Transcript for FDA Pulmonary-Allergy Drug Advisory Committee Meeting: Overview of the Clinical Program and Clinical and Statistical Considerations

NDA 214070: budesonide/albuterol sulfate metered dose inhaler for the as needed treatment of asthma

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Part 1 of 3: Introduction and Overview of Trials

Slide 1

Hello, my name is Elisabeth Boulos, and I am an adult pulmonary and critical care medicine physician, as well as a medical officer in the Division of Pulmonology, Allergy and Critical Care here at the FDA. I am the primary clinical reviewer for this program, and it is my pleasure to share this presentation with you today. We are convening this meeting of the Pulmonary-Allergy Drug Advisory Committee meeting to discuss NDA 214070 for budesonide/albuterol sulfate metered dose inhaler.

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First, I will provide an overview of the product, which we will refer to as BDA MDI or BDA. BDA is an oral inhalation aerosol, formulated as a pressurized metered dose inhaler that delivers a combination of either 40 or 80 micrograms of budesonide and 90 micrograms of albuterol sulfate per actuation. The Applicant has developed 2 dosing regimens and strengths: for patients 12 years of age and older, the Applicant proposes to market a dose of 2 inhalations of 80 micrograms budesonide and 90 micrograms albuterol sulfate, resulting in 160 micrograms of budesonide and 180 micrograms of albuterol per dose. For patients 4 to 11 years of age, the Applicant proposes 2 inhalations of 40 micrograms budesonide and 90 micrograms albuterol, resulting in 80 and 180 micrograms, respectively, per dose. For both populations, the recommended maximum usage is not to exceed 6 doses or 12 inhalations in 24 hours.

The indication proposed by the Applicant 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.” It is important to highlight that although the mono-components of BDA, budesonide and albuterol, have both been FDA-approved for many years, BDA would represent a novel product in several ways. First, the proposed indication “to prevent exacerbations” would be new for a reliever treatment for asthma. Second, BDA would be the first fixed dose combination product combining an inhaled corticosteroid and short-acting beta agonist, thus representing a new intended use for an inhaled corticosteroid in the treatment of asthma.

Slide 3

Before moving on, I will summarize abbreviations we will use frequently throughout this talk. We will use standard abbreviations for commonly referenced drugs classes, including SCS for systemic corticosteroids. On the bottom half of the slide, you can see abbreviations for both the mono-components of BDA and BDA itself. We will sometimes refer to as BDA 160/180 as “high dose” and to BDA 80/180 as “low dose.”

Slide 4

The Agency’s goal in convening this meeting of the advisory committee is to request the committee discuss the following issues. First, the data to support the efficacy of BDA for the proposed indication across all age groups. For pediatric age groups, we believe the evaluation of efficacy requires consideration of whether extrapolation of adult data is appropriate and whether additional data may be

needed. Next, we ask the committee to discuss the safety data for BDA, again with a focus on pediatric safety concerns, not only those observed in the BDA development program, but also based on anticipated real-world use of BDA and existing knowledge about inhaled corticosteroids in pediatric patients. Based on these first two points, we ask the committee to discuss the benefit risk assessment of BDA for the whole population, which we break down by age cohort, since we believe that the benefit risk considerations for each group may be different.

Slide 5

We believe that the concept of pediatric extrapolation will be central to this discussion. Pediatric extrapolation can extend what we understand about a drug in the adult population to pediatric subjects, based upon careful clinical and pharmacologic considerations. Thus, it can help reduce the burden of pediatric data requirements for drug development programs. The figure on the left provides a visual framework for how to approach extrapolation and is one we will revisit at the end of this talk, after we present results. As we discuss the data from the BDA development program, we request that the committee keep in mind the conditions in which a high degree of extrapolation with little independent confirmation is most appropriate. First, the disease is the same in adult and pediatric patients, as is the response to treatment. Second, the available evidence is of high quality and, last, there are no significant knowledge gaps.

Slide 6

To facilitate discussion of the issues just presented during the advisory committee meeting, in this talk, I will begin with a brief background to contextualize the BDA development program and provide a brief overview of the program. Then, in conjunction with the FDA statistical reviewer, we will summarize key efficacy and safety results, with a focus on pediatric subgroups. I will then identify key clinical concerns and uncertainties and finally present the questions for discussion to the committee.

