI, the percentage of patients who experienced at least 1 on treatment AE was similar across treatment groups, ranging from 30.8% to 35.3% (Table 23). The percentage of patients with at least 1 treatment-related AE was less than 6.0% in all treatment groups. No deaths occurred during the study and the percentages of patients who experienced at least 1 SAE or experienced an AE leading to IP discontinuation were low (≤2.0% of patients) across treatment groups.

Table 23 Overview of Adverse Events During the Randomized Treatment Period (Safety Analysis Set) – DENALI

Patients with	Number (%) of Patients[a]				
	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[b]	10 (5.1)	6 (2.9)	7 (3.5)	2 (1.0)	3 (1.5)
Any AE with outcome of death	0	0	0	0	0
Any SAE (including events with outcome of death)	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)

Abbreviations: AE = adverse event; AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; IP = investigational product; MDI = metered dose inhaler; SAE = serious adverse event.
Note: The randomized treatment period was defined as the date of randomization up to and including completion/discontinuation of randomized study treatment.
[a] Patients with multiple events in the same category were only counted once in that category. Patients with events in more than 1 category were counted once in each of those categories.
[b] As assessed by the investigator.

Phase 3: TYREE

Two patients (3.3%) reported a treatment-emergent AE during the study, both of which occurred following administration of placebo MDI (Table 24). No AEs were considered serious by the investigator.

Table 24 Overview of Adverse Events (Safety Analysis Set) – TYREE

Patients with	Number (%) of Patients	
	BDA MDI 160/180 (N=60)	Placebo MDI (N=59)
Any AE	0	2 (3.4)
Any AE causally related to randomized treatment	0	1 (1.7)
Any AE with outcome of death	0	0
Any SAE (including events with outcome of death)	0	0
Any AE leading to discontinuation of IP	0	0

Abbreviations: AE = adverse event; BDA = budesonide/albuterol sulfate; IP = investigational product; MDI = metered dose inhaler; SAE = serious adverse event.

7.2.2 Common Adverse Events

Phase 3: MANDALA

In MANDALA, the incidence (per 100 patient-years) and type of AEs were similar between the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 treatment groups (Table 25). Use of BDA MDI 160/180 and BDA MDI 80/180 as needed resulted in no clinically important increase in AE frequency compared with AS MDI 180, with no new safety concerns identified.

The most commonly reported AEs by preferred term (PT) across the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 treatment groups, respectively, were nasopharyngitis (7.5%, 5.8%, 5.1%), headache (4.3%, 4.7%, 4.7%), and COVID-19 (4.2%, 4.9%, 4.4%; Table 25). For most AEs, a similar (difference of ≤1.0%) percentage of patients and incidence rate was seen across treatment groups. Nasopharyngitis was reported more frequently in the BDA MDI 160/180 treatment group as compared with the BDA MDI 80/180 and AS MDI 180 treatment groups. There were no other notable differences in the number or types of individual AEs by PT experienced by patients between treatment groups.

Table 25 Most Common Adverse Events (Frequency ≥2%) During the Randomized Treatment Period by Preferred Term (Safety Analysis Set) – MANDALA

Preferred Term	BDA MDI 160/180 (N=1015)		BDA MDI 80/180 (N=1055)		AS MDI 180 (N=1057)	
	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
Patients with any AE	469 (46.2)	54.43	497 (47.1)	56.31	490 (46.4)	56.64
Nasopharyngitis	76 (7.5)	8.82	61 (5.8)	6.91	54 (5.1)	6.24
Headache	44 (4.3)	5.11	50 (4.7)	5.66	50 (4.7)	5.78
COVID-19	43 (4.2)	4.99	52 (4.9)	5.89	46 (4.4)	5.32
Upper respiratory tract infection	26 (2.6)	3.02	31 (2.9)	3.51	26 (2.5)	3.01
Bronchitis	25 (2.5)	2.90	27 (2.6)	3.06	28 (2.6)	3.24
Hypertension	22 (2.2)	2.55	27 (2.6)	3.06	26 (2.5)	3.01
Asthma	18 (1.8)	2.09	20 (1.9)	2.27	35 (3.3)	4.05
Back pain	27 (2.7)	3.13	23 (2.2)	2.61	20 (1.9)	2.31
Influenza	21 (2.1)	2.44	23 (2.2)	2.61	14 (1.3)	1.62

Preferred Term	BDA MDI 160/180 (N=1015)		BDA MDI 80/180 (N=1055)		AS MDI 180 (N=1057)	
	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
Sinusitis	15 (1.5)	1.74	17 (1.6)	1.93	24 (2.3)	2.77

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; MDI = metered dose inhaler; pt-yrs = patient-years.
Note: The randomized treatment period was defined as the date of randomization up to and including completion/discontinuation of randomized study treatment. AEs were coded using MedDRA version 24.0.

[a] With AEs, sorted in decreasing total frequency for preferred term. Patients with multiple events in the same preferred term were counted only once in that preferred term.

[b] Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100. The total duration of treatment across all patients in BDA MDI 160/180 = 861.588 years; in BDA MDI 80/180 = 882.645 years; AS MDI 180 = 865.046 years.

Phase 3: DENALI

In DENALI, the overall incidence and type of AEs was similar between the BDA MDI 160/180 QID, BDA MDI 80/180 QID, BD MDI 160 QID, AS MDI 180 QID, and placebo MDI QID treatment groups (Table 26). The safety profile of BDA MDI 160/180 and BDA MDI 80/180 was comparable to the mono-components BD MDI 160 and AS MDI 180 when administered QID for 12 weeks, with no new safety concerns identified.

The most common AEs across all treatment groups were nasopharyngitis and headache, with similar percentages of patients reporting these events across all treatment groups (Table 26). All other AEs occurred in less than 3.0% patients in all groups.

Table 26 Most Common Adverse Events (Frequency ≥2%) During the Randomized Treatment Period by Preferred Term (Safety Analysis Set) – DENALI

Preferred Term[a]	Number (%) of Patients				
	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)
Patients with any AE	66 (33.5)	72 (35.3)	67 (33.7)	62 (30.8)	69 (34.7)
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)
Diarrhea	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

Abbreviations: AE = adverse event; AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; MDI = metered dose inhaler.
Note: The randomized treatment period was defined as the date of first dose to date of last dose of randomized study treatment. AEs were coded using MedDRA version 24.0.

[a] Preferred terms were sorted by decreasing total frequency. Patients with multiple events in the same preferred term were counted only once in that preferred term. Percentages were based on the total numbers of patients in the treatment group (N).

Phase 3: TYREE

In TYREE, 2 patients (3.3%) had an AE, both while receiving placebo.

7.2.3 Treatment-Related Adverse Events

Phase 3: MANDALA

In MANDALA, the percentage of patients who experienced treatment-related AEs across the BDA MDI 160/180 (2.1%), BDA MDI 80/180 (1.9%), and AS MDI 180 (1.5%) treatment groups, was low and comparable (Table 27). The 3 most commonly reported treatment-related AEs by PT across the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 treatment groups, respectively, were (percentage of patients [incidence rate per 100 patient-years]): oral candidiasis (0.3% [0.35], 0.3% [0.34], 0.2% [0.23]), dysphonia (0.2% [0.23], 0.3% [0.34], 0.1% [0.12]), and oropharyngeal candidiasis (0.2% [0.23], 0.3% [0.34], 0% [0]).

Table 27 Treatment-Related Adverse Events During the Randomized Treatment Period by System Organ Class and Preferred Term (Safety Analysis Set) – MANDALA

System Organ Class Preferred Term	BDA MDI 160/180 (N=1015)		BDA MDI 80/180 (N=1055)		AS MDI 180 (N=1057)	
	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
Patients with any treatment-related AE	21 (2.1)	2.44	20 (1.9)	2.27	16 (1.5)	1.85
Infections and infestations	**9 (0.9)**	**1.04**	**8 (0.8)**	**0.91**	**4 (0.4)**	**0.46**
Bronchitis	0	0	1 (0.1)	0.11	0	0
Candida infection	1 (0.1)	0.12	0	0	0	0
Oral candidiasis	3 (0.3)	0.35	3 (0.3)	0.34	2 (0.2)	0.23
Oropharyngeal candidiasis	2 (0.2)	0.23	3 (0.3)	0.34	0	0
Postoperative wound infection	1 (0.1)	0.12	0	0	0	0
Sinusitis	1 (0.1)	0.12	0	0	1 (0.1)	0.12
Upper respiratory tract infection	1 (0.1)	0.12	1 (0.1)	0.11	1 (0.1)	0.12
Endocrine disorders	**1 (0.1)**	**0.12**	**1 (0.1)**	**0.11**	**0**	**0**
Glucocorticoid deficiency	1 (0.1)	0.12	0	0	0	0
Secondary adrenocortical insufficiency	0	0	1 (0.1)	0.11	0	0
Nervous system disorders	**1 (0.1)**	**0.12**	**2 (0.2)**	**0.23**	**4 (0.4)**	**0.46**
Dysgeusia	1 (0.1)	0.12	1 (0.1)	0.11	1 (0.1)	0.12
Headache	0	0	0	0	2 (0.2)	0.23
Somnolence	0	0	1 (0.1)	0.11	0	0
Tremor	0	0	0	0	1 (0.1)	0.12

System Organ Class Preferred Term	BDA MDI 160/180 (N=1015)		BDA MDI 80/180 (N=1055)		AS MDI 180 (N=1057)	
	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
Cardiac disorders	**2 (0.2)**	**0.23**	**1 (0.1)**	**0.11**	**1 (0.1)**	**0.12**
Atrial fibrillation	1 (0.1)	0.12	0	0	0	0
Palpitations	1 (0.1)	0.12	1 (0.1)	0.11	1 (0.1)	0.12
Respiratory, thoracic, and mediastinal disorders	**4 (0.4)**	**0.46**	**7 (0.7)**	**0.79**	**2 (0.2)**	**0.23**
Asthma	1 (0.1)	0.12	0	0	0	0
Cough	1 (0.1)	0.12	3 (0.3)	0.34	0	0
Dry throat	0	0	1 (0.1)	0.11	1 (0.1)	0.12
Dysphonia	2 (0.2)	0.23	3 (0.3)	0.34	1 (0.1)	0.12
Oropharyngeal pain	0	0	1 (0.1)	0.11	1 (0.1)	0.12
Throat irritation	1 (0.1)	0.12	1 (0.1)	0.11	0	0
Gastrointestinal disorders	**5 (0.5)**	**0.58**	**0**	**0**	**3 (0.3)**	**0.35**
Dry mouth	3 (0.3)	0.35	0	0	1 (0.1)	0.12
Glossodynia	0	0	0	0	1 (0.1)	0.12
Nausea	1 (0.1)	0.12	0	0	1 (0.1)	0.12
Umbilical hernia	1 (0.1)	0.12	0	0	0	0
Skin and subcutaneous disorders	**2 (0.2)**	**0.23**	**1 (0.1)**	**0.11**	**1 (0.1)**	**0.12**
Dry skin	1 (0.1)	0.12	0	0	0	0
Pruritus	1 (0.1)	0.12	0	0	0	0
Rash	1 (0.1)	0.12	1 (0.1)	0.11	1 (0.1)	0.12
General disorders and administration site conditions	**1 (0.1)**	**0.12**	**0**	**0**	**0**	**0**
Edema	1 (0.1)	0.12	0	0	0	0
Investigations	**0**	**0**	**2 (0.2)**	**0.23**	**2 (0.2)**	**0.23**
Cortisol decreased	0	0	2 (0.2)	0.23	2 (0.2)	0.23
Injury, poisoning, and procedural complications	**0**	**0**	**0**	**0**	**1 (0.1)**	**0.12**
Procedural dizziness	0	0	0	0	1 (0.1)	0.12

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MedDRA = Medical Dictionary for Regulatory Activities; MDI = metered dose inhaler; pt-yrs = patient-years.

Note: The randomized treatment period was defined as the date of randomization up to and including completion/discontinuation of randomized study treatment. AEs were coded using MedDRA version 24.0.

[a] With treatment-related AEs, as assessed by the investigator. A patient could have had 1 or more preferred terms reported under a given system organ class.

[b] Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100. The total duration of treatment across all patients in BDA MDI 160/180 = 861.588 years; in BDA MDI 80/180 = 882.645 years; in AS MDI 180 = 865.046 years.

Phase 3: DENALI

In DENALI, the percentage of patients who had treatment-related AEs ranged from 1.0% to 5.1% across all treatment groups (Table 28). Treatment-related AEs were most commonly reported in the system organ classes of respiratory, thoracic, and mediastinal disorders, with 3.6% in BDA MDI 160/180, 2.0% in BDA MDI 80/180, and 2.0% in BD MDI 160 groups, compared with 0.5% each in AS MDI 180 and placebo MDI groups. Treatment-related AEs from other system organ classes occurred in <2.0% patients across all groups. The incidence rate (per 100 patient-years) of treatment-related AEs across treatment groups were as follows: 21.83 per 100 patient-years for the BDA MDI 160/180 group, 13.02 per 100 patient-years for the BDA MDI 80/180 group, 15.28 per 100 patient-years for the BD MDI 160 group, 4.40 per 100 patient-years for the AS MDI 180 group, and 6.74 per 100 patient-years for the placebo MDI group.

