BDA MDI for the as needed treatment and prevention of bronchoconstriction, and for the prevention of exacerbations in patients with asthma four years of age and older.

US Food & Drug Administration
Pulmonary-Allergy Drugs Advisory Committee
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Introduction
Dr. Ed Piper, Global Franchise head for core Inhaled Products at AstraZeneca

CI-2
My name is Dr. Ed Piper, I am the Global Franchise Head for Core Inhaled Products at AstraZeneca and I am delighted to introduce BDA MDI, a potential new asthma rescue treatment.

CI-3
Each year in the United States, there are approximately 10 million asthma attacks resulting in 1.6 million visits to the emergency department, and the number of annual asthma deaths has ranged between 3 and 4000 over the last decade. Asthma attacks are typically treated with courses of systemic corticosteroids which are themselves associated with adverse outcomes that contribute to the burden of living with asthma.
The long-established 'go-to' standard of care asthma rescue therapy is the short acting B2 agonist, albuterol. However, albuterol has no anti-inflammatory properties and does not treat the airway inflammation that drives asthma symptoms and attacks.
It is also recognized that SABA monotherapy is associated with an increased risk of asthma attacks on both an individual and a population level.

CI-4
BDA MDI is a first in class fixed dose combination product for inhaled use.
It has been conceived and developed as an asthma rescue treatment, with two component parts, albuterol to provide rapid relief of symptoms through bronchodilation and budesonide, an inhaled corticosteroid to treat airway inflammation.
The product has been developed in partnership between Avillion and AstraZeneca.

CI-5
There is considerable regulatory and clinical experience with budesonide and albuterol.
Budesonide was first approved by the Agency in 1998 and is approved as an asthma maintenance treatment for patients one year of age, and older.
Albuterol was approved in 1981 for the treatment or prevention of bronchospasm and also for the prevention of exercise induced bronchospasm. It is approved for patients from four years of age.

CI-6
BDA MDI was developed as a novel asthma rescue treatment to reduce the risk of severe asthma exacerbations.

Used as-needed, in response to symptoms, the two components are complementary; albuterol rapidly relieves symptoms while budesonide simultaneously reduces airway inflammation.
The clinical premise behind its development is that BDA MDI reduces the risk that worsening symptoms deteriorate into a severe exacerbation.
This premise was built on extensive trial evidence and clinical experience from outside the US that other ICS/fast acting bronchodilator rescue products have been shown to reduce the risk of exacerbations compared to SABA across all severities of asthma. Indeed, current GINA and NAEPP guidelines both include recommendations for ICS/fast acting bronchodilators as rescue therapy.

CI-7
The Companies have had constructive dialogue with the Agency on a variety of topics throughout BDA development, in particular with respect to studying BDA in children and adolescents.
From its inception, the BDA clinical program was designed to enable efficacy in children to be inferred from extrapolation of efficacy findings in adults and adolescents. This approach has a strong clinical rationale and is consistent with the FDA's advice and historical practice.
The Agency encouraged inclusion of children down to 4 years of age in the phase 3 program and agreed cohorts of approximately 100 4 -11-year olds and 12 -17-year olds in the pivotal exacerbation study MANDALA. Smaller numbers were to be included in the lung function study DENALI.
Given the small size of these cohorts, the Agency advised the Companies to consider additional analyses, such as a Bayesian approaches to support efficacy in the pediatric population.

CI-8
The BDA clinical development program included a package of phase 1 and 2 studies which established a scientific bridge for BDA MDI to the reference listed drugs Proventil HFA and Pulmicort
Three positive Phase III studies underpin the NDA.
The MANDALA Study evaluated BDA as a rescue treatment in moderate to severe asthma. Patients 4 years and older were included based on the specific feedback from the FDA. The study showed statistically significant and clinically meaningful reductions in the risk of severe asthma exacerbation for both doses of BDA MDI compared to albuterol. In adults and adolescents, the reduction in risk was 27% for BDA 160/180.
DENALI was a lung function study, conducted in mild to moderate asthma patients, which demonstrated the individual contribution of budesonide and albuterol in BDA, and thereby meeting the combination rule.
And TYREE demonstrated that BDA MDI was effective in protecting the airway against exercise induced bronchospasm.

CI-9
The positive clinical data underpin the proposed indication and dose for the product.

The indication sought is for the as needed treatment and prevention of bronchoconstriction, and for the prevention of exacerbations in patients with asthma four years of age and older. This reflects the clinical utility of BDA as a rescue that both relieves symptoms and reduces exacerbation risk.
And we propose two doses: for those 12 years and above, a combination of 160 micrograms of budesonide, and 180 micrograms of albuterol - delivered as two consecutive inhalations.
And for children aged 4 to 11, an 80-microgram dose of budesonide, with the same albuterol dose.
We propose a maximum daily dose of six times or 12 inhalations which is consistent with the maximum albuterol labeled dose and was studied in MANDALA

CI-10
BDA MDI is a first in class, fixed-dose albuterol/ICS combination rescue medicine that prevents severe asthma exacerbations with no new safety signals detected in development.
BDA therefore has important potential to address the continuing high rate of exacerbations for all severities of adult and pediatric asthma.
The major topic that the Agency requests the Committee consider is whether the totality of the data is sufficient to support approval of BDA in adolescents and children

- We view the benefit-risk assessment in both populations to be favorable based on
- The observed safety profile of BDA MDI, which is consistent with the well-established safety profiles of albuterol and budesonide
- A strong clinical and pharmacologic rationale to extrapolate efficacy from the overall population to adolescents and children
- Supportive efficacy and safety data from other ICS/fast-acting bronchodilator combinations in pediatric asthma

CI-11
Subsequent presentations provide information to support the Committee discussions on November the 8th.
Dr. Njira Lugogo, Professor in the division of Pulmonary and Critical Care Medicine and head of the asthma program at the University of Michigan will discuss the disease background & unmet need.
Dr. Mark Weinberg from Avillion will review the BDA clinical development program and the key efficacy & safety outcomes.
Dr. Alison Church from AstraZeneca will focus on BDA efficacy and safety in pediatrics.
And Dr. Kevin Murphy, pediatric pulmonologist and director of clinical research at Boys Town National Research Hospital in Nebraska, will discuss the clinical context for BDA MDI in pediatric asthma.
And I provide a short concluding presentation. Thank you.

Unmet Need and Disease Background
Dr. Njira Lugogo, Clinical Professor, Department of Internal Medicine in the Division of Pulmonary and Critical Care, University of Michigan and Director of the Michigan Medicine Asthma Program, Pulmonary Division

CU-1
Hello…my name is Dr. Njira Lugogo and I am a Clinical Professor in the Dept of Internal Medicine in the Division of Pulmonary and Critical Care at the University of Michigan in Ann Arbor.
I am also the Director of the Michigan Medicine Asthma Program within the Pulmonary Division.
I manage a large severe asthma population and my patients continue to experience significant morbidity related to asthma.
I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.
I am honored to be here today to present the Unmet Medical Need for Patients with Asthma to the Committee.