Slide 7

Slide 8

The characteristics of asthma are well-known to this audience. In brief, asthma is a chronic respiratory disease, characterized by inflammation, bronchoconstriction, and airway hyperresponsiveness. Asthma is a common disease with an estimated US prevalence of approximately 8% in both adults and children, representing one of the most common chronic childhood diseases. Asthma is a heterogenous disease with a spectrum of phenotypes and a range of symptoms and severities. All patients with asthma, however, of all severities and age, are vulnerable to episodic increases in airway inflammation in response to triggers or acute exacerbations. Many exacerbations may be managed with as needed SABA or with systemic corticosteroids, which may, themselves, be associated with morbidity. Severe exacerbations may require hospitalization, higher or prolonged systemic corticosteroids, and may result in death. The goals of asthma treatment are to control symptoms and prevent exacerbations. The foundation of treatment has traditionally comprised controller (or long-acting) inhalers, such as budesonide, and reliever treatments to alleviate symptoms.

Slide 9

Since BDA was developed for use as a reliever inhaler, I will provide additional background on the current landscape of reliever treatments. Presently, only one class of drug, SABA, is approved in the US

as a reliever treatment for asthma, and albuterol accounts for the majority of clinical use. No reliever therapies carry the indication to prevent severe exacerbations.

However, in recent years, there has been a paradigm shift in the approach to reliever treatment, informed by the literature on asthma and subsequently reflected in recent guideline revisions. The first concept is that of concomitant, as-needed use of an ICS and quick-onset LABA as both maintenance and reliever therapy, often known as SMART, which is now recommended by both GINA and NAEPP guidelines for some steps in the asthma management algorithms. We note that no ICS/LABA fixed dose combination inhaler is currently FDA-approved for this indication.

Similarly, there is literature regarding concomitant as needed use of an ICS with SABA in response to symptoms, which is recommended by both sets of guidelines as an alternative treatment for patients with mild asthma. BDA would represent the first FDA approved ICS/SABA fixed dose combination.

Finally, we note an extensive literature on escalating ICS doses at the first signs of loss of asthma control in order to prevent or abort exacerbations; however, the totality of data on this approach remains inconclusive, particularly for pediatrics patients.

Slide 10
I will now move on to present the pivotal trials submitted for registration.

Slide 11
The two trials relevant to BDA approval are MANDALA and DENALI. MANDALA was designed to demonstrate the contribution of the ICS to the ICS/SABA combination when used as needed to prevent severe acute asthma exacerbations, and the Agency views this trial as the primary source of efficacy data because of the size of the trial, the exacerbation primary endpoint, and the administration of the investigative products as intended in real world practice.

DENALI was designed to assess the contribution of each mono-component to the effect on lung function. The Agency views DENALI as a source of supportive evidence, safety data on higher doses of BDA in a milder population, and data to support the combination rule, which I will discuss shortly.

Slide 12
MANDALA will be the focus of this presentation.

Slide 13
MANDALA was an event-driven, variable-duration, minimum 24 week, randomized, double-blind, active-comparator controlled trial in subjects with moderate to severe asthma. Starting on the left side of this figure, approximately 3000 subjects 12 years of age and older were randomized 1:1 to the three treatment arms shown here; of note, within this group, only 100 subjects were between 12 and 18 years old. Subjects 4 to 11 were randomized 1:1 to either low dose BDA or albuterol only. During the screening period, all subjects replaced their pre-enrollment reliever treatment with Applicant-provided Ventolin HFA but controller medications were not adjusted; throughout both the screening and treatment periods, subjects continued their background controller medications, listed in the bottom rectangle. During the treatment period, subjects were instructed to use the investigative product PRN, in response to triggers and to alleviate symptoms. The key efficacy analyses were performed at the Primary Completion Date, when 570 severe acute exacerbations had occurred, and the last enrolled

adult reached 24 weeks of treatment. For all subjects who met the Primary Completion Date or discontinued treatment early, there was a 2-week safety follow up period.

Slide 14
The MANDALA population was consistent with a moderate to severe asthma population, correlating approximately with GINA guideline steps 2 through 5 in terms of background treatment. The left column lists the key inclusion criteria, which included parameters for controller medications, baseline FEV1, and Asthma control questionnaire scores, as well as the requirement for at least 1 severe exacerbation within the previous 12 months; use of Ventolin HFA during the screening period was also evaluated prior to randomization.