Table 28 Treatment-Related Adverse Events During the Randomized Treatment Period by System Organ Class and Preferred Term (Safety Analysis Set) – DENALI

System Organ Class Preferred Term[a]	Number (%) of Patients				
	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)
Patients with any treatment-related AE	10 (5.1)	6 (2.9)	7 (3.5)	2 (1.0)	3 (1.5)
Infections and infestations	**3 (1.5)**	**0**	**0**	**0**	**0**
Oral candidiasis	1 (0.5)	0	0	0	0
Oropharyngeal candidiasis	2 (1.0)	0	0	0	0
Nervous system disorders	**0**	**0**	**2 (1.0)**	**0**	**0**
Somnolence	0	0	1 (0.5)	0	0
Tremor	0	0	1 (0.5)	0	0
Cardiac disorders	0	0	0	0	1 (0.5)
Palpitations	0	0	0	0	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	**7 (3.6)**	**4 (2.0)**	**4 (2.0)**	**1 (0.5)**	**1 (0.5)**
Asthma	0	1 (0.5)	0	1 (0.5)	0
Dry throat	0	1 (0.5)	0	0	0
Dysphonia	4 (2.0)	1 (0.5)	2 (1.0)	0	0
Dyspnea	0	0	0	0	1 (0.5)
Increased bronchial secretion	1 (0.5)	0	0	0	0
Oropharyngeal pain	0	0	2 (1.0)	0	0
Rhinorrhea	1 (0.5)	0	0	0	0
Throat clearing	0	1 (0.5)	0	0	0
Throat irritation	1 (0.5)	0	0	0	0
Wheezing	0	0	1 (0.5)	0	0
Gastrointestinal disorders	**1 (0.5)**	**1 (0.5)**	**0**	**0**	**0**
Abdominal pain upper	1 (0.5)	0	0	0	0
Hypoesthesia oral	0	1 (0.5)	0	0	0
Skin and subcutaneous tissue disorders	**0**	**1 (0.5)**	**2 (1.0)**	**0**	**1 (0.5)**
Acne	0	1 (0.5)	0	0	0

System Organ Class Preferred Term[a]	Number (%) of Patients				
	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)
Erythema	0	0	1 (0.5)	0	0
Hyperhidrosis	0	0	0	0	1 (0.5)
Urticaria	0	0	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders	**1 (0.5)**	**0**	**0**	**0**	**0**
Muscle spasms	1 (0.5)	0	0	0	0
General disorders and administration site conditions	**0**	**1 (0.5)**	**2 (1.0)**	**1 (0.5)**	**0**
Chest discomfort	0	0	1 (0.5)	0	0
Chest pain	0	0	1 (0.5)	0	0
Feeling jittery	0	0	0	1 (0.5)	0
Sensation of foreign body	0	1 (0.5)	0	0	0
Investigations	**1 (0.5)**	**0**	**0**	**0**	**1 (0.5)**
Forced expiratory volume decreased	0	0	0	0	1 (0.5)
Heart rate increased	1 (0.5)	0	0	0	0

Abbreviations: AE = adverse event; AS = albuterol sulfate; BD = budesonide; BDA = budesonide/albuterol sulfate; MedDRA = Medical Dictionary for Regulatory Activities; MDI = metered dose inhaler.
Note: The randomly assigned treatment period was defined as the date of first dose to the date of last dose of randomly assigned study treatment. AEs were coded using MedDRA version 24.0.
[a] A patient could have had 1 or more preferred terms reported under a given system organ class.

Phase 3: TYREE

One patient experienced an AE (anxiety/heightened anxiety with tearfulness) that was considered to be related to study treatment. The patient was a 15-year-old female who experienced anxiety on Day 1 of randomization while receiving placebo MDI. The AE had a duration of 2 days and was considered moderate in intensity (not serious).

7.2.4 Adverse Events by Mean Daily IP Use (MANDALA Only)

The overall frequency of AEs was comparable between treatment groups, including with increasing mean daily IP use (Table 29). Nasopharyngitis, headache, and COVID-19 remained the most commonly reported AEs across the BDA MDI treatment groups when mean daily IP use was >0 to <3 inhalations or ≥3 to <6 inhalations per day. In the small percentage of patients (approximately 5%) with mean daily use of BDA MDI ≥6 inhalations, there was no clinically important increase in AEs compared with AS MDI.

Table 29 Most Common Adverse Events (Frequency of ≥2%) During the Randomized Treatment Period by Preferred Term and Mean Daily IP Use (Safety Analysis Set) – MANDALA

Mean Daily IP Use	Preferred Term	BDA MDI 160/180		BDA MDI 80/180		AS MDI 180	
		Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
>0 to <3 inhalations[c]	N	607		614		600	
	Patients with any AE	265 (43.7)	50.52	272 (44.3)	51.79	269 (44.8)	53.35
	Nasopharyngitis	47 (7.7)	8.96	32 (5.2)	6.09	31 (5.2)	6.15
	COVID-19	27 (4.4)	5.15	27 (4.4)	5.14	29 (4.8)	5.75
	Headache	18 (3.0)	3.43	30 (4.9)	5.71	26 (4.3)	5.16
	Upper respiratory tract infection	14 (2.3)	2.67	17 (2.8)	3.24	16 (2.7)	3.17
	Back pain	16 (2.6)	3.05	16 (2.6)	3.05	12 (2.0)	2.38
	Hypertension	14 (2.3)	2.67	11 (1.8)	2.09	16 (2.7)	3.17
	Bronchitis	10 (1.6)	1.91	15 (2.4)	2.86	15 (2.5)	2.98
	Sinusitis	7 (1.2)	1.33	6 (1.0)	1.14	12 (2.0)	2.38
≥3 to <6 inhalations[d]	N	350		375		395	
	Patients with any AE	176 (50.3)	59.99	191 (50.9)	62.60	191 (48.4)	61.03
	Nasopharyngitis	25 (7.1)	8.52	24 (6.4)	7.87	22 (5.6)	7.03
	Headache	24 (6.9)	8.18	18 (4.8)	5.90	18 (4.6)	5.75
	COVID-19	14 (4.0)	4.77	23 (6.1)	7.54	16 (4.1)	5.11
	Asthma	8 (2.3)	2.73	10 (2.7)	3.28	21 (5.3)	6.71
	Bronchitis	11 (3.1)	3.75	10 (2.7)	3.28	10 (2.5)	3.20
	Upper respiratory tract infection	10 (2.9)	3.41	11 (2.9)	3.61	9 (2.3)	2.88
	Sinusitis	8 (2.3)	2.73	9 (2.4)	2.95	12 (3.0)	3.83
	Influenza	9 (2.6)	3.07	13 (3.5)	4.26	6 (1.5)	1.92
	Hypertension	6 (1.7)	2.05	12 (3.2)	3.93	7 (1.8)	2.24
	Back pain	10 (2.9)	3.41	7 (1.9)	2.29	7 (1.8)	2.24
	Rhinitis allergic	8 (2.3)	2.73	9 (2.4)	2.95	7 (1.8)	2.24
	Acute sinusitis	5 (1.4)	1.70	7 (1.9)	2.29	8 (2.0)	2.56
	Arthralgia	8 (2.3)	2.73	4 (1.1)	1.31	4 (1.0)	1.28
	Dyspepsia	9 (2.6)	3.07	5 (1.3)	1.64	0	0

Mean Daily IP Use	Preferred Term	BDA MDI 160/180		BDA MDI 80/180		AS MDI 180	
		Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
≥6 to <9 inhalations[e]	N	46		55		45	
	Patients with any AE	27 (58.7)	73.04	28 (50.9)	60.77	22 (48.9)	63.01
	Nasopharyngitis	4 (8.7)	10.82	5 (9.1)	10.85	1 (2.2)	2.86
	Bronchitis	4 (8.7)	10.82	2 (3.6)	4.34	3 (6.7)	8.59
	Hypertension	2 (4.3)	5.41	4 (7.3)	8.68	2 (4.4)	5.73
	Headache	2 (4.3)	5.41	1 (1.8)	2.17	4 (8.9)	11.46
	Asthma	1 (2.2)	2.71	1 (1.8)	2.17	3 (6.7)	8.59
	COVID-19	2 (4.3)	5.41	2 (3.6)	4.34	1 (2.2)	2.86
	Influenza	2 (4.3)	5.41	1 (1.8)	2.17	2 (4.4)	5.73
	Lower respiratory tract infection	3 (6.5)	8.12	2 (3.6)	4.34	0	0
	Upper respiratory tract infection	2 (4.3)	5.41	3 (5.5)	6.51	0	0
	Cough	2 (4.3)	5.41	1 (1.8)	2.17	1 (2.2)	2.86
	Nausea	1 (2.2)	2.71	2 (3.6)	4.34	1 (2.2)	2.86
	Oral candidiasis	1 (2.2)	2.71	3 (5.5)	6.51	0	0
	Arthralgia	0	0	3 (5.5)	6.51	0	0
	Rhinitis allergic	1 (2.2)	2.71	2 (3.6)	4.34	0	0
	Viral upper respiratory tract infection	0	0	1 (1.8)	2.17	2 (4.4)	5.73
	Back pain	1 (2.2)	2.71	0	0	1 (2.2)	2.86
	Dizziness	1 (2.2)	2.71	1 (1.8)	2.17	0	0
	Dyspepsia	0	0	0	0	2 (4.4)	5.73
	Gastroesophageal reflux disease	1 (2.2)	2.71	1 (1.8)	2.17	0	0
	Hyperglycemia	1 (2.2)	2.71	0	0	1 (2.2)	2.86
	Musculoskeletal chest pain	1 (2.2)	2.71	0	0	1 (2.2)	2.86
	Oropharyngeal pain	0	0	1 (1.8)	2.17	1 (2.2)	2.86
	Pain in extremity	0	0	0	0	2 (4.4)	5.73
	Rash	2 (4.3)	5.41	0	0	0	0
	Seasonal allergy	0	0	1 (1.8)	2.17	1 (2.2)	2.86
	Sinusitis	0	0	2 (3.6)	4.34	0	0
	Tremor	0	0	1 (1.8)	2.17	1 (2.2)	2.86
	Acute myocardial infarction	1 (2.2)	2.71	0	0	0	0

Mean Daily IP Use	Preferred Term	BDA MDI 160/180		BDA MDI 80/180		AS MDI 180	
		Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
≥6 to <9 inhalations[e]	Allergy to arthropod bite	1 (2.2)	2.71	0	0	0	0
	Benign prostatic hyperplasia	1 (2.2)	2.71	0	0	0	0
	Blood chloride decreased	0	0	0	0	1 (2.2)	2.86
	Blood sodium decreased	0	0	0	0	1 (2.2)	2.86
	Cat scratch disease	1 (2.2)	2.71	0	0	0	0
	Chest discomfort	1 (2.2)	2.71	0	0	0	0
	Dry skin	1 (2.2)	2.71	0	0	0	0
	Dry throat	0	0	0	0	1 (2.2)	2.86
	Dysphonia	0	0	0	0	1 (2.2)	2.86
	Eczema	1 (2.2)	2.71	0	0	0	0
	Hematochezia	1 (2.2)	2.71	0	0	0	0
	Hypersensitivity	1 (2.2)	2.71	0	0	0	0
	Hypoglycemia	0	0	0	0	1 (2.2)	2.86
	Hypokalemia	0	0	0	0	1 (2.2)	2.86
	Lung neoplasm malignant	1 (2.2)	2.71	0	0	0	0
	Multiple allergies	1 (2.2)	2.71	0	0	0	0
	Noncardiac chest pain	0	0	0	0	1 (2.2)	2.86
	Oral herpes	0	0	0	0	1 (2.2)	2.86
	Paranasal cyst	1 (2.2)	2.71	0	0	0	0
	Pharyngitis	0	0	0	0	1 (2.2)	2.86
	Platelet count increased	1 (2.2)	2.71	0	0	0	0
	Pneumothorax	1 (2.2)	2.71	0	0	0	0
	Polycystic ovaries	0	0	0	0	1 (2.2)	2.86
	Procedural dizziness	0	0	0	0	1 (2.2)	2.86
	Renal cyst	1 (2.2)	2.71	0	0	0	0
	Respiratory tract infection	0	0	0	0	1 (2.2)	2.86
	Respiratory tract infection viral	0	0	0	0	1 (2.2)	2.86
	Restless legs syndrome	0	0	0	0	1 (2.2)	2.86
	Sciatica	0	0	0	0	1 (2.2)	2.86
	Sinus tachycardia	1 (2.2)	2.71	0	0	0	0

Mean Daily IP Use	Preferred Term	BDA MDI 160/180		BDA MDI 80/180		AS MDI 180	
		Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
	Somnolence	1 (2.2)	2.71	0	0	0	0
	Spinal osteoarthritis	0	0	0	0	1 (2.2)	2.86
	Splinter	1 (2.2)	2.71	0	0	0	0
	Subcutaneous emphysema	1 (2.2)	2.71	0	0	0	0
	Urinary tract infection	0	0	0	0	1 (2.2)	2.86
≥9 inhalations[f]	N	4		3		7	
	Patients with any AE	1 (25.0)	20.87	3 (100.0)	102.79	5 (71.4)	88.74
	Asthma	0	0	0	0	2 (28.6)	35.50
	Headache	0	0	1 (33.3)	34.26	1 (14.3)	17.75
	Acute sinusitis	0	0	0	0	1 (14.3)	17.75
	Arthralgia	0	0	0	0	1 (14.3)	17.75
	Benign prostatic hyperplasia	0	0	0	0	1 (14.3)	17.75
	Cough	0	0	1 (33.3)	34.26	0	0
	Dyspepsia	0	0	1 (33.3)	34.26	0	0
	Gastroenteritis viral	1 (25.0)	20.87	0	0	0	0
	Groin pain	0	0	0	0	1 (14.3)	17.75
	Hypertension	0	0	0	0	1 (14.3)	17.75
	Upper respiratory tract infection	0	0	0	0	1 (14.3)	17.75
	Urinary retention	0	0	0	0	1 (14.3)	17.75
	Urinary tract infection	0	0	0	0	1 (14.3)	17.75

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; COVID-19 = coronavirus disease 2019; IP = investigational product; MDI = metered dose inhaler; MedDRA = Medical Dictionary for Regulatory Activities; pt-yrs = patient-years.