CU-2
25 million Americans are diagnosed with asthma, making asthma a very common disease, with 1 in 10 children carrying the diagnosis. There is significant burden of disease across the age spectrum.
Asthma is the #1 reason for missing school, with almost 14 million days missed annually. Adults with asthma miss a similar staggering number of days of work, costing the US economy an estimated 80 billion dollars annually.
Most people with asthma limit their physical activity, leading to other related health conditions that can be attributed to a sedentary lifestyle. Dr. Murphy will discuss the significant morbidity of asthma in adolescents and children that he sees in his pediatric pulmonary clinic.

CU-3
This significant burden of asthma includes a high rate of emergency room visits in the United States, and this high rate has remained relatively stable over this recent 8-year period.
As shown in orange, emergency room visits are highest among the pediatric population, which Dr. Murphy will also discuss.

CU-4
In addition to ED visits, deaths due to asthma in the US have also remained relatively constant since 2007.
As Dr. Piper stated, on average, 3 to 4 thousand deaths due to asthma occur yearly.
15 to 20% of these deaths occur in patients with reasonable asthma control prior to developing symptoms leading to a severe exacerbation. These developing symptoms are then treated with increasing doses of SABA monotherapy.
Nearly all of these deaths are avoidable with the right treatment and care.

CU-5

Despite therapeutic advances in asthma treatment in recent years, approximately 50% of patients of all ages have uncontrolled asthma as you can see here.
As shown on the right, exacerbations are present across the spectrum of disease severity, with approximately half of all patients experiencing at least 1 severe exacerbation per year.
In fact, more patients with mild asthma experience severe exacerbations annually in comparison to those with moderate to severe disease.
These data highlight a significant unmet need to prevent severe exacerbations across the population of patients with asthma.

CU-6

By definition, severe asthma exacerbations require treatment with systemic corticosteroids which are associated with significant risks.
Systemic corticosteroids were first used in the late 1950s and were considered miracle drugs for patients with asthma. Within the first decade of use, it became apparent that they also had significant side effects with frequent use.
In 2018, Dr. David Price published a study, depicted on this slide, that changed our thinking about the safety of systemic corticosteroids.
The squares represent increasing lifetime doses, with the turquoise square representing a dose of 500 to less than 1000 mg, and the maroon box representing over 10,000 mg.
As you can see, the risk of adverse outcomes increases in a dose-dependent fashion, with thresholds for harm being quite low at just 500 to <1000 mg. And there is real-word administrative claims data demonstrating that ~65% of children with asthma aged 4-11 years received >500mg of prednisone in one year.
500 mg is equivalent to 2 short courses of prednisone, a threshold many patients exceed in one year.
This is an unacceptable level of exposure and risk. Nationally, there is a call-to-action by patient advocacy groups, professional medical societies, and pharmaceutical companies all partnering together to raise awareness of oral corticosteroid use and to develop strategies to curb reliance on their use.

CU-7

This high exacerbation and systemic corticosteroid burden remains high despite great advances in asthma care over the past many years depicted on this slide.
Even with these medication developments, SABAs remain the most commonly prescribed medications for asthma. They were discovered and first used nearly 70 years ago, first with isoproterenol and epinephrine.
It is notable that at that time, asthma was thought to be a disease of bronchoconstriction. Our understanding of asthma pathophysiology has advanced significantly, and we now recognize that asthma is associated with both inflammation and bronchoconstriction.
Inhaled corticosteroids were first approved in 1982. They are highly effective and associated with improved asthma outcomes, such as asthma control, exacerbations, and mortality.

In the US, ICSs are approved for maintenance, however they are not approved as rescue therapy either alone or in combination with a fast-acting bronchodilator.

CU-8

A fundamental change occurred in the Global Initiative in Asthma or GINA Strategy in 2019 and the treatment of asthma with short-acting bronchodilators alone was no longer recommended for adults and adolescents with asthma.
This fundamental change was driven by the totality of data showing SABA monotherapy use as rescue is associated with increases in asthma exacerbations and mortality.
Thus, SABA use for rescue without concomitant ICS is no longer considered appropriate therapy.

CU-9

The most recent versions of GINA and the National Asthma Education and Prevention Program, NAEPP, reflect the data supporting higher efficacy of ICS containing rescue approaches in preventing severe exacerbations compared with SABA monotherapy.
Exacerbation prevention is now the most important goal of these guidelines.
On this slide, we focus on the recommendations for adolescents and adults. Dr. Murphy will present data and recommendations for children.
ICS fast acting bronchodilator strategies have demonstrated severe asthma exacerbation risk reduction with and without maintenance therapy.
Dr. Weinberg will present data from the MANDALA study that demonstrates a 27% reduction in exacerbations with BDA MDI therapy.
Implementation of the current guidelines poses a challenge for clinicians as ICS/fast-acting bronchodilators are not approved for rescue in the US.

CU-10

Furthermore, clinicians are faced with pre-existing patient beliefs and behaviors that drive SABA rescue use.
The INSPIRE study evaluated patient beliefs that influence treatment choices and self-management and help us understand why SABAs are so frequently used.
38% of patients believed there was no need to take medications every day when they feel well, and 90% wanted medications that provided immediate relief.
Patients experience immediate relief from SABAs thus reinforcing continued use of this medication.
However, regular use of SABA monotherapy without accompanying ICS results in poor asthma control, beta-2-receptor down regulation, enhanced exercise induced bronchoconstriction and increased airway inflammation, leading to increased exacerbation frequency.

CU-11

Achieving a significant shift in clinical practice requires a fundamental change in approach and underlying assumptions.
To accomplish our goals of reducing severe exacerbation risk, we need to meet patients where they are, and leverage patient behavior driven by a preference for obtaining immediate symptom relief.

If we follow the science, which supports concurrently targeting the key factors driving severe exacerbations, both inflammation and bronchoconstriction, we will make a significant difference.
We should align with current treatment approaches and guideline-based recommendations by incorporating a switch in rescue therapy to BDA MDI, which is supported by the favorable benefit-risk assessment.
And now I encourage you to watch Dr. Mark Weinberg's presentation where he will discuss the efficacy and safety of BDA MDI. Thank you.

Efficacy
Mark Weinberg, Chief Medical Officer, Avillion

CE-1
Hello, I'm Mark Weinberg, the chief medical officer for Avillion.
Over the next few minutes I will be summarizing key efficacy and safety data for the overall population in the BDA program.