Key exclusion criteria are listed on the right and include use of any biologic therapy or a history of unstable or life-threatening asthma. Overall, these criteria capture patients with a reasonable probability of another exacerbation in the following year.

Slide 15
The primary efficacy endpoint for MANDALA was time to first severe asthma exacerbation. Secondary endpoints, analyzed under a hierarchical testing procedure to maintain Type-1 error control, were annualized rate of severe asthma exacerbations, total systemic corticosteroid exposure over the treatment period, and responder analyses for two patient-reported outcome assessments validated in asthma: the Asthma Control Questionnaire 5 and the Asthma Quality of Life questionnaire 12 or Pediatric Asthma Quality of life Questionnaire. The Agency agreed that, taken together, these endpoints would provide clinically meaningful data on the effects of BDA.

Slide 16
I will now provide an abbreviated overview of DENALI, the source of supportive evidence and the trial designed to satisfy the combination rule.

Slide 17
The combination rule refers to the regulatory principle that two or more drugs may be combined into a single fixed dose when each component has been demonstrated to make a contribution to the claimed effect of the drug. For BDA, since albuterol is already approved as a reliever treatment, the focus of our review was examining whether the ICS contributes benefit that outweighs any additional risk.

Slide 18
DENALI was a 12-week, randomized, double-blind, placebo and active-comparator controlled trial in subjects with mild asthma. Starting on the left side of this figure, approximately 1000 subjects 12 years of age and older were randomized 1:1 to the five treatment arms shown here; within this group, only 25 subjects were between 12 and 18 years old. Subjects 4 to 11 were randomized 1:1 to either low dose BDA, albuterol, or placebo only. During the screening period, all subjects used the placebo MDI four times daily, and during the treatment period subjects used the investigative product four times daily on top of background Applicant-provided Ventolin HFA. All subjects were followed for an additional 2 week safety follow up period.

Slide 19
The DENALI population was consistent with a mild asthma population, correlating approximately with GINA guideline steps 1 through 2 in terms of background treatment. The left column lists the key inclusion criteria, which included parameters for baseline medications (low dose ICS or SABA only),

FEV1, and screening-period Ventolin use. Key exclusion criteria listed on the right include excessive use of Ventolin during the screening period.

Slide 20
The dual primary efficacy endpoints for DENALI were change from baseline in FEV1 area under the curve over the 12-week treatment period and change from baseline in trough FEV1. Secondary endpoints, analyzed under a hierarchical testing procedure to maintain Type-1 error control, are listed here and included additional pharmacodynamic assessments via FEV1, as well as a responder analysis for the patient-reported outcome, the Asthma Control Questionnaire 7. The Agency agreed these endpoints were appropriate for the purposes of this trial.

Slide 21
I will now turn the presentation over to my statistical colleague, Dr. Dong-Hyun Ahn, to present a summary of the key efficacy results from the BDA development program.

Part 2 of 3: Summary of Efficacy Results

Slide 1
Hello, my name is Dong-Hyun Ahn, I am a senior mathematical statistician in the Division of Biometrics III, Office of Biostatistics at the FDA. I am the primary statistical reviewer for this program, and I will go over a summary of the key efficacy results from the BDA development program.

Slide 2
The primary objective of MANDALA was to assess the contribution of ICS to ICS/SABA when used as needed in preventing severe acute asthma exacerbations, and the Agency views the result from this trial as primary source of efficacy data.

Slide 3
In MANDALA, among the 3132 randomized subjects, 3123 subjects were qualified for full analysis set, defined as all subjects who were randomly assigned and took any amount of IP, and these subjects were composed of adults, adolescents, and children.

Slide 4
The study was powered on the adults and adolescents combined population.

Slide 5
And 83 children 4 to 11 years of age were additionally randomized in this trial,

Slide 6
Receiving only low dose BDA combination product and AS mono product.

Slide 7
This is a subject disposition table. Among the 3132 randomized subjects, 363 subjects discontinued randomized treatment, which accounted for 11.6%, and 352 subjects withdrew from the study, indicating that the majority of subjects who discontinued randomized treatment have also discontinued from the study. The Agency normally recommends the Applicant follow patients and collect efficacy and safety data after treatment discontinuation to minimize missing data; however, only a small portion of such retrieved dropout data was available in this trial. Treatment and study discontinuation rates were slightly higher in the AS group compared with the BDA groups.