Note: The randomized treatment period was defined as the date of randomization up to and including completion/discontinuation of randomized study treatment. AEs were coded using MedDRA version 24.0.

[a] With AEs, sorted by alphabetical order for preferred term. Patients with multiple events in the same preferred term were counted only once in that preferred term.

[b] Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100.

[c] The total duration of treatment across all patients in BDA MDI 160/180 = 524.515 years; in BDA MDI 80/180 = 525.229 years; in AS MDI 180 = 504.189 years.

[d] The total duration of treatment across all patients in BDA MDI 160/180 = 293.361 years; in BDA MDI 80/180 = 305.109 years; in AS MDI 180 = 312.977 years.

[e] The total duration of treatment across all patients in BDA MDI 160/180 = 36.964 years; in BDA MDI 80/180 = 46.078 years; in AS MDI 180 = 34.916 years.

[f] The total duration of treatment across all patients in BDA MDI 160/180 = 4.791 years; in BDA MDI 80/180 = 2.919 years; in AS MDI 180 = 5.634 years.

7.2.5 Adverse Events by Total Daily Dose of Background ICS (MANDALA Only)

In MANDALA, when stratified by daily dose of background maintenance ICS (low, medium, and high daily dose), the frequency of AEs was similar between treatment groups (Table 30). Nasopharyngitis, headache, and COVID-19 remained the most commonly reported AEs across daily dose of background maintenance ICS, with similar frequencies across treatment groups.

Table 30 Most Common Adverse Events (Frequency of ≥2%) During the Randomized Treatment Period by Preferred Term and Daily Dose of Background ICS (Safety Analysis Set) – MANDALA

Daily Dose of Background Maintenance ICS	Preferred Term	BDA MDI 160/180		BDA MDI 80/180		AS MDI 180	
		Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
Overall[c]	N	1015		1055		1057	
	Patients with any AE	469 (46.2)	54.43	497 (47.1)	56.31	490 (46.4)	56.64
	Asthma	18 (1.8)	2.09	20 (1.9)	2.27	35 (3.3)	4.05
	Back pain	27 (2.7)	3.13	23 (2.2)	2.61	20 (1.9)	2.31
	Bronchitis	25 (2.5)	2.90	27 (2.6)	3.06	28 (2.6)	3.24
	COVID-19	43 (4.2)	4.99	52 (4.9)	5.89	46 (4.4)	5.32
	Headache	44 (4.3)	5.11	50 (4.7)	5.66	50 (4.7)	5.78
	Hypertension	22 (2.2)	2.55	27 (2.6)	3.06	26 (2.5)	3.01
	Influenza	21 (2.1)	2.44	23 (2.2)	2.61	14 (1.3)	1.62
	Nasopharyngitis	76 (7.5)	8.82	61 (5.8)	6.91	54 (5.1)	6.24
	Rhinitis allergic	17 (1.7)	1.97	21 (2.0)	2.38	18 (1.7)	2.08
	Sinusitis	15 (1.5)	1.74	17 (1.6)	1.93	24 (2.3)	2.77
	Upper respiratory tract infection	26 (2.6)	3.02	31 (2.9)	3.51	26 (2.5)	3.01
Low[d]	N	231		254		235	
	Patients with any AE	106 (45.9)	54.14	109 (42.9)	50.90	107 (45.5)	55.30
	Asthma	5 (2.2)	2.55	7 (2.8)	3.27	5 (2.1)	2.58
	Back pain	7 (3.0)	3.58	3 (1.2)	1.40	3 (1.3)	1.55
	Bronchitis	5 (2.2)	2.55	7 (2.8)	3.27	6 (2.6)	3.10
	COVID-19	9 (3.9)	4.60	15 (5.9)	7.01	9 (3.8)	4.65
	Headache	11 (4.8)	5.62	8 (3.1)	3.74	13 (5.5)	6.72
	Hypertension	3 (1.3)	1.53	7 (2.8)	3.27	8 (3.4)	4.13
	Nasopharyngitis	13 (5.6)	6.64	13 (5.1)	6.07	13 (5.5)	6.72
	Oropharyngeal pain	6 (2.6)	3.06	2 (0.8)	0.93	2 (0.9)	1.03
	Pharyngitis	2 (0.9)	1.02	5 (2.0)	2.34	1 (0.4)	0.52
	Rhinitis allergic	2 (0.9)	1.02	6 (2.4)	2.80	6 (2.6)	3.10
	Sinusitis	1 (0.4)	0.51	4 (1.6)	1.87	6 (2.6)	3.10

Daily Dose of Background Maintenance ICS	Preferred Term	BDA MDI 160/180		BDA MDI 80/180		AS MDI 180	
		Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
Medium[e]	N	457		513		499	
	Patients with any AE	209 (45.7)	53.96	239 (46.6)	55.95	224 (44.9)	56.45
	Arthralgia	12 (2.6)	3.10	10 (1.9)	2.34	9 (1.8)	2.27
	Asthma	6 (1.3)	1.55	9 (1.8)	2.11	17 (3.4)	4.28
	Back pain	11 (2.4)	2.84	15 (2.9)	3.51	11 (2.2)	2.77
	Bronchitis	11 (2.4)	2.84	13 (2.5)	3.04	13 (2.6)	3.28
	COVID-19	19 (4.2)	4.91	16 (3.1)	3.75	24 (4.8)	6.05
	Headache	21 (4.6)	5.42	29 (5.7)	6.79	22 (4.4)	5.54
	Hypertension	10 (2.2)	2.58	14 (2.7)	3.28	10 (2.0)	2.52
	Gastroenteritis	9 (2.0)	2.32	3 (0.6)	0.70	2 (0.4)	0.50
	Influenza	12 (2.6)	3.10	14 (2.7)	3.28	9 (1.8)	2.27
	Nasopharyngitis	38 (8.3)	9.81	28 (5.5)	6.55	20 (4.0)	5.04
	Rhinitis allergic	10 (2.2)	2.58	8 (1.6)	1.87	7 (1.4)	1.76
	Sinusitis	9 (2.0)	2.32	11 (2.1)	2.58	10 (2.0)	2.52
	Upper respiratory tract infection	13 (2.8)	3.36	17 (3.3)	3.98	9 (1.8)	2.27
High[f]	N	319		288		319	
	Patients with any AE	151 (47.3)	55.60	149 (51.7)	61.74	158 (49.5)	58.79
	Asthma	6 (1.9)	2.21	4 (1.4)	1.66	13 (4.1)	4.84
	Back pain	9 (2.8)	3.31	5 (1.7)	2.07	6 (1.9)	2.23
	Bronchitis	9 (2.8)	3.31	7 (2.4)	2.90	9 (2.8)	3.35
	Cough	2 (0.6)	0.74	4 (1.4)	1.66	7 (2.2)	2.60
	COVID-19	15 (4.7)	5.52	21 (7.3)	8.70	13 (4.1)	4.84
	Headache	12 (3.8)	4.42	13 (4.5)	5.39	15 (4.7)	5.58
	Hypertension	9 (2.8)	3.31	6 (2.1)	2.49	8 (2.5)	2.98
	Influenza	6 (1.9)	2.21	6 (2.1)	2.49	4 (1.3)	1.49
	Nasopharyngitis	25 (7.8)	9.21	20 (6.9)	8.29	21 (6.6)	7.81
	Oropharyngeal pain	1 (0.3)	0.37	1 (0.3)	0.41	8 (2.5)	2.98
	Rhinitis	4 (1.3)	1.47	6 (2.1)	2.49	3 (0.9)	1.12
	Rhinitis allergic	5 (1.6)	1.84	7 (2.4)	2.90	5 (1.6)	1.86
	Sinusitis	5 (1.6)	1.84	2 (0.7)	0.83	8 (2.5)	2.98

Daily Dose of Background Maintenance ICS	Preferred Term	BDA MDI 160/180		BDA MDI 80/180		AS MDI 180	
		Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]	Number (%) of Patients[a]	Incidence Rate (per 100 pt-yrs)[b]
	Upper respiratory tract infection	9 (2.8)	3.31	12 (4.2)	4.97	12 (3.8)	4.46
	Urinary tract infection	5 (1.6)	1.84	0	0	7 (2.2)	2.60

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; COVID-19 = coronavirus disease 2019; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; MDI = metered dose inhaler; MedDRA = Medical Dictionary for Regulatory Activities; pt-yrs = patient-years.
Note: Daily dose of background maintenance ICS was based on prescribed maintenance medication at baseline and categorized per GINA 2020 guidelines. The randomized treatment period was defined as the date of randomization up to and including completion/discontinuation of randomized study treatment. AEs were coded using MedDRA version 24.0.

[a] With AEs, sorted by alphabetical order for preferred term.
[b] Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100.
[c] The total duration of treatment across all patients in BDA MDI 160/180 = 861.588 years; in BDA MDI 80/180 = 882.645 years; in AS MDI 180 = 865.046 years.
[d] The total duration of treatment across all patients in BDA MDI 160/180 = 195.786 years; in BDA MDI 80/180 = 214.125 years; in AS MDI 180 = 193.498 years.
[e] The total duration of treatment across all patients in BDA MDI 160/180 = 387.307 years; in BDA MDI 80/180 = 427.170 years; in AS MDI 180 = 396.808 years.
[f] The total duration of treatment across all patients in BDA MDI 160/180 = 271.576 years; in BDA MDI 80/180 = 241.350 years; in AS MDI 180 = 268.775 years.

7.2.6 Deaths, Serious Adverse Events, and Other Significant Adverse Events

7.2.6.1 Fatal Adverse Events

Phase 3: MANDALA

Seven patients died in MANDALA during the randomized treatment period: 4 in the BDA MDI 160/180, 2 in the BDA MDI 80/180, and 1 in the AS MDI 180 as-needed groups, respectively. Four of the 7 deaths were associated with COVID-19: 2 in the BDA MDI 160/180 group, 1 in the BDA MDI 80/180 group, and 1 in the AS MDI 180 group. Of the 3 non-COVID-19 associated deaths, 2 occurred in the BDA MDI 160/180 group (cardiac arrest and blood glucose increased) and 1 in the BDA MDI 80/180 group (pneumothorax with metastases to the lung) treatment groups. One additional death occurred 1 day after the safety follow-up period in the AS MDI 180 group (intestinal infarction). None of the deaths were considered by the investigator to be causally related to study treatment. None of the deaths were adjudicated as asthma related.

Phase 3: DENALI

There were no fatal AEs in DENALI.

Phase 3: TYREE

There were no fatal AEs in TYREE.

7.2.6.2 Serious Adverse Events

Overall, no clinically important differences in the incidence of SAEs were noted between the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed groups in the pivotal studies.

Phase 3: MANDALA

In MANDALA, the most common SAE was COVID-19, with 1.1%, 0.5%, 0.8%, respectively, across the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed groups.

Phase 3: DENALI

In DENALI, no SAE occurred in more than 1 patient per treatment group.

Phase 3: TYREE

There were no SAEs in TYREE.

7.2.6.3 Adverse Events Leading to Discontinuation

All treatments were well tolerated. Overall, no clinically important differences in the incidence of AEs leading to discontinuations were noted between the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed groups in the pivotal studies.

Phase 3: MANDALA

In MANDALA, the most common AE leading to discontinuation was COVID-19, with 0.5%, 0%, 0.5%, respectively, across the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed groups.