CE-2
Each of the three phase 3 studies in our clinical development program was designed to address a specific question.
MANDALA, the main focus for efficacy, evaluated BDA MDI for at least 24 weeks in all patients. BDA was used as needed in response to, or to prevent, symptoms.
DENALI evaluated the contribution of the individual components of BDA to satisfy the combination rule. BDA MDI was administered on a qid schedule over 12 weeks. The contributions of albuterol and budesonide were assessed based on pulmonary function testing.
TYREE utilized a crossover design to evaluate the efficacy of BDA MDI in preventing bronchoconstriction induced by exercise.

CE-3
MANDALA tested BDA MDI as it is intended to be used. More than 3000 patients with moderate to severe asthma were maintained on their maintenance therapy (ICS +/- LABA with or without one additional maintenance therapy).
Adults and adolescents age 12 and older were randomized to one of the three arms, and children age 4-11 were randomized to the 80/180 dose of BDA or to albuterol. I will focus on the overall population including all patients and Dr. Church will focus on the pediatric subgroups.
Each dosage of study drug was 2 inhalations which totaled to the values seen here: BDA with 160ug of budesonide and 180ug of albuterol, BDA with 80ug of budesonide and 180ug albuterol, or 180ug of albuterol. Patients were instructed to use study drug as they would their pre-enrollment SABA, PRN in response to symptoms or triggers (including prior to exercise).
Patients enrolled had a history of exacerbation in the past year.
The primary endpoint was time to first severe exacerbation defined as at least 1 of: a bolus/burst of systemic corticosteroids for at least 3 consecutive days to treat symptoms

of asthma worsening; an ER or urgent care visit due to asthma that required systemic corticosteroids; or an in-patient hospitalization due to asthma.
MANDALA was a variable length, event driven study with the analysis occurring once 570 severe acute exacerbations occurred and the last enrolled adult reached 24 weeks. 92.9% of patients remained in the study for at least 24 weeks. The COVID pandemic did not have a notable effect on data collection, although it did cause a pause in enrollment during the study and complicated the enrollment of children.

CE-4
Demographics and baseline characteristics were balanced across all 3 treatment arms.
Approximately 3% of patients were aged 12-18 and approximately 3% were aged 4-12.
The majority of the patients were White, with 13% black or African American and 3% Asian.
Approximately a quarter of patients were Hispanic or Latinx.
Lung function at baseline was an FEV1 of about 2L, ~70% predicted.

CE-5
The prespecified statistical testing procedure used the Hochberg method at an alpha of 0.05 for the primary endpoint.
Secondary endpoints were tested in a prespecified hierarchical order, first for the high dose and then for the low dose.
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.

CE-6
The primary endpoint was met for both doses with a statistically significant and clinically meaningful reduction in risk of a severe exacerbation.
The 160/180 dose evaluation includes all patients >=12 years old and had a hazard ratio of .733, that represents a 27% reduction in the risk of a severe exacerbation, with a p value of <0.001.
The 80/180 dose evaluation includes all patients >=4 years old and had a hazard ratio of 0.835, that represents a 17% reduction in the risk of a severe exacerbation, with a p value of 0.041.
As described in the briefing document a number of demographic and baseline characteristic subgroup analyses were performed with hazard ratio point estimates consistently favoring BDA.

CE-7
This Kapan Meyer curve is a graphical representation of the meaningful results for the primary endpoint.
First, shown in gray, is the probability of severe exacerbation for albuterol.
Adding BDA MDI 160/180 in dark purple you see that separation of the curves begins within the first few weeks.
Adding the BDA MDI 80/180 dose in light purple you see that this dose falls in between the high dose and albuterol curves.

CE-8

An integral aspect of understanding the effect of BDA is the usage pattern.
Allow me to orient you to the data on this slide. First in the upper right is the mean, median, and standard error for the number of inhalations used by each treatment arm. The mean daily use ranged from 2.6 to 2.8 inhalations, slightly more than 1 dose, and was similar across treatment arms.
The figure on the slide has an x axis categorized by number of inhalations/day, starting with no use of study drug and going up in two's corresponding to doses of BDA MDI – for example 1-2 inhalations would be one dose, 3-4 for two doses and so forth.
The y-axis has the mean % of study days where that dose was used.
First, you can see that use varied across the study.
Second, BDA use and albuterol use were similar.
Third, most days during the study, patients used 0, 1, or 2 doses (up to 4 inhalations) with no use whatsoever on ~25% of study days, ≤2 inhalations on approximately 55% of study days, ≤4 inhalations on approximately 85% of study days and more than >8 inhalations on fewer than 2% of study days.
It is also notable from the data collected that 90% of patients used study drug at least one time for prophylaxis related to exercise.

CE-9

The annualized severe exacerbation rate, the first tested secondary endpoint, was met for both doses with a statistically significant and clinically meaningful reduction in risk.
The annualized severe event rate ratio showed a rate reduction of 24% for the 160/180 dose, as shown on the left, and a 20% reduction for the 80/180 dose, as shown on the right.

CE-10

Additional secondary endpoints demonstrated further benefits of BDA as needed treatment and favored the 160/180 dose.
For the 160/180 dose, the annualized total systemic corticosteroid exposure was reduced by 33%, with a P value of 0.002.
The systemic corticosteroid reduction for the 80/180 dose was 25%; however, the p value was 0.06 so the multiple testing procedure stopped at that point.
On the bottom of this slide, you see QoL and symptom control measures, treatment arm responses, and the nominal p values for the comparison. A consistent pattern emerges for ACQ-5 and AQLQ+12 with nominally significant odds ratios demonstrating favorable results for the BDA 160/180 dose.
Broadly the data from MANDALA show that BDA used as needed reduces severe exacerbations and reduces annualized systemic steroid exposure in patients on a wide range of background therapies.
The data support selection of the high dose.

CE-11

Now let's consider DENALI.

DENALI evaluated the BDA MDI components individually using dual primary endpoints to determine the post-dose bronchodilatory effect for albuterol and the pre-dose FEV1 improvement for budesonide.
Patients with mild to moderate asthma being treated with as-needed SABA with or without low dose ICS were taken off their maintenance therapy and randomized evenly to one of 5 arms receiving QIDstudy drug for 12 weeks.
This chronic dosing represents substantially higher use than is anticipated for as-needed administration as was seen in the MANDALA study.

CE-12
The first dual primary endpoint in DENALI was designed to assess the contribution of albuterol in BDA MDI. The 160/180 BDA arm was compared to budesonide alone arm.
Albuterol in BDA increased the FEV1 AUC 0-6 by 81 mL.

CE-13
The second dual primary endpoint in DENALI was designed to assess the contribution of budesonide in BDA MDI.
The 160/180 and 80/180 BDA arms were compared to the albuterol alone arm.
160ug of budesonide in BDA increased the trough FEV1 by 133 mL.
80ug of budesonide in BDA increased the trough FEV1 by 121 mL.