Slide 8
A major reason for treatment and study discontinuation was “subject decision” and “withdrawal by subject”, which provides limited information about the treatment discontinuation and study withdrawal.

Slide 9
This is the primary endpoint efficacy result, using a cox regression model for time to first severe exacerbation, based on the efficacy estimand, which is based on data observed while-on-treatment.

Slide 10
The hazard ratio was 0.73 in comparing high dose BDA (the combination treatment) vs. AS (mono comparator), and the risk reduction was statistically significant, indicating a significant delay in time to first severe exacerbation for high dose BDA when compared with AS. Descriptively, the proportion of subjects with a severe exacerbation was 6% lower for the high dose BDA group compared with the AS group.

Slide 11
The hazard ratio was 0.83 in comparing low dose BDA with AS; however, the reduction was marginal with a p-value of 0.041 and with a 3% difference in the proportion of subjects with the event. To remind the committee, the low dose BDA efficacy comparison included children 4-11 yo, increasing sample sizes for low dose BDA group and AS group. ~~And~~ The Type I error rate for these comparisons was controlled under Hochberg’s step-up method.

Slide 12
This is a Kaplan Meyer curve for the primary endpoint, which shows that the red curve representing the high dose BDA group was separated from the blue curve for the AS group from the beginning, demonstrating consistently lower cumulative probability of severe exacerbation throughout the study duration. By design, subjects had a variable treatment duration, with some followed ~~over~~ beyond week 96.

Slide 13
However, the study subjects were asked to complete a minimum 24-week treatment duration and were followed until the primary completion date, when 570 first severe exacerbation events occurred.

Slide 14
~~And~~ This is the secondary endpoints efficacy results, and the endpoints listed in the table are under the order defined by a pre-specified hierarchical testing procedure to control type I error rate.

For the first secondary endpoint, an annualized severe exacerbation rate, using a negative binomial model, the rate ratio was 0.76 for high dose BDA compared with AS and the reduction was statistically significant. For low dose BDA, the rate reduction was also statistically significant.

Moving to the next secondary endpoint, ~~a~~ total annualized dose of systemic corticosteroid use, measured by mg per subject, the result showed that the mean use of systemic corticosteroid was 33.4% lower for high dose BDA compared with AS, and according to a Wilcoxon rank sum test, the difference was statistically significant. However, the result was not statistically significant for low dose BDA, and according to the Type I error rate control plan, the evaluation for the rest of the endpoints was considered exploratory,

Slide 15
although nominally significant results were observed, in favoring high dose BDA, for the Asthma Control Questionnaire 5 and Asthma Quality of Life Questionnaire 12.

Slide 16
These are the main efficacy findings for consideration in the MANDALA trial. Efficacy for adults was supported by significant delay in time to first severe exacerbation. On the other hand, there was uncertainty regarding efficacy for high dose BDA in adolescents due to the small sample size of 68 and there was uncertainty regarding efficacy for low dose BDA in children 4 to 11 which included 83 subjects. To further explore the pediatric efficacy, the division asked the Applicant to conduct a Bayesian borrowing approach to see how much borrowing of adult data would be needed to show meaningful results, and we took a careful look at these additional analyses.

With regards to low dose BDA efficacy, marginal benefit was observed in primary analysis population; subjects 4 year of age and older. From a statistical perspective, we identified 2 potential issues with the low dose efficacy data. First, the sensitivity analysis to the missing data assumption did not appear to support robustness of the efficacy and no statistically significant benefit was demonstrated under the supplementary estimand recommended by FDA. We note that the high dose is proposed for adults and adolescents. Given that the low dose is proposed for children 4 to 11, we wanted to briefly discuss these statistical findings for the AC panel consideration.

Slide 17
To further explore pediatric efficacy, we want to point out that, according to the statistical analysis plan, MANDALA ~~trial~~ was powered on adult and adolescent subjects, with a total planned sample size of 3000, to provide 87% power to observe 25% reduction in the risk of severe exacerbation. And in addition, up to 100 subjects in the 4-to-11-year age group was planned to be equally randomized to AS group or low dose BDA group.

Slide 18
This is the primary endpoint age-based subgroup analysis forest plot.

Slide 19
In the adolescent subgroup, the point estimate of hazard ratio was 1.44, not in favor of high dose BDA.