Phase 3: DENALI

In DENALI, the only AE leading to discontinuation that occurred in more than 1 patient per treatment group was asthma, which occurred in 2 (1.0%) patients each in AS MDI 180 and placebo MDI QID treatment groups.

Phase 3: TYREE

There were no AEs resulting in discontinuation in TYREE.

7.2.7 Adverse Events of Special Interest

AEs of special interest were not collected in any of the Phase 3 studies, as agreed with FDA.

7.2.8 ICS-Associated Adverse Events

Local and systemic ICS-associated AEs are described below. All ICS-associated AEs were selected by the Sponsor before database lock and unblinding.

7.2.8.1 Local ICS-Associated Adverse Events

Overall, the number of patients with any local ICS-associated AEs was low and generally comparable across the treatment groups, with the exception of oral and oropharyngeal candidiasis, which is a well-known local AE associated with ICS.

Phase 3: MANDALA

In MANDALA, where no mouth rinsing instructions were provided, the overall percentage of patients who experienced a local ICS-associated AE during the randomized treatment period was low and similar between the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed groups: 2.0%, 1.8%, 1.3%, respectively (Table 31). When stratified by low, medium, and high daily dose of background maintenance ICS, the frequency of local ICS-associated AEs was comparable between treatment groups.

Table 31 Local ICS-Associated Adverse Events During the Randomized Treatment Period (Safety Analysis Set) – MANDALA

Groups With Selected Preferred Terms	Number (%) of Patients		
	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Patients with any local ICS-associated AE	20 (2.0)	19 (1.8)	14 (1.3)
Local candidiasis infection	14 (1.4)	13 (1.2)	7 (0.7)
Aphonia/dysphonia	5 (0.5)	6 (0.6)	4 (0.4)

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; ICS = inhaled corticosteroid; MDI = metered dose inhaler.

Phase 3: DENALI

In DENALI, where patients were instructed to mouth rinse after each dose, the percentage of patients reporting local ICS-associated AEs was low (≤2%) and similar between the BDA MDI QID and BD MDI QID treatment groups.

7.2.8.2 Systemic ICS-Associated Class Effects

Overall, the number of patients with any systemic ICS-associated AE was low and comparable across the treatment groups.

Phase 3: MANDALA

In MANDALA, the overall percentage of patients who experienced any systemic ICS-associated AE during the randomized treatment period was low and similar between the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed groups (3.3%, 3.2%, 3.8%, respectively; Table 32). When stratified by low, medium, and high daily dose of background maintenance therapy, the frequency of systemic ICS-associated AEs was comparable between treatment groups. The type of maintenance medication did not impact this analysis.

Table 32 Systemic ICS-Associated Adverse Events During the Randomized Treatment Period (Safety Analysis Set) – MANDALA

Groups With Selected Preferred Terms	Number (%) of Patients		
	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Patients with any systemic ICS-associated AE	33 (3.3)	34 (3.2)	40 (3.8)
Adrenal disorders	0	7 (0.7)	2 (0.2)
Diabetes and glucose disorders	11 (1.1)	5 (0.5)	11 (1.0)
Ocular disorders	2 (0.2)	0	2 (0.2)
Skeletal disorders	5 (0.5)	8 (0.8)	12 (1.1)

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; ICS = inhaled corticosteroid; MDI = metered dose inhaler.
Adrenal disorders: Adrenocortical insufficiency acute, cortisol decreased, secondary adrenocortical insufficiency.
Diabetes and glucose disorders: Blood glucose increased, diabetes mellitus, diabetes mellitus inadequate control, diabetic metabolic decompensation, hyperglycemia, type 2 diabetes mellitus.
Ocular disorders: Cataract, glaucoma.
Skeletal disorders also includes one report of osteopenia in the BDA MDI 160/180 group.

Phase 3: DENALI

In DENALI, potential systemic steroid class effects were negligible.

7.2.9 COVID-19 Adverse Events

Phase 3: MANDALA

Overall in MANDALA, COVID-19 was the third most commonly reported AE by PT and was reported for 4.2%, 4.9%, and 4.4% of patients in the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed groups, respectively.

Phase 3: DENALI

Overall in DENALI, COVID-19 was the ninth most commonly reported AE by PT and was reported for 1.0%, 0.5%, 1.0%, 0%, and 2.0% of patients in the BDA MDI 160/180, BDA MDI 80/180, BD MDI 160, AS MDI 180, and placebo MDI QID treatment groups, respectively.

7.2.10 Pneumonia Adverse Events (MANDALA Only)

In MANDALA, there was a small numerical imbalance in pneumonia AE reports for BDA MDI 160/180 compared with AS MDI 180 (Table 33). This was mainly driven by nonserious AE reports and not SAE reports.

After the start of the COVID-19 pandemic, additional Medical Dictionary for Regulatory Activities (MedDRA) PTs of COVID-19 and COVID-19 pneumonia were included, and it was noted that some patients had AE reports of COVID-19 pneumonia while others had an AE of pneumonia with a concurrent AE of COVID-19. In a post hoc analysis, patients with either the AE of COVID-19 pneumonia or the AE of pneumonia and a concurrent AE of COVID-19 were analyzed as pneumonia AEs associated with COVID-19, which showed that most of the pneumonia AE reports were associated with COVID-19 (33 of 50 patients).

The post hoc analysis showed a similar number of patients with COVID-19 associated pneumonia AEs across treatment groups. For patients with pneumonia AEs not associated with COVID-19, a small numerical imbalance between BDA MDI 160/180 (n=9), BDA MDI 80/180 (n=6), and AS MDI 180 (n=3) was noted.

The post hoc analysis assessing patients with SAEs of COVID-19-associated pneumonia or pneumonia not associated with COVID-19 showed a similar number of patients in each treatment group.

Following the post hoc analyses and a thorough review of supporting data (including narratives, listings, and available imaging), the small numerical imbalance of pneumonia AEs observed in the MANDALA study, which included more than 3100 patients and was conducted in the context of the COVID-19 pandemic, was not considered to constitute a safety concern.

Table 33 Pneumonia Adverse Events (COVID-19 and Non-COVID-19 Associated) During the Randomized Treatment Period (Safety Analysis Set) – MANDALA

Adverse Event	Number (%) of Patients		
	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Patients with any pneumonia AEs	**23 (2.3)**	**14* (1.3)**	**13 (1.2)**
COVID-19-associated pneumonia[a]	14 (1.4)	9 (0.9)	10 (0.9)
Pneumonia (non-COVID-19 associated)	9 (0.9)	6 (0.6)	3 (0.3)
Patients with SAEs of pneumonia	**9 (0.9)**	**8 (0.8)**	**7 (0.7)**
COVID-19-associated pneumonia[a]	7 (0.7)	6 (0.6)	7 (0.7)
Pneumonia (non-COVID-19 associated)	2 (0.2)	2 (0.2)	0

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; COVID-19 = coronavirus disease 2019; MDI = metered dose inhaler; SAE = serious adverse event.

[a] Post hoc analysis patients with either an AE of COVID-19 pneumonia or AE of pneumonia and a concurrent AE of COVID-19 were analyzed as pneumonia AEs associated with COVID-19.

* One patient ((b) (6)) was found to have 2 nonserious AE reports of pneumonia at different times, 1 not associated with COVID-19 (Day 204) and the other associated with COVID-19 (Day 274).

7.3 Long-Term Safety

MANDALA provides data for long-term safety evaluating real-world use and DENALI represents chronic dosing of the BDA MDI rescue product with higher daily dosing (see Section 7.1). Overall, no long-term safety concerns were detected in the analysis of patients with >24 weeks of exposure and with >1 year of exposure.

7.4 Overall Safety Conclusions

The overall safety profile of BDA MDI is consistent with the established profiles of the individual components with no new safety concerns identified. The safety profile of BDA MDI in MANDALA reflects as-needed use and long-term exposure of ≥24 weeks in asthma patients on background maintenance therapy, whereas the safety profile of BDA MDI in DENALI reflects chronic, regular dosing at relatively high daily doses in asthma patients on SABA alone or low-dose ICS maintenance therapy plus SABA as needed. In TYREE, only 2 AEs were reported, both in patients who were receiving placebo. In MANDALA, there were similar percentages of patients with AEs irrespective of background maintenance ICS or frequent daily use across treatment groups, and the number of patients with systemic or local ICS-associated AEs was low.

8.0 PEDIATRIC POPULATIONS

This section provides an overview of the efficacy and safety data from 2 pediatric subgroups: adolescents (aged ≥12 to <18 years) and children (aged ≥4 to <12 years) in the MANDALA study. As described in Section 6.1.1, patients ≥12 years of age were randomized to BDA MDI 160/180, BDA MDI 80/180, or AS MDI 180, whereas children 4 to 11 years of age were randomized only to BDA MDI 80/180 or AS MDI 180. All patients were given the same MDI administration and cleaning instructions, with additional instructions for children to use the MDI with an adult's help as instructed by the child's healthcare provider.

Data from both adolescents and children were included in the analysis of efficacy and safety of the overall population presented in Section 6.0 and Section 7.0, respectively.

Both the Agency and Sponsor recognize the scientific rationale for extrapolating the overall efficacy findings in MANDALA to the pediatric subgroups to better understand potential effects of BDA MDI compared with albuterol. GINA and NAEPP asthma guidelines use similar principles to guide diagnosis, assessment, and treatment strategies of asthma across the ages.[1] This is based on the broadly similar airway inflammation and bronchoconstriction during exacerbations,[27] immunopathology and disease characteristics,[28] and asthma biology across the age subgroups. Although there are some differences between children and adults with asthma, there is sufficient scientific justification for extrapolation of adult findings to pediatric populations.[29] In addition, the same endpoints are used to measure efficacy in asthma clinical trials across all ages. Furthermore, budesonide/formoterol rescue studies conducted outside of the US demonstrate similar treatment effects across adults, adolescents, and children.[30] Therefore, it is reasonable to expect that the efficacy of BDA MDI is similar across all ages. Finally, when adult data are available in conditions that exist in both adults and children, evidence of clinical benefit from the drug in adults can provide support for the prospect of direct benefit in children,[31] as is the case in asthma.

The FDA requested we include small numbers of children aged 4 to 11 years in the BDA MDI Phase 3 program due to the similar nature of the asthma across the ages. The limited number of patients (100 adolescents [≥12 to <17 years of age] and 83 children [≥4 to <11 years of age]) in MANDALA precluded meaningful statistical inference of treatment benefits. However, modeling using a Bayesian approach[32] across age and dose groups indicated a point estimate in favor of BDA MDI for the primary endpoint in pediatric subpopulations (Figure 21). See Section 8.1 for details on clinical efficacy results and refer to Section 8.3 for details on the Bayesian analysis.

8.1 Efficacy

8.1.1 Adolescents (Aged ≥12 to <18 Years)

Demographic and baseline characteristics of the adolescent subgroup were similar across the treatment groups (Table 34).

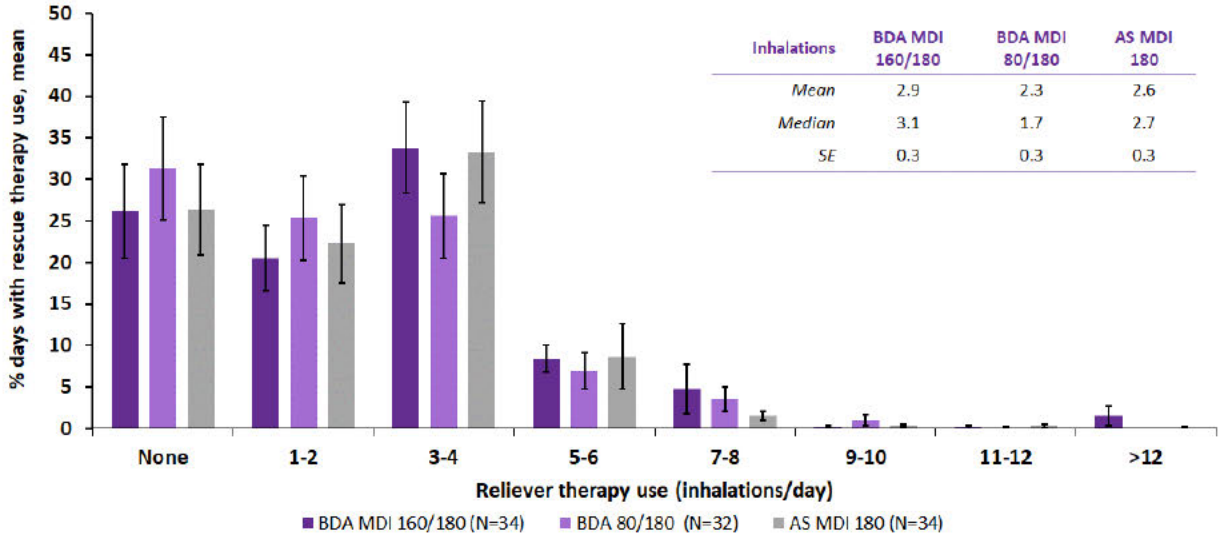
Table 34 Demographic and Baseline Characteristics in Adolescents ≥12 to <18 Years (Full Analysis Set) – MANDALA

Characteristic	BDA MDI 160/180 (N=34)	BDA MDI 80/180 (N=32)	AS MDI 180 (N=34)	Total (N=100)
Age, years				
Mean (SD)	14.3	13.3	14.3	14.0
SD	1.9	1.3	1.8	1.8
Sex, n (%)				
Male	20 (58.8)	16 (50.0)	15 (44.1)	51 (51.0)
Female	14 (41.2)	16 (50.0)	19 (55.9)	49 (49.0)
Race, n (%)				
White	18 (52.9)	19 (59.4)	19 (55.9)	56 (56.0)
Black or African American	10 (29.4)	7 (21.9)	13 (38.2)	30 (30.0)
Asian	3 (8.8)	4 (12.5)	1 (2.9)	8 (8.0)
Other	3 (8.8)	2 (6.3)	1 (2.9)	6 (6.0)
Ethnicity, n (%)				
Hispanic or Latinx	12 (35.3)	12 (37.5)	9 (26.5)	33 (33.0)
Not Hispanic or Latinx	22 (64.7)	20 (62.5)	25 (73.5)	67 (67.0)
Lung Function at Baseline				
FEV_1 prebronchodilator % predicted mean (SD)	77.3 (12.7)	77.2 (14.1)	78.1 (12.6)	77.6 (13.1)

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; FEV_1 = forced expiratory volume in 1 second; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.