CE-14
TYREE was a crossover study of BDA vs. placebo. 30 patients on SABA alone and 30 on SABA plus low to medium dose ICS maintenance were enrolled.
On the right side you see that BDA shown in blue prevented bronchoconstriction, reducing the change in FEV1 which was observed when patients were treated with placebo.
BDA 160/180 taken 30 minutes prior to an exercise challenge test protected subjects with asthma from bronchoconstriction.
While we acknowledge that TYREE does not provide information beyond what is already established for albuterol in exercise induced bronchoconstriction, we did wish to confirm that in the event that patients use BDA MDI as they currently use albuterol they would be protected.
This is how patients used BDA MDI in place of albuterol in the MANDALA study.

CE-15
I would now like to briefly address safety.
Given the more than 25-year history of use of both budesonide and albuterol, the fact that their safety profiles are well understood, and most importantly the lack of any new safety signals identified by either the sponsor or the FDA during the BDA program, we do not plan to present extensive safety data.
I will cover a few things from MANDALA at a high level.
Additional information can be found in the briefing document.

CE-16
AE rates in MANDALA were similar across treatment groups.

The proportion of patients with an adverse event *related* to study drug or with an adverse event *leading to discontinuation* of study drug was very low at 1-2%.
Serious adverse events were reported in 4-5% of patients and none of these were considered related to study drug.
The most commonly reported SAEs were in the SOC of infections and infestations and the majority of these events were COVID-19 related.
In MANDALA, 7 fatalities were reported, 4 of these were COVID-19 related, 2 in the 160/180 BDA group, 1 in the 80/180 BDA group and 1 in the albuterol group.
The other 3 fatalities were reported as elevated glucose (in the 160/180 group), cardiac arrest (in the 160/180 BDA group) and lung metastases (in the 80/180 BDA group).

CE-17
The most common AEs were nasopharyngitis, headache and COVID 19.
As you peruse this slide you see that broadly rates are similar across treatment arms with a few numerical differences and nothing that is unexpected given what is known about budesonide and albuterol.

CE-18
Finally, for safety, we conducted an analysis of corticosteroid-associated AEs across the study population in MANDALA. The Preferred Terms selected were defined prior to database lock.
The number of patients with any systemic ICS associated AE was low and comparable across treatment groups.
The number of patients with any local ICS associated AE was also low and generally comparable across the treatment groups with the exception of Oral and Oropharyngeal candidiasis which are well known local AEs for inhaled corticosteroids.

CE-19
In conclusion, BDA MDI has a positive benefit risk ratio.
Both doses of BDA MDI used as needed had a statistically significant and clinically meaningful reduction in severe exacerbation events compared to albuterol.
BDA MDI 160/180 used as needed reduced systemic corticosteroid exposure and was more likely to be associated with clinically relevant changes in asthma control and quality of life.
Both albuterol and budesonide components contributed to BDA MDI efficacy.
BDA was effective in protecting subjects with asthma from exercise induced bronchoconstriction.
No new safety signals emerged when BDA MDI was used as needed or when it was used at chronically high doses for 12 weeks.
BDA 160/180 taken as-needed by patients receiving a wide range of ICS-containing maintenance therapies had a superior benefit-risk ratio compared to albuterol.
Next please watch the presentation by Dr. Church which will address the benefit/risk in children and adolescents. Thank you.

Pediatric Benefit-Risk
Alison Church, Pediatric Allergist and Immunologist, AstraZeneca

CD-1
Hello…my name is Alison Church. I'm a pediatric allergist and immunologist at AstraZeneca. Today I am going to present the efficacy and safety data from the adolescent subgroup and from the subgroup of children from the MANDALA Study. However, first I would like to briefly review the unmet need for BDA MDI in these two patient groups.

CD-2
Despite the availability of albuterol and inhaled corticosteroids such as budesonide, adolescents and children with asthma continue to experience severe asthma exacerbations which are treated with systemic corticosteroids.
Approximately 50% of children with mild to moderate asthma and 2 out of 3 children with severe asthma receiving maintenance therapy suffer from one or more asthma exacerbations per year which are treated with systemic corticosteroids.
Systemic corticosteroids are associated with adverse effects in both adolescents and children.
A recent retrospective study evaluating patients younger than 18 years of age found that one course of systemic corticosteroids used for up to 14 days was associated with a 1.4 to 2.2-fold increased risk of significant adverse events within the first month after dosing.
In a meta-analysis of steroid use in children, vomiting, mood swings, behavioral issues and sleep disturbance were the most common adverse drug effects reported after a short course of systemic corticosteroids.
Therefore, different treatment options are needed to prevent severe exacerbations in adolescents and children.

CD-3
One approach to meeting this unmet need in asthma is through a rescue inhaled corticosteroid/fast-acting bronchodilator combination which can treat both increasing airway inflammation and bronchoconstriction when symptoms occur to prevent severe exacerbations.
The concept of an inhaled corticosteroid combined with a fast-acting bronchodilator has demonstrated efficacy and tolerability in children and adolescents as well as in adults in several studies including STAY and TREXA, which are described by Dr. Murphy in another presentation.
Based on these studies, GINA and NAEPP treatment guidelines increasingly recommend ICS/fast-acting bronchodilator as rescue treatment for children, adolescents and adults with asthma.
However, no ICS/ bronchodilator products are approved for this use in the US. The fixed dose combination product BDA MDI was developed to meet this unmet need.

CD-4
As you know, budesonide and albuterol are the 2 components of BDA MDI.

Budesonide, the inhaled corticosteroid component of BDA, was first approved for asthma in 1997 for adults and adolescents and in 2000 for children. Budesonide is a commonly used maintenance treatment for children, adolescents, and adults with asthma in the US.
Albuterol was approved for use in adults in 1981, followed by approvals for adolescents and children down to the age of 4 in 1998 and 1999, respectively. It has a well characterized safety and efficacy profile in the treatment and prevention of bronchospasm in children, adolescents and adults.
Before I present the results in the MANDALA study, I would like to first summarize the feedback we received from the FDA on our pediatric development plans.

CD-5

We had several regulatory interactions with the FDA regarding pediatrics.
In our initial discussions with the FDA on BDA MDI, we proposed to include patients 12 years of age and older in the Phase 3 studies, as it is generally accepted by the FDA, and in line with the development programs of other asthma products. However, the FDA wanted us to consider including children and in 2018 recommended to include children down to 4 years in the BDA MDI development program because albuterol is approved down to this age.
The initial Pediatric Study Plan agreed to target inclusion of 100 adolescents and 100 children in MANDALA and it was clear these numbers were not statistically driven.
The FDA has agreed that requirements for Pediatric Research Equity Act, the pediatric legislation, have been met in the MANDALA study. The FDA recommended that we consider Bayesian modeling to support efficacy in the small subgroups of adolescents and children based on the scientific rationale for extrapolation in these patient groups, which we have done.
Extrapolation of clinical benefit from adults to adolescents and children is considered appropriate when there is similarity of disease and response to treatment between the adult population and the pediatric population.