Slide 20
In the children 4 to 11 subgroup, the point estimate of hazard ratio for the low dose was 1.09, again, not in favor of BDA. However, since the confidence intervals were wide due to small sample and included the null value of 1, these results might not be statistically reliable. And I want to add here that, 37 of these pediatric subjects were in their early treatment duration when the study was completed, and they were censored in the primary efficacy analysis, which made the pediatric analysis results even less reliable. So, it is possible that these point estimates are results of random high, and it is known that there is a considerable chance of observing a negative trend in a subgroup due to relatively small sample size given that positive treatment effect is observed on the overall population.

Slide 21
In order to support efficacy in pediatric subjects, Bayesian analyses were used to incorporate the adult information in the pediatric analyses. One possible decision rule for concluding a statistically significant

treatment effect of BDA in the pediatric subgroups is evaluating whether the 95% credible interval excludes the null value of hazard ratio equal to 1.

We will show you two different Bayesian borrowing approaches that were conducted which are robust mixture prior and Bayesian hierarchical model. These are two different Bayesian methods that implement borrowing from other groups using different approaches. But we note that findings from these methods were overall consistent.

Slide 22
This is a Bayesian analysis borrowing adult data for high dose BDA efficacy in adolescents 12 to 17, using a robust mixture prior approach conducted by the Agency. This table shows that, to obtain median hazard ratio less than 1, approximately 85% of the total events in the analysis would need to be borrowed from adults. To derive a statistically significant effect of high dose BDA in adolescent, with an upper 95% credible limit less than 1, approximately 96% of the total events in the analysis would need to be borrowed from adults.

Slide 23
Similarly, here is a Bayesian analysis borrowing adult data for low dose BDA efficacy in children 4 to 11, again, using a robust mixture prior approach conducted by the Agency. This table shows that, to obtain median hazard ratio less than 1, approximately 89% of the total events in the analysis would need to be borrowed from adults and adolescents. To derive a statistically significant effect of low dose BDA in children 4- 11, with an upper 95% credible limit less than 1, approximately 96% of the total events in the analysis would need to be borrowed from adults and adolescents.

Slide 24
This is a Bayesian analysis borrowing data from all 7 subgroups defined by age cohorts and doses, using a Bayesian hierarchical model approach conducted by the Applicant. In the subgroup of children 4 to 11 with low dose BDA, to obtain the mean hazard ratio less than 1, approximately 78% of the total events in the analysis would need to be borrowed from other subgroups. In the adolescent subgroup with high dose BDA, to obtain the mean hazard ratio less than 1, approximately 80% of the total events in the analysis would need to be borrowed from other subgroups.

The Applicant claims that these results consistently show favorable estimates of efficacy across age subgroups even with relatively weak levels of borrowing. However, we note that the posterior inferences in the pediatric subgroups do not provide statistical significance and percentage of total events borrowed is almost as high as 80%. In summary, our findings from the Bayesian analyses indicate that a high degree of borrowing of adult data is necessary to derive meaningful results in the pediatric subgroups.

Slide 25
In order to discuss the marginal efficacy of low dose BDA in the overall population, we looked at the pre-specified estimand strategies in MANDALA. The Applicant proposed “while-on-treatment” strategy to handle intercurrent events of treatment discontinuation or change in maintenance therapy in their primary estimand. To reflect this estimand in the analysis, follow-up for events was censored among subjects with these intercurrent events. De facto estimand was proposed as a supplementary estimand with a treatment policy strategy. The primary analysis included all severe exacerbations, including those post randomized treatment discontinuation, or following changes in maintenance therapy.

Slide 26
This is a frequency distribution table for intercurrent events that occurred across the treatment groups, and the numbers were comparable in general, between high dose BDA and AS comparison, and low dose BDA and AS comparison. Although slightly higher discontinuation rates were observed in AS groups, most subjects who discontinued from the randomized treatment were for reasons of "subject decision" which does not seem to contain much information about the treatment. In addition, the majority of treatment discontinued patients also discontinued from the trial, potentially making the estimate of "treatment policy" estimand not much different from "while-on-treatment" estimand.

Slide 27
This is a primary analysis result under the supplementary estimand using a treatment policy strategy. Under this supplementary estimand, high dose BDA comparison was still statistically significant, however, low dose BDA comparison was not statistically significant, with a nominal p-value greater than 0.05.