Mean daily IP use during the randomized treatment period for adolescents in MANDALA was similar to the overall population, with 2.9, 2.3, and 2.6 inhalations per day in the BDA MDI 160/180, BDA MDI 80/180, and AS MDI 180 as-needed treatment groups, respectively (Figure 17). The patterns of use were also similar to the overall population with adolescents using ≤4 inhalations per day on 85% of study days and >8 inhalations per day on <1% of study days. Only 1 adolescent in the AS MDI 180 treatment group used more than the maximum allowed 12 inhalations per day on ≥2 consecutive days.

Figure 17 Pattern of Use in Adolescents ≥12 to <18 Years (Full Analysis Set) – MANDALA



Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler; SE = standard error.

As shown in Table 35, 32 to 34 adolescents were included in each treatment group, much lower than the approximately 1000 patients per group included in the overall population that was powered appropriately to demonstrate statistical significance. For the comparison of BDA MDI 160/180 dose to AS MDI 180 for the primary endpoint, the HR was 1.441. For the comparison of BDA MDI 80/180 dose to AS MDI 180, the HR was 0.570. As expected, given the size of the subgroup, the CIs were wide and crossed 1. It was therefore not possible to infer treatment benefits from these data.

Table 35 Severe Asthma Exacerbation Endpoints in Adolescents ≥12 to <18 Years (Full Analysis Set) – MANDALA

Parameter	BDA MDI 160/180 (N=34)	BDA MDI 80/180 (N=32)	AS MDI 180 (N=34)
Time to first severe exacerbation (comparison vs AS MDI 180)			
Patients with ≥1 severe exacerbation, n (%)	9 (26.5)	4 (12.5)	7 (20.6)
Total time at risk (patient-years)	15.0	17.8	19.0
Hazard ratio (95% CI)	1.441 (0.536, 3.869)	0.570 (0.167, 1.946)	--
P value	0.469	0.369	--
Annualized rate of exacerbation (comparison vs AS MDI 180)			
Total number of severe exacerbations	10	6	10
Total time at risk (patient-years)	18.9	21.0	21.4
Annualized rate estimate (95% CI)	0.54 (0.23, 1.23)	0.27 (0.10, 0.73)	0.70 (0.29, 1.66)
Rate ratio (95% CI)	0.77 (0.23, 2.54)	0.39 (0.10, 1.44)	--
P value	0.664	0.157	--

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; MDI = metered dose inhaler.

In the adolescent subgroup, both doses of BDA MDI showed a numerical decrease in the annualized total SCS dose compared with AS MDI. The percentage of patients with improvements in ACQ-5 and AQLQ+12 was numerically higher with BDA MDI groups than AS MDI (Table 36).

Table 36 Secondary Endpoints in Adolescents ≥12 to <18 Years (Full Analysis Set) – MANDALA

Secondary Endpoint (BDA MDI vs AS MDI 180)	BDA MDI Estimate (n)	AS MDI Estimate (n)	Treatment Comparison (95% CI)	*P* Value
BDA MDI 160/180 (N=34) vs AS MDI (N=34)				
Annualized total SCS dose, % difference in arithmetic means	73.6 mg/patient (34)	193.6 mg/patient (34)	-62%	0.72
ACQ-5 MCID at Week 24, responder analysis (odds ratio)	50.0% (34)	41.2% (34)	1.47 (0.56, 3.86)	0.44
AQLQ+12 MCID at Week 24, responder analysis (odds ratio)	37.5% (32)	27.3% (33)	1.54 (0.52, 4.54)	0.44
BDA MDI 80/180 (N=32) vs AS MDI (N=34)				
Annualized total SCS dose, % difference in arithmetic means	29.4 mg/patient (32)	193.6 mg/patient (34)	-84.8%	0.50
ACQ-5 MCID at Week 24, responder analysis (odds ratio)	65.6% (32)	41.2% (34)	2.9 (1.06, 7.94)	0.04
AQLQ+12 MCID at Week 24, responder analysis (odds ratio)	46.9% (32)	27.3% (33)	2.36 (0.81, 6.87)	0.12

Abbreviations: ACQ-5 = Asthma Control Questionnaire 5-item; AQLQ+12 = Asthma Quality of Life Questionnaire for 12 years and older; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; MCID = minimal clinically import difference; MDI = metered dose inhaler; SCS = systemic corticosteroid.

8.1.2 Children (Aged ≥4 to <12 Years)

Demographic and baseline characteristics of children were similar across the treatment groups (Table 37).

Table 37 Demographic and Baseline Characteristics in Children ≥4 to <12 Years (Full Analysis Set) – MANDALA

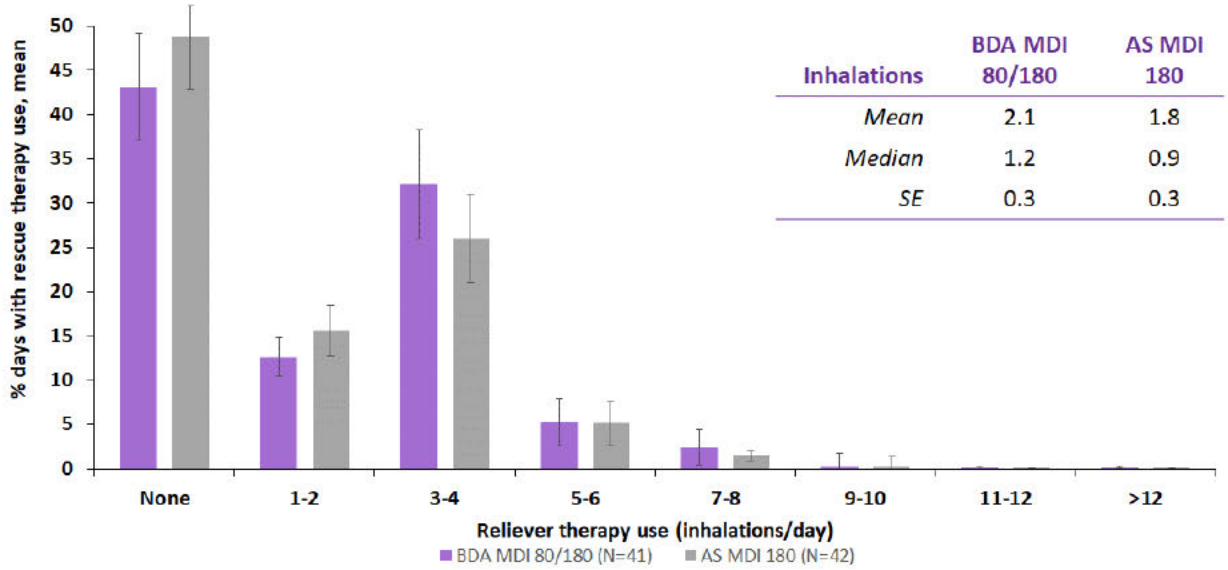
Characteristic	BDA MDI 80/180 (N=41)	AS MDI 180 (N=42)	Total (N=83)
Age, years			
Mean	9.2	9.1	9.2
SD	1.83	1.79	1.80
Median	9.0	9.0	9.0
Min, Max	5, 11	4, 11	4, 11
Sex, n (%)			
Male	27 (65.9)	29 (69.0)	56 (67.5)
Female	14 (34.1)	13 (31.0)	27 (32.5)
Race, n (%)			
White	28 (68.3)	25 (59.5)	53 (63.9)
Black or African American	10 (24.4)	12 (28.6)	22 (26.5)
Asian	1 (2.4)	2 (4.8)	3 (3.6)

Characteristic	BDA MDI 80/180 (N=41)	AS MDI 180 (N=42)	Total (N=83)
Other	2 (4.9)	3 (7.1)	5 (6.0)
Ethnicity, n (%)			
Hispanic or Latinx	19 (46.3)	22 (52.4)	41 (49.4)
Not Hispanic or Latinx	22 (53.7)	20 (47.6)	42 (50.6)
Lung function at baseline			
FEV_1 prebronchodilator (L) mean (SD)	1.580 (0.559)	1.568 (0.534)	1.574 (0.543)
FEV_1 prebronchodilator % predicted mean (SD)	83.51 (19.518)	84.90 (15.186)	84.21 (17.367)

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; FEV_1 = forced expiratory volume in 1 second; Max = maximum; MDI = metered dose inhaler; Min = minimum; SD = standard deviation.

Daily IP use during the randomized treatment period for children enrolled in MANDALA was lower than in the overall population, with a mean of 2.1 and 1.8 inhalations per day in the BDA MDI 80/180 and AS MDI 180 as-needed treatment groups, respectively (Figure 18). Children had a greater number of days without BDA MDI use, with approximately 45% of study days with no use compared with approximately 25% in the overall population. Only 2 children in each treatment arm used a maximum of ≥12 inhalations per day on ≥1 occasion. Only 1 child in MANDALA, in the BDA MDI 80/180 group, used ≥12 inhalations per day on ≥2 consecutive days.

Figure 18 Pattern of Use in Children ≥4 to <12 Years (Full Analysis Set) – MANDALA



Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler; SE = standard error.

As shown in Table 38, 41 and 42 children were included in each of the treatment groups, limiting the ability to draw efficacy conclusions in this small subgroup of patients as few exacerbations were observed during the study. For both time to first exacerbation and exacerbation rate, the RRs were close to 1. For both endpoint measures, the CIs were wide and crossed 1, indicating variability in the data, which is an anticipated finding when the number of patients and events are low.

Table 38 Severe Asthma Exacerbation Endpoints in Children ≥4 to <12 Years (Full Analysis Set) – MANDALA

Parameter	BDA MDI 80/180 (N=41)	AS MDI 180 (N=42)
Time to first severe exacerbation (comparison vs AS MDI 180)		
Patients with ≥1 severe exacerbation, n (%)	11 (26.8)	10 (23.8)
Total time at risk (patient-years)	20.4	20.7
Rate ratio (95% CI)	1.09 (0.46, 2.56)	--
P value	0.847	--
Annualized rate of exacerbation (comparison vs AS MDI 180)		
Total number of severe exacerbations	13	13
Total time at risk (patient-years)	27.0	25.7
Annualized rate estimate (95% CI)	0.58 (0.27, 1.24)	0.60 (0.28, 1.26)
Rate ratio (95% CI)	0.97 (0.34, 2.82)	--
P value	0.962	--

Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; MDI = metered dose inhaler.

The total SCS dose numerically favored albuterol compared with BDA MDI. The percentage of patients with improvements in ACQ-5 and Pediatric Asthma Quality of Life Questionnaire (PAQLQ) was numerically higher with BDA MDI groups than AS MDI (Table 39).

Table 39 Secondary Endpoints in Children ≥4 to <12 Years (Full Analysis Set) – MANDALA

Secondary Endpoint (BDA MDI vs AS MDI 180)	BDA MDI 80/180 (N=41) vs AS MDI (N=42)			
	BDA MDI 80/180 Estimate (n)	AS MDI Estimate (n)	Treatment Comparison (95% CI)	*P* Value
Annualized total SCS dose, % difference in arithmetic means	2.1 mg/kg/patient (41)	1.8 mg/kg/patient (41)	+19%	0.559
ACQ-5[a] MCID at Week 24, responder analysis (odds ratio)	53.8% (39)	48.8% (41)	1.27 (0.53, 3.08)	0.595
PAQLQ MCID at Week 24, responder analysis (odds ratio)	50.0% (36)	43.2% (37)	1.29 (0.49, 3.41)	0.610

Abbreviations: ACQ-5 = Asthma Control Questionnaire 5-item; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; MCID = minimal clinically import difference; MDI = metered dose inhaler; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; SCS = systemic corticosteroid.
[a] ≥6 to <12 only; endpoint not validated for 4- and 5-year-olds.