CD-6

Furthermore, recent FDA guidance states that when adult data are available in conditions existing in adults, adolescents, and children, evidence of clinical benefit from the drug in adults can provide support for the prospect of *direct benefit* in pediatrics.
This approach is reasonable for BDA MDI because of similarities in clinical and pharmacologic aspects of asthma across all age groups.
These similarities include:
Airway inflammation and bronchoconstriction observed during exacerbations;
Treatment of severe asthma exacerbations;
Principles for diagnosis, assessment, and treatment strategies in asthma guidelines, such as NAEPP**;**
Treatment effects of budesonide/formoterol used as rescue on severe asthma exacerbations has been demonstrated in published studies;
And, the same endpoints are used to measure efficacy and safety in asthma clinical trials.

In addition, recent data indicates adolescents and adults with asthma have comparable inflammatory biomarker profiles.
Taken together, these points all support the clinical and pharmacologic rationale for extrapolation of efficacy and safety across all age groups with asthma.
Now I will share the efficacy and safety data in the adolescent subgroup and the subgroup of children from the MANDALA Study.

CD-7
To begin, this is a table of the demographic and baseline disease characteristics of the adolescent patient population.
As you can see, only 32 to 34 patients were included in each of the treatment groups.
Overall, the demographics and baseline characteristics were balanced across the treatment arms.

CD-8
In order to understand the potential exposure of adolescents to BDA MDI, it is important to understand the pattern of use in this patient population.
This graph shows the mean percent of days for each rescue use frequency category.
Along the X-axis are the categories of use, from none, to 1 to 2 inhalations, to 3 to 4 inhalations, and increasing in 1 to 2 inhalation increments up to more than 12 inhalations. Along the Y-axis, is the mean % of study days.
The BDA MDI 160/180 dose are the dark purple columns, the BDA MDI 80/180 dose are the light purple columns, and albuterol is represented in the gray columns.
The overall pattern of use for BDA mirrors the albuterol pattern. Use was variable with no use on approximately 25% of study days.
More than 8 inhalations per day were recorded on fewer than 2% of study days in either the BDA MDI or albuterol dose groups, which is reassuring and likely to reflect real world use. No adolescent used 12 inhalations per day for more than 2 consecutive days. This pattern of use is similar as to what was observed in the overall population.

CD-9
Adolescents were randomized to both BDA MDI doses, as in the adult population.
Here is the primary endpoint of time to first severe exacerbation. Within the table, the BDA MDI 160/180 dose group is followed by the 80/180 dose group and then the albuterol group.
As you can see, only 32-34 patients were included in each treatment group. For the 160/180 dose, the hazard ratio was 1.4 with a wide confidence interval that included 1.
For the 80/180 dose, the Hazard Ratio was 0.57, again with a wide confidence interval that included 1.
No comparisons were significant.
The confidence intervals did include the value of the point estimate observed in the overall population suggesting that the true effect size in adolescents could be similar to the overall population.
Now I will present the secondary endpoints all of which suggest a numerical trend toward benefit with both doses of BDA MDI compared with albuterol.

CD-10

Here is the first secondary endpoint which is annualized rate of severe exacerbations.
For the exacerbation rate ratios, the point estimates for both doses favor BDA MDI vs. albuterol, however, again, the confidence intervals were wide and included 1.
No comparisons were significant.
However, the confidence intervals did include the value of the point estimate observed in the overall population again suggesting that the true effect size in adolescents could be similar to the overall population.

CD-11

The remaining 3 secondary endpoints for adolescents are presented on this slide. The results for the BDA 160/180 dose are presented in the first row followed by BDA 80/180 and albuterol.
The total systemic corticosteroid annualized dose as measured by mg/subject, was numerically lower for both BDA MDI dose groups in adolescents with arithmetic mean reductions of 62 and 85% compared with albuterol.
For both ACQ-5 and AQLQ-12, the odds of having a clinically meaningful response were numerically higher in the BDA MDI groups compared with albuterol.
Taken together, the secondary endpoints including the exacerbation rate indicated numerical trends in treatment effects in favor of both doses of BDA MDI for adolescents.
Now I will present the efficacy data in the subgroup of children.

CD-12

This is a table of the demographic and baseline disease characteristics in the subgroup of children.
As you can see, only 41 and 42 children were included in each treatment group.
Overall, the demographics and baseline characteristics were balanced across treatment arms.

CD-13

A similar pattern of use was observed with 80/180 BDA MDI and albuterol in children.
Overall use of BDA MDI or albuterol was, as expected, variable.
On over 40% of days, no BDA MDI or albuterol was used, which is a different pattern compared with the adolescent and overall populations, who had approximately 25% of study days without investigational product use.
As in the adolescent and overall populations, more than 8 inhalations were recorded on less than 1% of study days in either the BDA MDI or albuterol dose groups which is reassuring and likely to reflect real world use.

CD-14

Here are the exacerbation endpoint results for the subgroup of children. Only the 80/180 BDA MDI dose was studied in this population.
Like in adolescents, with the small number of children enrolled, we have limited ability to draw efficacy conclusions.
For time to first exacerbation, the hazard ratio is close to 1, as is the rate ratio for exacerbation rate, both of which have wide confidence intervals.

For both time to first severe exacerbation and the exacerbation rate, the confidence intervals did include the value of the point estimate observed in the overall population suggesting that the true effect size in children could be similar to that observed in the overall population.

CD-15

These are the results for the other secondary endpoints for children.
Total annualized systemic corticosteroid dose for asthma exacerbations favored the albuterol treatment group. In a post-hoc analysis, we normalized annualized systemic corticosteroid dose for weight, and although the % difference was smaller, it still favored albuterol.
For ACQ-5 and PAQLQ, the odds of having a clinically meaningful response were numerically higher in the BDA MDI treatment group compared with the albuterol group, a similar finding as observed in the adolescent population as well as the overall population.
I will now share the modeling analyses we conducted for both groups.

CD-16

We used Bayesian analyses, a method of extrapolation used to integrate evidence based on the rationale that the data from the other age and dose groups within MANDALA should help inform us about the efficacy of BDA in the children and adolescent groups and is consistent with advice we received from the FDA.
The Bayesian analysis approach is commonly used in clinical trials to provide more rigorous estimates across subgroups, which by nature have low numbers, and has been used to estimate treatments effects in pediatric subgroups for respiratory medicines for approval.
The estimates are considered more rigorous because they have been shown to be less influenced by random highs and lows than the stand-alone estimates from small subgroups.