Slide 28
To evaluate the sensitivity of the primary analysis to missing data, we first note that the missing rate was less than 10%, and the amount of missing data was balanced among treatment groups. However, according to the two-dimensional tipping point analyses conducted by the Applicant, the result for high dose BDA was robust to the missing data assumption which was censoring-at-random. However, the result for low dose BDA was not likely robust to the missing data assumption.

Slide 29
Now I will move onto next pivotal trial, DENALI. The objective of this trial was to demonstrate the contribution of each component, both ICS and SABA, to effect on lung function. And the Agency views the result from this trial as supportive evidence, offering safety data for higher dose and mild population, satisfying the combination rule.

Slide 30
This table summarizes the dual primary endpoints analysis results from DENALI. The dual primary endpoints assessed the change from baseline in FEV1 area under the curve (AUC) from 0 to 6 hours post-inhalation, averaged over all treatment visits, and the change from baseline in trough FEV1 at the end of the treatment period, week 12. Including subjects ≥12 from the full analysis set under the hierarchical testing procedure to control type-I error for these multiple comparisons, BDA demonstrated statistically significant benefit compared to placebo and each mono component.

Slide 31
So, in all comparisons, the results were statistically significant. And this result satisfied combination rule which was the main objective of this study.

Slide 32
This is a summary of efficacy results.

In MANDALA, primary and key secondary efficacy endpoints were met, and results in adults are statistically significant; however, results in the two pediatric subgroups are uncertain. Confidence intervals were wide with upper bounds exceeding 1. A high degree of Bayesian borrowing was required to achieve meaningful results.

The low dose BDA provided marginal benefit for the overall population, and statistical significance was lost under the supplementary treatment policy estimand. The low dose BDA results are not likely robust to departures from the missing data assumption.

In DENALI, dual primary endpoints achieved statistical significance, and the combination rule was satisfied.

Slide 33
I will now turn the presentation over to my clinical colleague, Dr. Elisabeth Boulos, to present a summary of safety results and conclusions.

Part 3 of 3: Summary of Safety and Conclusions

Slide 1
I will now provide a brief summary of safety data from the BDA development program, again with a focus on MANDALA.

Slide 2
Some important features of our safety review are presented here. The Applicant and Agency agreed in advance not to pool safety data from the pivotal trials, because of their disparate designs and enrolled populations. In each trial, safety events were analyzed in the Safety Analysis Set, defined as all subjects who received any amount of investigative product, classified by the treatment they actually received.

The Applicant and Agency also agreed to pre-specify adverse events related to known risks and toxicities of inhaled corticosteroids. Finally, although we do not have time to present all findings here today, we analyzed adverse events not only by randomized treatment arm but also by background ICS and controller treatment to gain the most insight about the additive effects of using BDA on top of background ICS.

Slide 3
This table summarizes the size of the safety database available for review. As previously noted, MANDALA provides the largest proportion of subjects and data on BDA when used as intended. DENALI provides data on a higher standing dose of BDA (although without the addition of continued background ICS use). In red in the last row, we note the total number of subjects in the pediatric age cohorts available for review.

Slide 4
For an inhalation and locally-acting drug, such as BDA, the systemic exposure can affect the drug's safety profile. Therefore, it is important to understand the systemic exposure level of BDA, particularly in pediatric subjects relative to adults.

First, we look at the top table. The Applicant conducted two PK studies comparing the budesonide systemic exposure between BDA and the listed budesonide inhalation drug products in both adult healthy volunteers (Study ELBRUS, on the left) and pediatric asthma patients, aged 4 to 8 years (Study BLANC, on the right). Results from both studies demonstrate that the budesonide systemic exposures following a single dose of BDA 160/180 are lower than the listed budesonide inhalation drug products at their respective approved doses. Furthermore, the cross-study PK comparison (as highlighted by the numbers in red) shows that, following inhalation of the same BDA 160/180 dose, budesonide systemic exposure in children is about half of that in adults.

In the lower table, we summarize results from additional simulations we conducted to mimic 'worst-case scenario' conditions, in which BDA 160/180 is inhaled 12 times per day in addition to the approved maximum budesonide controller dose. As highlighted by the numbers in red, under these conditions, the total systemic exposure of budesonide in children aged 4 to 17 years is about 20-70% of the total exposure in adults. In summary, these data suggest that the systemic exposure of budesonide from BDA is both lower than currently marketed budesonide-containing products and lower in children compared to adults.