8.2 Safety

8.2.1 Adolescents (Aged ≥12 to <18 Years)

In the adolescent subgroup, the overall incidence of AEs was generally similar in both BDA MDI groups compared with albuterol (Table 40). Similar events in each system organ class were observed for each dose of BDA MDI versus albuterol. Reports of SAEs were rare and there were no deaths. Overall for the adolescent subgroup, BDA MDI was well tolerated and its safety profile was consistent with the well-established safety profiles of albuterol and budesonide. No new safety findings were identified.

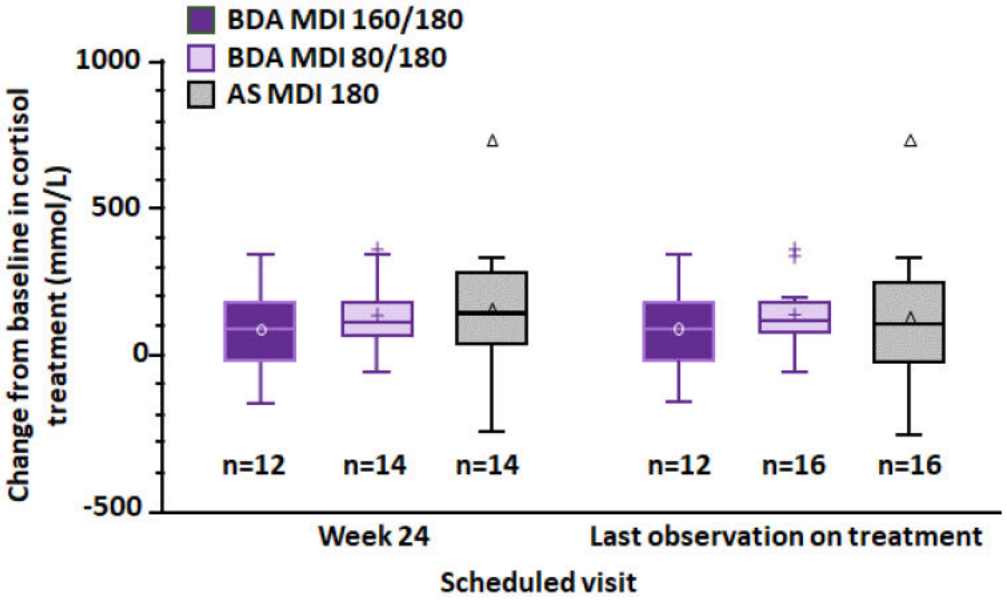
Table 40 Overview of Adverse Events in Adolescents ≥12 to <18 Years (Safety Analysis Set) – MANDALA

Category and System Organ Class	Number (%) of Patients		
	BDA MDI 160/180 (N=34)	BDA MDI 80/180 (N=32)	AS MDI 180 (N=34)
Any AE (≥12 to <18 years)	**13 (38.2)**	**11 (34.4)**	**15 (44.1)**
Infections and infestations (≥12 to <18 years)	7 (20.6)	9 (28.1)	8 (23.5)
Nervous system disorders	2 (5.9)	0	2 (5.9)
Respiratory, thoracic, and mediastinal disorders	4 (11.8)	1 (3.1)	4 (11.8)
Gastrointestinal disorders	2 (5.9)	2 (6.3)	2 (5.9)
Skin and subcutaneous tissue disorders	0	1 (3.1)	2 (5.9)
General disorders and administration site conditions	0	0	2 (5.9)
Injury, poisoning, and procedural complications	1 (2.9)	2 (6.3)	3 (8.8)
Any SAE	**1 (2.9)**	**0**	**2 (5.9)**

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler; SAE = serious adverse event.

To determine the effect of BDA MDI as-needed use on the hypothalamic-pituitary-adrenal axis, morning serum cortisol levels were measured at baseline, Week 24, and at the end of treatment. This measurement was implemented with the first protocol amendment, dated July 2019, and reported with the primary database lock data. In the adolescent subgroup, no appreciable differences were observed in change from baseline in cortisol measurements across the treatment groups (Figure 19).

Figure 19 Change From Baseline in Morning Serum Cortisol Levels in Adolescents ≥12 to <18 Years (Full Analysis Set) – MANDALA



Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; IQR = interquartile range; MDI = metered dose inhaler.
The box represents the IQR. The whiskers represent 1.5*IQR. Values outside of the 1.5*IQR are plotted as individual points. The plotted symbol within the box represents the mean; the horizontal line within the box represents the median.

A formal growth study with consistent calibrated stadiometer use and Tanner staging was not included in MANDALA due to the well-known effects of budesonide and other ICS on growth. However, height was measured as part of standard physical examinations at baseline and end of treatment. Due to the variable length of study duration for each patient in MANDALA, growth velocity was calculated in a post hoc analysis. Results from this analysis showed significant overlap in the CIs for growth rates across all treatments (Table 41).

Table 41 Analysis of Growth Rate in Adolescents ≥12 to <18 Years (Full Analysis Set; ≥12 to <18) – MANDALA

	Excluding Outliers[a]		
Treatment Group	N	LS Mean Growth Rate (cm/year)	95% CI
BDA MDI 160/180 (N=34)	25	1.555	0.150, 2.961
BDA MDI 80/180 (N=32)	26	3.284	1.878, 4.690
AS MDI 180 (N=34)	25	2.600	1.175, 4.025

Abbreviations: ANCOVA = analysis of covariance; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; LS = least squares; MDI = metered dose inhaler.
Growth rate is defined as the change from baseline in height, from randomization up to the last height observation on treatment, divided by the exposure time on study (years). Growth rate is analyzed using ANCOVA, adjusted for age, gender, and randomized treatment group.
[a] One patient who had a baseline height of 137 cm versus Week 48 height of 130 cm was excluded from the summary.

8.2.2 Children (Aged ≥4 to <12 Years)

In children, the overall incidence of AEs was similar in both the BDA MDI and albuterol groups (Table 42). In both treatment groups, similar AEs were observed in each system organ class. One patient in each group had an SAE, neither of which resulted in death. Overall, the safety profile of BDA MDI in children was similar to that of albuterol and to the known safety profile of budesonide. No new safety findings were identified.

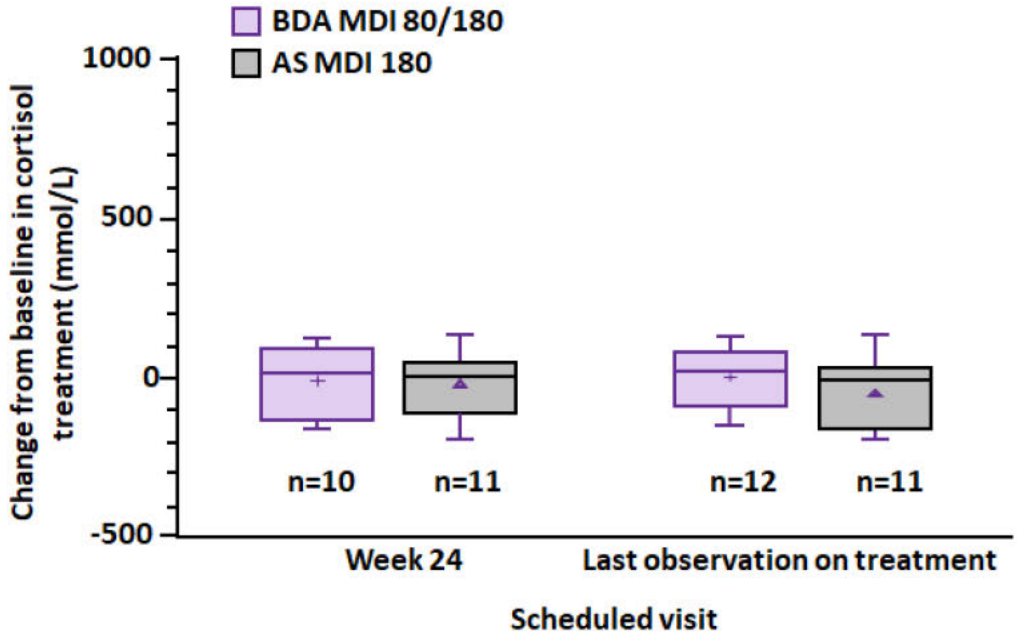
Table 42 Overview of Adverse Events in Children ≥4 to <12 Years (Safety Analysis Set) – MANDALA

	Number (%) of Patients	
Category and System Organ Class	BDA MDI 80/180 (N=41)	AS MDI 180 (N=42)
Any AE (≥4 to <12 years)	**17 (41.5)**	**17 (40.5)**
Infections and infestations (≥4 to <12 years)	11 (26.8)	11 (26.2)
Respiratory, thoracic, and mediastinal disorders	4 (9.8)	6 (14.3)
Skin and subcutaneous tissue disorders	2 (4.9)	0
Injury, poisoning, and procedural complications	2 (4.9)	1 (2.4)
Any SAE	**1 (2.4)**	**1 (2.4)**

Abbreviations: AE = adverse event; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler; SAE = serious adverse event.

Similar to adolescents, no differences were observed in the change from baseline in cortisol measurements between the BDA MDI and albuterol treatment groups in children (Figure 20).

Figure 20 Change From Baseline in Morning Serum Cortisol Levels in Children ≥4 to <12 Years (Full Analysis Set) – MANDALA



Abbreviations: AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; IQR = interquartile range; MDI = metered dose inhaler.
The box represents the IQR. The whiskers represent 1.5*IQR. Values outside of the 1.5*IQR are plotted as individual points.
The plotted symbol within the box represents the mean; the horizontal line within the box represents the median.

As described in Section 8.2.1 for adolescents, a formal growth study was not included in MANDALA. Results from a post hoc analysis of growth velocity in children showed significant overlap in the CIs for growth rates across all treatments (Table 43).

Table 43 Analysis of Growth Rate in Children ≥4 to <12 Years (Full Analysis Set; ≥4 to <12) – MANDALA

	Excluding Outliers[a]		
Treatment Group	N	LS Mean Growth Rate (cm/year)	95% CI
BDA MDI 80/180 (N=41)	28	5.441	2.567, 8.316
AS MDI 180 (N=42)	29	5.244	2.323, 8.164

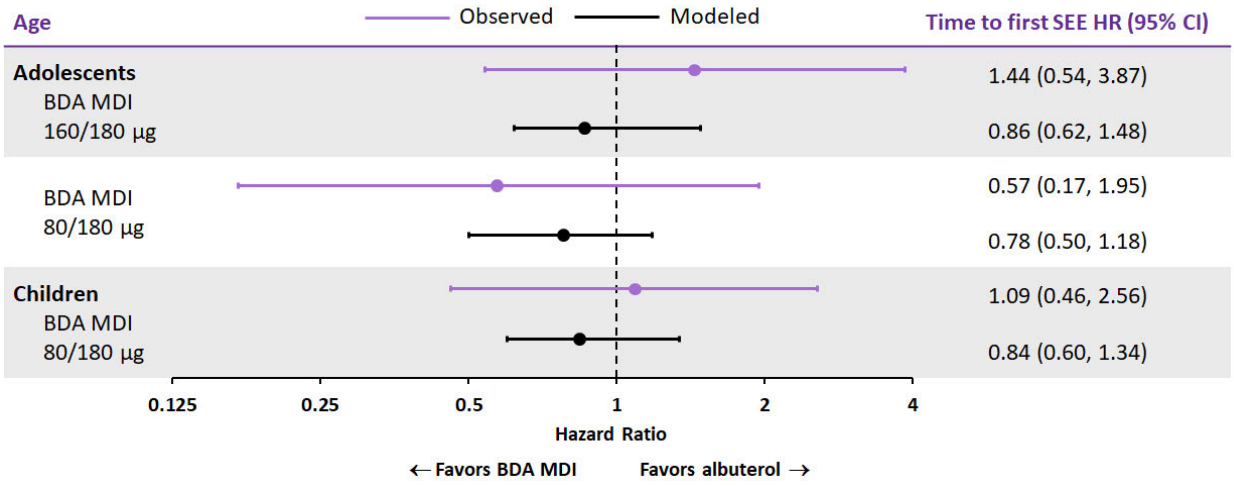
Abbreviations: ANCOVA = analysis of covariance; AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; CI = confidence interval; LS = least squares; MDI = metered dose inhaler.
Growth rate is defined as the change from baseline in height, from randomization up to the last height observation on treatment, divided by the exposure time on study (years). Growth rate is analyzed using ANCOVA, adjusted for age, gender, and randomized treatment group.
[a] One patient who had a baseline height of 132 cm versus Week 24 height of 77 cm was excluded from the summary.