CD-17

In any Bayesian approach based solely on the MANDALA data, to achieve Hazard Ratios with credible intervals <1, which is a high standard of evidence, large amounts of borrowing are needed. This is due to the small sample sizes of both adolescents and children enrolled in the MANDALA study.
However, much less borrowing is needed to observe favorable point estimates as demonstrated in this slide. This slide displays the results of our Bayesian analyses.
The observed results in MANDALA are presented in purple and the modeled data is presented in black, with adolescent results on top followed by the results in children on bottom.
In our Bayesian modeling, borrowing approximately 10% of the available exacerbation events from the overall population was sufficient to observe point estimates of around 15% reduction in risk for adolescents and children, suggesting favorable treatment responses with the proposed BDA MDI doses compared to albuterol.
Now I will present the safety data in adolescents and children.

CD-18

This is a table of the adverse events in each system organ class and for serious adverse events for the three treatment groups in adolescents.

Similar or lower adverse events in each system organ class were observed with each dose of BDA MDI compared with albuterol. Only 3 serious adverse events were reported in the study with one in the 160/180 BDA MDI group and 2 in the albuterol group.

In the BDA MDI 160/180 group, 1 patient reported a serious adverse event of mixed anxiety and depressive disorder. Two patients in the albuterol group reported serious adverse events of asthma. No deaths were reported.

Overall, for the adolescent subgroup, the safety of BDA MDI was similar to albuterol in the MANDALA study and to the known safety profile of budesonide with no new safety findings identified.

CD-19

This is a table of the adverse events overall, in each system organ class, and for serious adverse events for BDA MDI and albuterol in children.

Similar adverse event rates in each system organ class were observed across the treatment groups with one serious adverse event in each group.

One subject in the BDA MDI group reported a serious adverse event of COVID 19, and one subject in the albuterol group reported a serious adverse event of asthma.

The safety profile of BDA MDI in children was similar to the albuterol group, and to the known safety profile of budesonide, with no new safety findings identified.

CD-20

In order to determine the effect of BDA MDI as needed usage on the HPA axis, morning serum cortisol levels were measured from subjects at baseline, at week 24, and at the end of treatment.

This is a graph of change from baseline in morning serum cortisol at week 24 and at last observation while on treatment.

No differences were observed in the mean change from baseline in cortisol measurements between the BDA MDI 160/180, BDA MDI 80/180, and albuterol groups in adolescents nor between the BDA 80/180 and albuterol treatment groups in children.

CD-21

A formal growth study with consistent calibrated stadiometer use and Tanner staging was not included in the MANDALA study due to the well-known effects of budesonide and other inhaled corticosteroids on growth.

However, we measured height as part of standard physical exams at baseline and at the end of treatment. Due to the variable length of study duration for each subject in MANDALA, we calculated growth velocity in a post-hoc analysis.

This is a forest plot of least square means of growth rate by treatment group.

Here we see the results for adolescents on the top and for children on the bottom. The confidence intervals for growth velocities overlapped between BDA MDI dosing groups and albuterol in both pediatric subgroups.

CD-22

Considering all available information, we believe there is support for a favorable benefit-risk profile for BDA MDI for both adolescents and children that is underpinned by a wealth of clinical experience and the well-established safety profiles of albuterol and budesonide in these pediatric populations.

In MANDALA, no new safety findings with BDA MDI were identified in the pediatric subgroups recognizing, of course, we have limited numbers enrolled.

The clinical and pharmacological rationale for extrapolation from the overall population to adolescents and children is based on similarities across all ages in airway inflammation and bronchoconstriction during an exacerbation.

Treatment of severe exacerbations is the same across populations.

Guidelines use the same principals for asthma diagnosis, assessments, and treatment strategies across ages.

Similar treatment effects on severe exacerbations were observed with inhaled corticosteroid/fast-acting bronchodilators as rescue in published studies in adults, adolescents and children, which you will hear about from Dr. Murphy.

Overall there is a high plausibility of BDA MDI rescue decreasing severe exacerbation risk in adolescents and children based on the MANDALA overall population results and published literature.

In summary, we believe that the significant unmet need for both adolescents and children with asthma could be filled by BDA MDI in these vulnerable pediatric populations.

Pediatric Clinical Context

Kevin Murphy, Director of Clinical Research, Boys Town National Research Hospital and Clinical Professor of Pediatrics, The University of Nebraska Medical Center

CA-1

My name is Kevin Murphy. I'm a pediatric pulmonologist who has cared for pediatric asthma patients for over 35 years.

I'm also the Director of Clinical Research at Boys Town National Research Hospital in Omaha Nebraska, and Clinical Professor of Pediatrics at the University of Nebraska Medical Center.

I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting

CA-2

Over the last 35 years, caring for pediatric asthma patients, I have seen first-hand, adolescents and children who struggle with their asthma.

So, today I would like to speak to and share with you the IMPACT of asthma and the UNMET NEED, in adolescents, children and their families.

I will also discuss some of the studies with combination fast acting bronchodilators and inhaled corticosteroids used as rescue that have driven the evolution of treatment guidelines and why I think together with the overall MANDALA efficacy and safety data, that BDA MDI has a favorable benefit-risk profile in the pediatric populations to fulfill this UNMET NEED. Asthma as we can see on the next slide

CA-3
is the most common chronic disease in children and adolescents and has a significant BURDEN OF DISEASE.

That BURDEN includes severe asthma exacerbations, with corresponding repeated courses of systemic corticosteroids, often requiring emergency room visits and hospitalizations.

In my practice, severe asthma exacerbations treated with oral corticosteroids have significant effects on the quality of life in adolescents, children, and their families.

Adolescents and children miss school, struggle with sleep and the ability to concentrate. Parents miss work, and in many cases struggle with the financial impact due to increased healthcare resource utilization through the cost of acute care, especially emergency room visits and hospitalizations.

The next slide reminds us that pediatric asthma patients have a greater burden of disease than adults.

CA-4
This slide is a graphic representation of asthma emergency department visit rates by age group and year in the United States from 2010 to 2018.

The number of Emergency Department visits from 2010 to 2018, with corresponding repeated courses of systemic corticosteroids, are significantly higher in adolescents and children than adults.

What is concerning is this asthma burden has remained unchanged since 2010. This higher incidence of asthma exacerbations and especially the corresponding need for systemic corticosteroids in both adolescents and children is unacceptable. Turning to the next slide

CA-5
As the FDA stated in their briefing document, there are two approaches to address the UNMET NEED of preventing severe asthma exacerbations, including both adolescents and children. One approach is increasing the inhaled corticosteroid maintenance dose AFTER worsening symptoms appear, which may be too late to prevent a severe exacerbation, as this approach, has had inconsistent results, as exemplified in the STICS study.

In comparison, the second approach is the use of an inhaled corticosteroid/fast-acting bronchodilator combination as rescue to TREAT worsening symptoms when they first begin. And the scientific literature with this second approach supports that inhaled corticosteroids plus short acting beta agonists reduces exacerbations across all ages. So, turning to the next slide let me share with you the STICS study.

CA-6

The STICS study, evaluated the clinical the question, does quintupling the dose of inhaled corticosteroids for 7 days after worsening symptoms first appear, prevent severe asthma exacerbations in school-aged children with mild-to-moderate persistent asthma?

The STICS study evaluated 254 children 5-11 years of age with mild-to-moderate persistent asthma with 1 or more severe exacerbations in the previous year. After a 4-week run in period where patients received fluticasone 88 mcg twice a day, patients were randomized to one of two groups.
The low dose group, represented in blue, received fluticasone 88 mcg twice a day as maintenance, that continued after worsening symptoms first appear, referred to as the yellow zone.

The high dose group, represented in red, also received fluticasone 88 mcg twice a day as maintenance. However, when patients entered the yellow zone, fluticasone was increased to 440 mcg twice a day for 7 days.

The yellow zone was defined as occurrence of any of the following: the use of 2 doses (4 inhalations) of albuterol in 6 hours or 3 doses (6 inhalations) in 24 hours, or one night-time awakening due to asthma treated with albuterol.

Patients were treated for 48 weeks with the primary end point being time to first severe exacerbation requiring oral corticosteroids.

Turning to the next slide…

CA-7

In the STICS study, administering five times the maintenance dose of inhaled corticosteroid, in the yellow zone, did not reduce the rate of severe asthma exacerbations, the primary outcome, or other asthma outcomes, including treatment failures and the time to first severe asthma exacerbation requiring prednisone use, as seen on this slide, with a p value of 0.2.

The total glucocorticoid exposure was 16% higher in the high-dose group than in the low-dose group, with an associated decrease in linear growth.

This study is one example of the uncertainties regarding escalating inhaled corticosteroid alone AFTER worsening symptoms first appear.

So now, let's focus on studies the FDA included in their briefing document, that more uniformly demonstrate, that as-needed budesonide administered concomitantly with fast-acting beta agonists prevent severe exacerbations in pediatric patients with asthma.

On the next slide…

CA-8

You see first a post-hoc pooled meta-analysis from 6 studies in over 1800 adolescents with asthma, showing a treatment benefit for the combination of a fast-acting bronchodilator, in this case formoterol, and the inhaled corticosteroid budesonide used as rescue therapy. These studies included the 160-mcg dose of budesonide used in MANDALA.

The forest plot on this slide displays the point estimates in blue circles for the treatment effects for the primary endpoint in these trials, time to a first severe asthma exacerbation, the same primary endpoint in MANDALA, which Dr. Weinberg and Dr. Church reported.

Point estimates on the left side of 1 indicate a treatment benefit for formoterol/budesonide combination used as rescue. This treatment benefit occurred in 5 of the 6 studies and was similar to the comparator in the remaining study.

If one looks at the pooled analysis, represented by the blue diamond at the top of the slide, the reduction in risk for severe exacerbations was 51%.

Now as I build this slide, the adult subgroup is represented in red, demonstrating that the results observed for the adolescent population, both in individual studies and in the pooled analysis, were consistent with those observed for the adult population.

The incidence of adverse events and the types of adverse events reported were similar in all 6 studies among all treatment groups. The proportion of adolescents experiencing a serious adverse event or discontinuing due to an adverse event was very low and similar between treatment comparisons.

Thus, the scientific evidence in adolescents, consistent with those observed for the adult population, demonstrates that the combination of formoterol/budesonide used as rescue provides a positive treatment effect of preventing asthma exacerbations with the safety profile consistent with the known effects of budesonide and formoterol.

Turning then to the next few slides, let me share with you, data from the STAY and TREXA studies.

CA-9
The STAY study was a 12-month trial that evaluated budesonide in combination with a fast-acting bronchodilator, formoterol, and included adults, adolescents, and 341 children 4 to 11 years of age, the same ages of children in MANDALA.

On this slide you see the STAY Study Design, that describes the arms of the study for children only.

In children, the STAY study evaluated the clinical question, “What is the efficacy and safety of budesonide and formoterol used as both maintenance and rescue compared with budesonide and formoterol maintenance or a 4-fold higher maintenance dose of budesonide, the latter 2 arms using short acting beta agonists as rescue?”

Turning to the next slide…

CA-10
You see, the comparison of the 2 arms receiving daily budesonide and formoterol maintenance therapy.
Over a year, the risk of having an exacerbation was 66% lower, in the group receiving the combination of budesonide and formoterol as rescue therapy, as shown in red.

Importantly, on average, children did not use rescue on approximately 70% of study days. This infrequent use is consistent with my experience, of the episodic nature of pediatric asthma. Thus, demonstrating the importance of having an approved medication to treat episodic symptoms in children, instead of adding additional medications or increasing the inhaled corticosteroid maintenance dose.

Turning to the next slide…

CA-11
Let me share with you, safety DATA regarding the effects on growth and adrenal function. The red bars represent budesonide and formoterol used as both maintenance and rescue; the purple bars represent budesonide and formoterol used as maintenance, and the green bars represent the high fixed dose budesonide group.

Looking first at growth on the left side of the slide, which is something that patients and their families frequently ask me about.

The Y axis represents mean growth in cm. over 12 months. The X axis represents the three treatment groups.
Patients receiving Budesonide/Formoterol daily and as needed, had the same growth rate, as the Budesonide/Formoterol daily group.

Both groups grew significantly more with a p value of <0.01, than patients in the high fixed-dose budesonide group.

Turning then to the right side of this slide are the effects on adrenal function. The y axis represents the maximal cortisol response to ACTH. The X axis represents the three treatment groups at baseline and end of treatment.

Although, no formal statistical analyses were completed, there appears to be no appreciable difference on mean ACTH response and the number of patients with abnormal response was low and similar in all 3 groups.

Thus, the STAY DATA, including growth and adrenal function, finds that the combination of budesonide with a fast-acting bronchodilator as rescue on top of maintenance therapy, results in a favorable benefit risk assessment in children 4-11 years of age.

Turning to the next slide, let me share with you the TREXA study.

CA-12

The TREXA study, evaluated two clinical questions. I'm going to focus on the question, "Does beclomethasone plus albuterol as rescue (plus or minus daily beclomethasone) reduce exacerbation risk compared with albuterol rescue alone?"

The study included 288 patients 6-18 years of age with mild persistent asthma with 1 to 2 exacerbations in the previous year. After a 4-week run in period, where patients received beclomethasone 40 mcg twice a day, patients were randomized to one of 4 groups.