8.3 Bayesian Analysis

As described in Section 8.0, there is a strong scientific rationale for extrapolation of efficacy from adults to adolescents and children based on similar immunopathology of asthma across age groups[29]; similar principles used by asthma treatment guidelines for treatment of children, adolescents, and adults[1]; and similar treatment effects observed with budesonide/formoterol as needed in children and adults.[30] Bayesian modeling, a widely used method to extrapolate efficacy findings across age groups,[32] further supports the expectation of efficacy in patients across all age groups.

A Bayesian model was constructed that borrowed across the other age and dose groups in MANDALA. This model improves estimation and reduces uncertainty, particularly for small or outlying subgroups, such as the pediatric population (Figure 21). Refer to Appendix for details.

Figure 21 Bayesian Analysis – MANDALA, Primary Endpoint



Abbreviations: BDA = budesonide/albuterol sulfate; CI = confidence interval; HR = hazard ratio; MDI = metered dose inhaler; SEE = severe exacerbation event.

8.4 Pharmacokinetic Modeling of Budesonide Exposure

One aspect to consider in the safety profile of BDA MDI is the systemic exposure of budesonide in children. Overall, systemic exposure to budesonide in children was similar to or lower than that in adults (Section 5.2).

8.5 Pediatric Efficacy and Safety Conclusions

In MANDALA, limited exacerbation data from 83 patients aged ≥4 to <12 years and 100 patients aged ≥12 to <18 years in MANDALA precludes meaningful statistical inference of treatment benefits and safety. However, the safety profiles of albuterol and budesonide are well known, and the MANDALA safety data are consistent with these profiles.

A positive benefit-risk profile for BDA MDI for adolescents and children is expected based on the strong scientific rationale for extrapolation of severe exacerbation risk reduction across the age groups, supported by Bayesian analyses, with an anticipated reduction in SCS use, reducing overall morbidity. In addition, the positive benefit-risk profile is supported by a wealth of clinical

experience and the well-established safety profiles of albuterol and budesonide mono-components in children with asthma as young as 4 years and 12 months of age, respectively.

9.0 BENEFIT-RISK SUMMARY

9.1 Therapeutic Context

Asthma is a common, heterogeneous disease with significant prevalence and imposes a considerable burden on individual patients and the healthcare system overall. Severe asthma exacerbations are associated with significant morbidity and mortality and can occur in patients of all ages across the spectrum of disease severity.[7] Prevention of severe exacerbations and their impact continues to be a substantial unmet need in many patients with asthma.

In 2019, a fundamental change occurred in the GINA strategy and treatment of asthma with SABAs alone was no longer recommended for adults and adolescents.[12] The current versions of GINA and NAEPP (US guidelines) for all patients ≥12 years of age reflect the data on ICS-containing reliever approaches and recommend the addition of ICS to rescue treatment.[1,13] Numerous published studies demonstrate the use of fast-acting bronchodilators (such as formoterol) with ICS to be superior to SABA alone in reducing exacerbation risk.[14-20] This has been observed across the asthma severity spectrum regardless of background maintenance therapy.

Although there are several monotherapy products in the US that contain either a SABA or ICS, the latter of which is only approved for maintenance use, there is currently no product that combines both components in a single inhaler.

9.2 Benefits of BDA MDI

BDA MDI is a novel, first-in-class, fixed-dose albuterol/ICS rescue combination product delivering the bronchodilatory efficacy of albuterol and the anti-inflammatory effects of budesonide in the most widely used device for the treatment of asthma. The development rationale was that co-administration of an ICS with a fast-acting β_2 agonist would provide rapid relief of asthma symptoms while simultaneously treating increasing underlying airway inflammation, thereby reducing severe exacerbation risk.

The MANDALA study demonstrated that as-needed use of BDA MDI in patients ≥4 years of age with moderate to severe asthma resulted in statistically significant and clinically meaningful reductions in the risk and rate of a severe exacerbation, compared with albuterol. Mean SCS exposure was lower in the BDA MDI treatment groups compared with albuterol, and higher percentages of patients in the BDA MDI treatment groups showed clinically relevant improvements in asthma control and quality of life. In patients ≥12 years of age, dose ordering was apparent across all efficacy endpoints, with BDA MDI 160/180 demonstrating consistently larger treatment effects compared with BDA MDI 80/180.

The benefits of BDA MDI taken as needed were observed in patients taking different background ICS-containing maintenance therapies and at low, medium, and high doses. BDA MDI demonstrated consistent effects regardless of sex, adult age group, race, severe exacerbation history, smoking history, region, maintenance therapy, and baseline lung function.

The pattern of as-needed use for BDA MDI was similar to albuterol. Daily use of the product was generally low with ≤2 inhalations used on the majority of study days and ≥8 inhalations used on <2% of study days.

DENALI and TYREE further support BDA MDI benefit. The DENALI study demonstrated that BDA MDI is an effective bronchodilator and the TYREE study demonstrated that BDA MDI is effective in the prevention of acute bronchoconstriction when administered prophylactically.

9.2.1 Benefits of BDA MDI in Pediatric Populations

Definitive efficacy conclusions in adolescents and children could not be drawn from the limited data for these age groups in the MANDALA study alone. Based on similarities in underlying pathophysiology and biology of asthma across age groups, efficacy in children and adolescents is expected to be consistent with the overall population studied, and extrapolation of efficacy findings from the overall population to pediatric subgroups is justified. This extrapolation is accomplished by Bayesian modeling, which under conservative prior assumptions, provided favorable point estimates across the age subgroups.

9.3 Risks of BDA MDI

The BDA MDI mono-components, albuterol and budesonide, have been in use for >25 years and have well-known safety profiles. Budesonide and albuterol are licensed for daily use in children as young as 12 months and 4 years of age, respectively. During the BDA MDI clinical development program, there were no new or unexpected safety concerns identified when compared to the RLDs Proventil, Pulmicort Flexhaler, and Pulmicort Respules. The overall safety profile of BDA MDI is consistent with the safety profiles of these products.

Patients who persistently use high daily doses of BDA MDI may be at increased risk of AEs. Data from MANDALA suggests the likelihood of persistent high use is low. Only 5% of patients used >8 inhalations per day on ≥7 consecutive days and <1% of patients used 12 inhalations on ≥2 consecutive days (the maximum proposed dose is 12 inhalations per day). The safety data from the Phase 3 program suggests that the impact of persistent high use is low. In MANDALA, no important safety differences were observed between BDA MDI and albuterol based on increasing mean daily use. In DENALI, the chronic use of 8 inhalations per day over 12 weeks was not associated with a significant increase in AEs compared to albuterol.

Patients taking as-needed BDA MDI in addition to regular ICS-containing maintenance therapies will be exposed to occasional higher doses of ICS. However, a study in adults has shown that although quadrupling background ICS doses for up to 14 days in response to symptoms increased the frequency of local AEs, the frequency of SAEs did not increase.[54] A study in children aged 5 to 11 years of age where background doses were quintupled for up to 7 days[55] also showed that AE frequency was similar to patients who remained on fixed-dose maintenance therapy.

The risks of overuse and additive steroid exposure should be balanced by the benefits of reductions in exacerbation risk and the consequent reduction in the need for SCS (33% reduction observed in MANDALA).

9.3.1 Risks of BDA MDI in Pediatric Populations

In MANDALA, no new safety findings were identified in adolescents and children, recognizing the limited number of patients enrolled in these subgroups. Use of BDA MDI as needed in patients 4 to 17 years of age resulted in no clinically important increase in AE incidence or frequency compared to albuterol. The safety profile of BDA MDI in these pediatric subgroups is similar to the well-known safety profiles of albuterol and budesonide.

The potential for exposure to corticosteroids, including budesonide, to cause a reduction in growth velocity when administered to pediatric patients is known. A formal growth study with consistent calibrated stadiometer use and Tanner staging was not included in MANDALA due to the well-known effects of budesonide and other ICSs on growth. However, height was measured as part of standard physical exams at baseline and end of treatment. Due to the variable length of study duration for each patient in MANDALA, growth velocity was calculated in a post hoc analysis. Similar rates were observed for BDA MDI and AS MDI. In the Warnings and Precautions and Pediatric Use sections, as with other ICS-containing medications, a warning regarding the potential for a reduction in growth velocity in pediatric patients and guidance to routinely monitor growth in these patients is included.

9.4 Benefit-Risk Conclusions

Asthma can impose a significant burden on patients across age groups, and the risk of severe asthma exacerbations is associated with increased use of SCSs and significant morbidity and mortality. Asthma exacerbations are caused by increased inflammation, and use of SABA alone does not adequately address the underlying pathophysiologic inflammatory process. Published data led to revisions in clinical practice guidelines to recommend as-needed co-administration of ICS with a fast-acting bronchodilator used as rescue to prevent exacerbations. The combination of budesonide and albuterol in BDA MDI administered as needed provides rapid relief of asthma symptoms through bronchodilation while simultaneously treating increasing underlying inflammation. MANDALA demonstrated that as-needed BDA MDI prevents asthma exacerbations and significantly reduces associated SCS use. The overall safety profile of BDA MDI is consistent with the well-established safety profiles of budesonide and albuterol in all age groups across all asthma severities, and no new safety concerns were identified. The Phase 3 program demonstrated a positive benefit-risk profile for BDA MDI. The totality of the data supports the proposed indication of BDA MDI 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.

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11.0 APPENDIX: BAYESIAN HIERARCHICAL MODELING

Introduction

We used a Bayesian hierarchical model to assess the hazard ratios (HRs) for time to severe exacerbation for budesonide/albuterol sulfate (BDA) metered dose inhaler (MDI) versus albuterol sulfate (AS) MDI 180 across subgroups defined by both age and dose. Age groups were defined as children (ages 4 to <12 years), adolescent (ages 12 to <18 years), adult (ages 18 to <65 years), and older adult (ages ≥65 years). The subgroup of primary interest for estimation in the context of this model is the children age group. This age group was randomized (1:1) between the BDA MDI 80/180 dose and AS MDI 180.

A traditional approach to examining treatment effects across subgroups in a clinical trial considers each subgroup as stand-alone. This approach assumes that patients outside a particular subgroup provide no relevant information for estimation. This is likely not the case because patients outside a particular subgroup were still enrolled and treated in the same clinical trial. Additionally, subgroup definitions are univariate and categorical in nature, but patients outside a particular subgroup could still have many characteristics in common with patients inside the subgroup of interest. Another common approach ignores subgroups and pools all trial patients together for analysis. This approach, however, does not allow for any consideration or estimation of possible heterogeneity in the treatment effect across different important patient groups.

Using a Bayesian hierarchical model to evaluate treatment effects across subgroups within a clinical trial represents a middle ground between evaluating subgroups as stand-alone or pooled together. We use a Bayesian hierarchical model to estimate HRs for time to first severe exacerbation within each subgroup, with consideration to what was observed across all age and dose subgroups. This analysis method and its resulting estimates may also be referred to as "shrinkage," "borrowing," "extrapolating," "partial extrapolation," "synthesis," or "meta-analysis." Importantly, when modeling at least 3 groups, such model-based estimates have been shown to be better estimators as compared to the stand-alone observed results in terms of mean squared error.[1-3] Mean squared error is a quantity that combines both bias and variance, and is commonly used to evaluate the quality of an estimator.

Methods

Bayesian hierarchical modeling is analogous in many respects to a standard random effects meta-analysis model. Both approaches synthesize the available data and assume that the quantities in the model have been sampled from a larger underlying population. In this setting, this larger underlying population would be a super-population of subgroups that the observed age by dose subgroup results from MANDALA are assumed to arise from.

We assume the observed log HR for time to first severe exacerbation from each age by dose subgroup k are normally distributed

$$Y_k \sim N(\theta_k, \sigma^2) \text{ for k = 1,2,…, 7}$$

As described above, the θ_k are modeled as arising from a larger underlying population, such that

$$\theta_k \sim N(\mu, \tau^2)$$

where μ is the population mean and τ is the variability around this population mean. In the Bayesian framework, we treat these as unknown parameters and place hyperprior distributions on them. We choose

$$\mu \sim N(0, 2^2)$$

$$\tau \sim HalfNormal(2)$$

We can characterize these priors by describing their corresponding 95% conditional predictive interval for the HR. Conditioning on the selected parameter values for μ and τ, we have the prior belief that the log HRs for subgroups arising from the MANDALA trial are distributed as

$$\theta_k \sim N(0, 2^2)$$

As such, the prior is centered at the null hazard ratio and the 95% interval for θ_k is then approximately $0 \pm 1.96*2$ which is (-3.92 to 3.92). On the HR scale this is (0.02, 50). These choices for the priors in the model are weak, allowing for substantial heterogeneity between the subgroups arising from MANDALA.