The top 2 groups both received beclomethasone as maintenance therapy and the bottom 2 groups received no maintenance therapy. The two groups who received beclomethasone albuterol as rescue were the solid red arm and the solid blue arm. The open red and the open blue arms both received albuterol alone as rescue.

Three outcomes were assessed, time to first severe exacerbation, the primary outcome, severe exacerbation frequency, and the frequency of treatment failures, defined as 2 courses of oral corticosteroid within 6 months. These analyses compared the beclomethasone containing treatment groups with albuterol alone.

Important to note is the study, with a planned enrollment of only 70 per treatment group, was on the small side for an exacerbation study and was powered to detect a relatively large treatment effect of a 50% reduction in severe asthma exacerbation risk.

These data are summarized on the next two slides.

CA-13

On the left side of this slide is the Kaplan-Meier plots for time to first exacerbation that required a prednisone course for each of the four treatment groups.

Compared with albuterol as rescue, the hazard ratios were significantly lower in the daily beclomethasone and the daily plus rescue beclomethasone groups.

There was a numerical, however not significant difference, in the rescue beclomethasone group, compared with albuterol.

On the right side of the slide, you see that the severe exacerbation frequencies were lower in the three groups receiving inhaled corticosteroids for maintenance and/or rescue.

On our next slide…

CA-14

We see the results for the outcome, that is most important to me and especially my patients, and that is treatment failures that require oral corticosteroids.
The Y axis represents percent failures over 12 months, and the X axis represents the four treatment groups.

The frequency of treatment failures was 5.6% in the beclomethasone daily and rescue group, 2.8% in the beclomethasone daily group, 8.5% in the beclomethasone rescue group, and 23% in the albuterol group.

Compared with albuterol alone, all three groups, had significantly less treatment failures, representing a reduction in exacerbations requiring oral corticosteroids.

These DATA support the use of inhaled corticosteroids plus short acting beta agonists used as rescue, with the authors concluding, that children with mild persistent asthma should not be treated with rescue albuterol alone.

Now, let me share with you the growth data from this study.

CA-15

The graph that you see on this slide, displays linear growth over 44 weeks in the four treatment groups.

There are several points to be made about these data.

First, linear growth over 44 weeks was 1.1 cm less in the two groups in red, those patients receiving daily maintenance inhaled corticosteroids.

This effect on growth in children, receiving daily inhaled corticosteroid maintenance therapy has been demonstrated in other studies and is a well-known effect of daily inhaled corticosteroid maintenance therapy.

Secondly, and importantly, the patients in red, who received daily maintenance beclomethasone had the same linear growth, if they received albuterol or beclomethasone plus albuterol as rescue.

Thirdly, patients receiving albuterol/beclomethasone as rescue only, had NO effect on growth compared to albuterol alone.

The TREXA efficacy and safety data support the favorable benefit risk assessment of inhaled corticosteroids with albuterol used as rescue.

So, let's turn to the next few slides, you will see the most recent NAEPP and GINA guidelines.

CA-16

Both NAEPP and GINA guidelines are driven by the type of emerging data I've just shown you. Both guidelines increasingly recommend inhaled corticosteroid with short acting beta agonists for rescue use, similar to how BDA MDI is intended to be used. As seen on this slide, outlined in red, in addition to inhaled corticosteroid/formoterol combination as rescue, the combination of an inhaled corticosteroid plus short acting beta agonist for rescue was added to the most recent 2020 NAEPP update for the management of asthma.

Despite differences in preferred controller therapy across severities and ages, rescue recommendations are similar.

Turning then to the next slide…

CA-17

As you heard from Dr. Lugogo, GINA recommends that adolescents and adults be treated the same and no longer recommends short acting beta agonist alone, but instead recommends an inhaled corticosteroid plus formoterol rescue.

In children, rescue therapy recommendation, also now include inhaled corticosteroid plus formoterol.

Despite these recommendations, there is no combination reliever approved currently in the United States, underscoring the unmet need.

CA-18

In summary, the burden of pediatric asthma…is severe asthma exacerbations.

The unmet need…is preventing severe asthma exacerbations, and the corresponding burden of systemic corticosteroids.

The published scientific data, support the combination of inhaled corticosteroids/fast acting bronchodilators used as rescue in adolescents and children.

In adolescents and children, given the risks and limitations of albuterol alone as rescue therapy, NAEPP and GINA guidelines increasingly recommend inhaled corticosteroid/short acting beta agonist combination as rescue.

Thus, BDA MDI has the potential to fulfill the significant unmet need, preventing severe asthma exacerbations in both adolescents and children.

CA-19
So, when I walk into the exam room and talk with my patients, families, or one of my own family members about addressing the unmet need… of continuing to experience severe asthma exacerbations.

I can share with them, that collectively, the available data in thousands of pediatric patients justifies the favorable benefit-risk assessment of BDA MDI in both adolescents and children.
And the approval of BDA MDI will allow health care practitioners like me to prescribe rescue therapy that aligns with current asthma treatment guidelines.

Importantly, the use of BDA MDI as rescue would be a simple, yet substantial change, that for my pediatric patients, will not require specific educational training, when BDA MDI is used for symptom relief.

So, I believe the opportunity is now, to provide pediatric patients with a treatment, that prevents asthma exacerbations, resulting in a significant improvement in the care of both adolescents and children with asthma.

Thank you!

Conclusions
Dr. Ed Piper, Global Franchise head for core Inhaled Products at AstraZeneca

CC-1
Thank you for your attention to our presentations.

CC-2
To summarize, we agree with FDA that there is a need for a safe and effective rescue therapy to prevent severe asthma exacerbations for adults, adolescents, and children.
The BDA MDI clinical program showed that both doses of BDA MDI resulted in statistically significant and clinically-meaningful reductions in severe asthma exacerbation risk vs. albuterol.
In addition, BDA MDI 160/180 resulted in reductions in the annualized severe exacerbation rate and mean total systemic corticosteroid exposure as well as nominally higher odds of achieving clinically-relevant improvements in asthma control and quality-of-life measures.
No new safety signals were detected.

CC-3

Therefore, the benefit-risk assessment is favorable in adults and BDA MDI 160/180 is the proposed dose.

We acknowledge that the data available in adolescents and children are limited, however we have carefully considered the benefit-risk assessment for BDA MDI in both pediatric populations and believe it to be favorable based on

- The observed safety profile of BDA MDI which is consistent with the well-established safety profiles of albuterol and budesonide
- A strong clinical and pharmacologic rationale to extrapolate efficacy from the overall population to adolescents and children
- And supportive efficacy and safety data from other ICS/fast-acting bronchodilator combinations in pediatric asthma

THANK YOU and we look forward to the meeting on the 8th of November.