Under the Bayesian framework, these population parameters are updated based on the observed data from the subgroups in the model. This is how the Bayesian hierarchical model borrows dynamically according to how similar or different the subgroups are observed to be. If treatment effects across subgroups are very similar, the model will learn that the larger underlying population is very homogenous and stronger borrowing will result. Conversely, if treatment effects across subgroups are very different, the model will learn that the larger underlying population is very heterogeneous and weaker borrowing will result.

We can characterize the resulting strength of borrowing by quantifying the effective number of events in the modeled estimate of each subgroup versus the observed number of events in each subgroup. We base this calculation on the approximation that the standard error for an HR is equal to

$$\sqrt{\frac{4}{TotalEvents}}$$

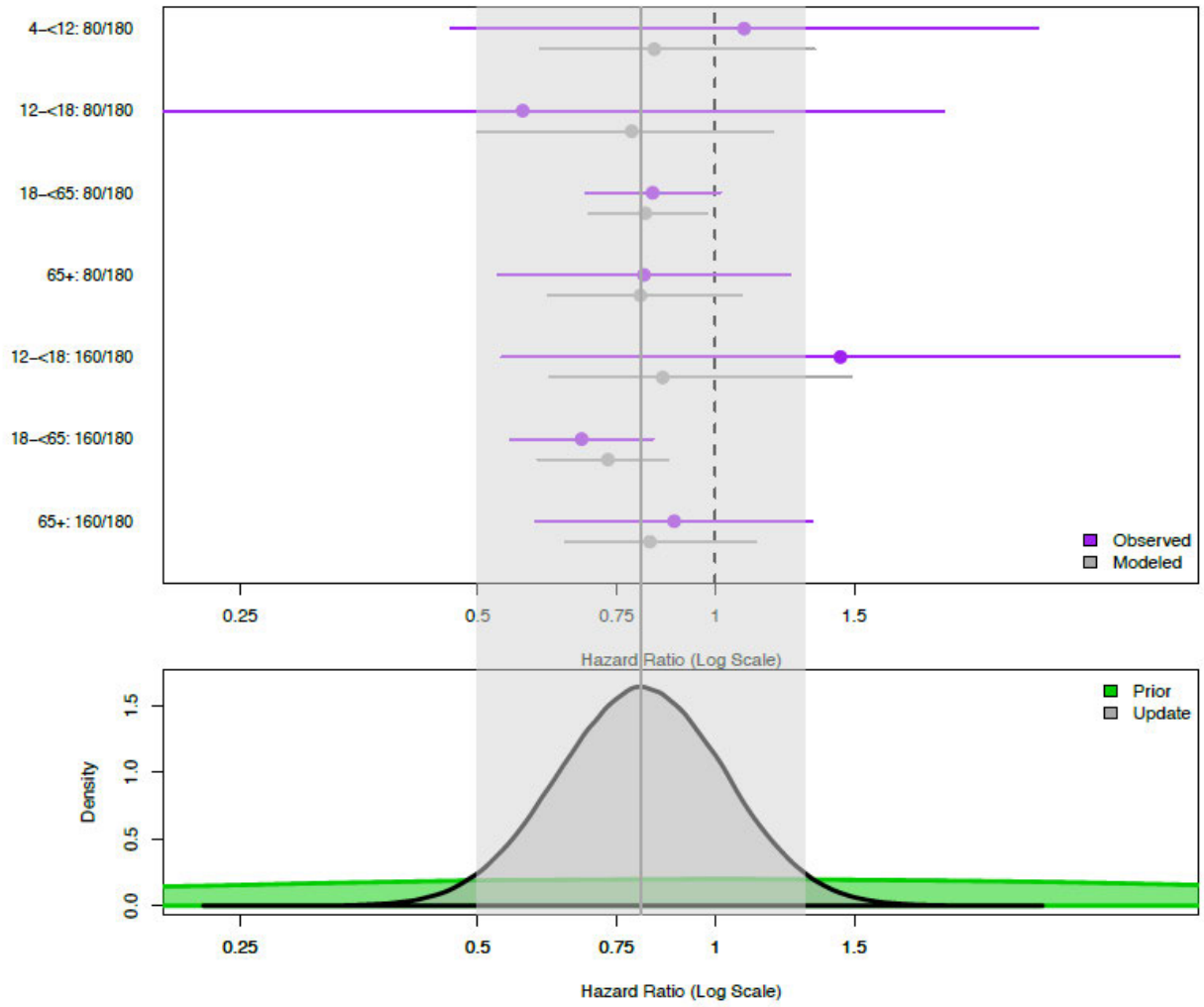
As such, the effective number of events is determined from the width of the 95% credible interval assuming that width is approximately

$$logHR \pm 1.96 * \sqrt{\frac{4}{TotalEvents}}$$

Results

Figure A1 visually demonstrates the fit of the Bayesian hierarchical model. The bottom panel of this figure characterizes the larger underlying population of HRs arising from MANDALA while the top panel shows the observed and modeled results for each of the included subgroups. First, the green density curve in the bottom panel represents the prior belief for the larger underlying population, as described above, representing a noninformative prior. The gray density curve in the bottom panel represents the updated belief about the larger underlying population based on the observed age by dose subgroups. The gray vertical line and gray shaded rectangle extending across both panels represent the mean and 95% credible interval of the larger underlying population for reference.

Figure A1 Bayesian Hierarchical Model Fit Across Age and Dose Subgroups



Abbreviation: HR = hazard ratio.
The bottom panel shows the prior (green) and the updated belief in the larger underlying population of HRs (gray). The top panel shows the observed (purple) and modeled (gray) subgroup estimates. The shaded gray rectangle and gray vertical line reference the larger underlying distribution of HRs (mean and 95% interval). The dotted vertical line is at a HR = 1 for reference.

Based on the observed data, the model estimates that on the HR scale the θ_k are centered at 0.81 with a 95% interval of (0.50, 1.37). The model then updates the estimates in each subgroup to be

consistent with this distribution, adjusting both the subgroup means and their corresponding 95% credible intervals to better fit within the distribution they arose from.

Table A1 shows the observed and modeled estimates in each subgroup along with the observed number of events and effective number of events in the modeled result. Focusing on the subgroup of children, the model estimates that the observed HR is outlying to the larger underlying population and pulls it in toward the population mean. The result is an estimated HR that is in favor of BDA MDI 80/180, specifically the mean and 95% credible interval for this group are 0.836 (0.601, 1.34). The effective sample size in this estimate is 96 severe exacerbation events. Given that 21 events were observed in this subgroup, 75 events worth of information was borrowed from the other MANDALA data.

Table A1 Observed and Modeled Estimates in Each Age Subgroup by Dose

Group	HR (95% Interval) [Events]	
	Observed	Modeled
BDA MDI 80/180		
4-<12	1.088 (0.462, 2.563) [21]	0.836 (0.601, 1.340) [96]
12-<18	0.570 (0.167, 1.946) [11]	0.836 (0.497, 1.178) [83]
18-<65	0.833 (0.684, 1.014) [398]	0.815 (0.692, 0.974) [526]
65+	0.812 (0.531, 1.242) [87]	0.803 (0.615, 1.076) [196]
BDA MDI 160/180		
12-<18	1.441 (0.536, 3.869) [16]	0.858 (0.616, 1.484) [80]
18-<65	0.677 (0.550, 0.834) [362]	0.731 (0.594, 0.872) [417]
65+	0.887 (0.593, 1.327) [95]	0.826 (0.645, 1.121) [201]

Abbreviations: BDA = budesonide/albuterol sulfate; HR = hazard ratio; MDI = metered dose inhaler.

Conclusion

In the subgroup of children, the HR estimated from the Bayesian hierarchical model represents an updated descriptive quantification of the BDA MDI 80/180 treatment effect, based on the assumption that the efficacy in children is expected to arise from the same larger underlying population as the other age and dose subgroups in MANDALA.

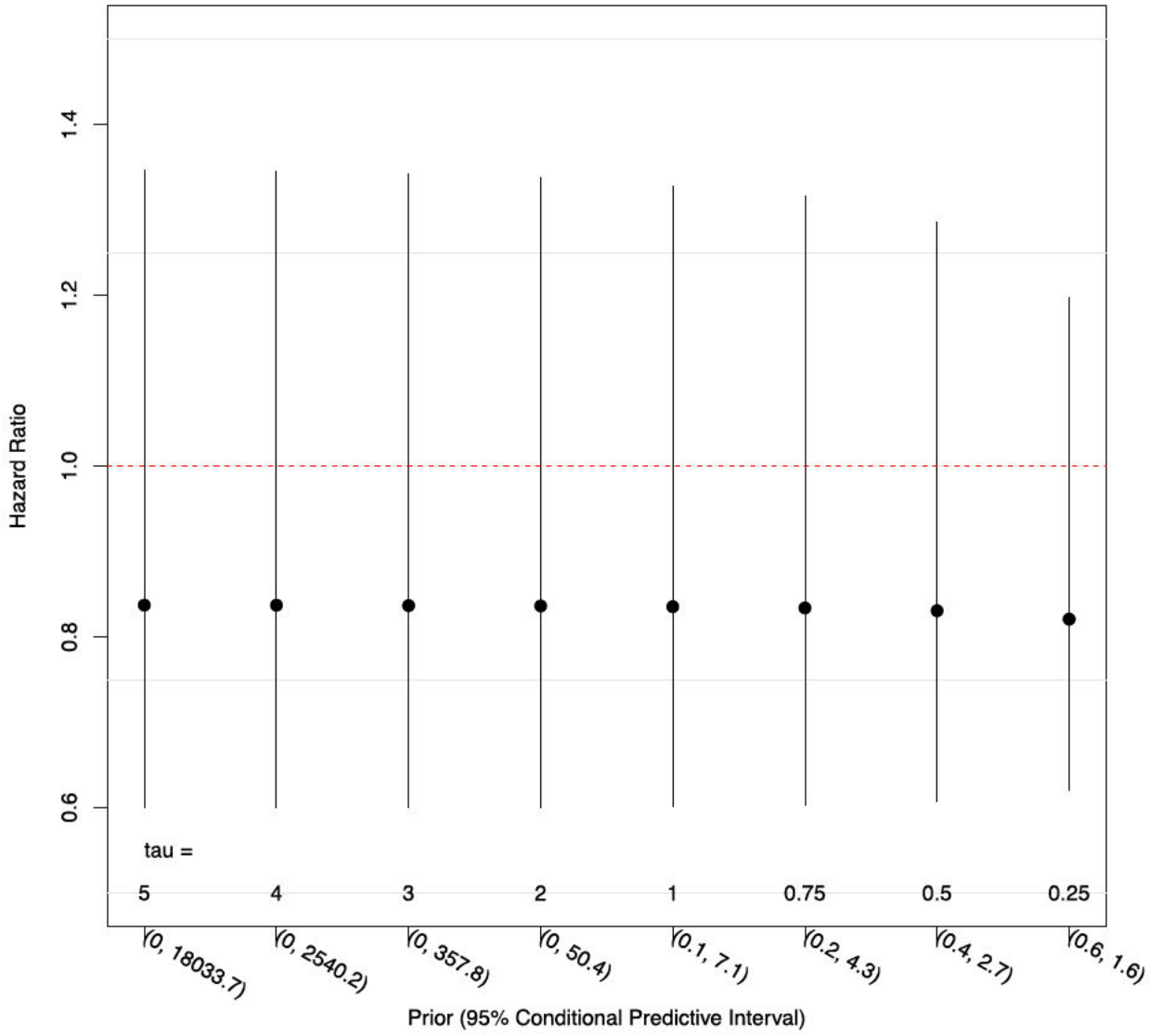
Sensitivity Analyses

We conducted a sensitivity analysis to understand how estimation for the pediatric population would vary with different assumptions on the prior distributions. This sensitivity analysis focuses on the prior value for τ. This parameter is the explicit measure of the heterogeneity across subgroups and, as demonstrated above, governs the amount of borrowing. If τ is very large, subgroups are allowed to be different and weaker borrowing occurs. If τ is very small, then subgroups are assumed to be very similar and stronger borrowing will occur. While we place a prior on τ, which is then updated by the observed data, the unit of analysis for this update is the number of subgroups, which in our model is 7. Therefore, it is possible that the observed data would not overwhelm the prior and the prior could have influence in the model results.

Figure A2 shows show the modeled estimates for the pediatric subgroups in terms of the mean and 95% credible interval across a range of prior value for τ from 5 to 0.25. The corresponding 95% conditional predictive interval for these values is also shown. This sensitivity analysis shows that the modeled mean HR in the pediatric subgroups is less than 1 regardless of the prior on τ. The effect of the different choices of τ is seen more in the width of the 95% credible interval as more

borrowing results in less uncertainty in the modeled estimates and greater precision. This sensitivity analysis also shows that the results presented above are conservative as larger values prior of values of τ do not result in different estimates or substantially wider 95% credible intervals for the pediatric group. The selected prior is weak enough that the amount of borrowing in the results is determined not by the prior assumptions, but by the data.

Figure A2 Sensitivity Analysis Evaluating the Prior on the Population Variance



Results shown for the children subgroup.

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