Slide 5
I'll now present safety data from MANDALA.

Slide 6
Since MANDALA was an event-driven, variable-duration trial, in which the investigative product was used as-needed, it is important to understand the drug use patterns. On average, as shown in the second column, adults were enrolled in the treatment period for longer than adolescents or children, a function of late randomization of pediatric subjects relative to the primary completion date. This means that a smaller proportion of the pediatric sample size accrued up to 24 weeks of observation on treatment.

In the last column, we see that mean and median number of daily inhalations, was not only relatively balanced between randomized treatment arms but also across age groups. Of note, children 4 to 11 reported a greater proportion of days without any investigative product use (45% compared to 25% in the total population).

Regarding over-use of the investigational product, this was a rare event with less than 1% of study subjects, including 1 adolescent and 2 children, using greater than 12 inhalations on more than 2 consecutive study days.

In conclusion, these data suggest that BDA over-use was not a frequent event during the MANDALA study period and that use patterns across between randomized treatments as well as across age cohorts were similar. A significant limitation is the smaller scope of time under observation for pediatric subjects.

Slide 7
This table summarizes the distribution of any category of adverse event in the safety analysis set for MANDALA. Overall, most adverse events were not serious or severe and, as shown in the first row, were balanced across treatment arms. The number of adverse events attributed to randomized treatment or resulting in discontinuation of randomized treatment were also low and balanced across arms. Serious adverse events were rare, with the slightly higher number in the BDA 160/180 arm driven by more COVID-19-related adverse events. Finally, 8 deaths occurred during the development program, 7 during the randomized treatment period, and 1 in the AS arm after the safety follow up period; 4 of the deaths were a result of COVID-19 and none were attributed by investigators to the investigational product.

Slide 8
As previously noted, the overall incidence of serious adverse events was low. Most were isolated events.

The only events occurring in greater than 1% of the study population were COVID-19, pneumonia, and asthma. The higher number reported in the BDA 160/180 arm were driven by COVID-19 infections, and

infection is a well-described risk of ICS. The other significant difference, although also small in magnitude, was the higher incidence of asthma-related events in the albuterol arm, which was largely driven by subjects on medium and high dose background ICS. Additional analyses stratified by background ICS and investigative product usage did not identify clear patterns or unearth other concerns. In conclusion, these results were not unexpected given the population and known safety profiles of the drug classes.

Slide 9
The most frequently reported preferred terms for MANDALA include nasopharyngitis, headache, and COVID-19. The overall incidence of these events was balanced across arms. Although we note the absence of a placebo arm to help calibrate rates, based on these data we did not identify new or unexpected safety signals.

Slide 10
Now, I will present results within the pediatric subgroups from MANDALA. The overall incidence of adverse events was balanced across both randomized treatment arms and between pediatric age cohorts, as shown in the first row. Adverse events related to randomized treatment or leading to discontinuation of randomized treatment were rare. Similarly, serious adverse events in these age cohorts were rare. In conclusion, most adverse events were not serious or severe and contributed a small number to the total population.

Slide 11
This table demonstrates that the overall incidence of serious adverse events among pediatric subjects was low. The only term occurring in more than one subject was asthma, with all 3 reports occurring in the albuterol treatment arm in subjects on medium or high dose background ICS. Based on these data, we did not identify any unexpected or concerning patterns.

Slide 12
This table summarizes adverse events among pediatric subjects reported with greater or comparable frequency in the BDA arms compared to albuterol. Even within these parameters, we see that the distribution of adverse events was largely balanced between randomized treatment arms

Consistent with the adult data, the nature of the events (for example, rhinitis, cough, nasopharyngitis) are not unexpected given the known risks of inhaled corticosteroids. Although not pictured here, when stratified by age cohort and background ICS, there were no significant imbalances between groups

Slide 13
Finally, in addition to our focus on pediatric subjects, another focus of our review was adverse events associated with the known toxicities, both local and systemic, of inhaled corticosteroids. Regarding local toxicities, the overall incidence was low and largely balanced between arms; imbalances, such as oral candida infections, were small and not unexpected. Adverse events associated with systemic ICS-related toxicities were mostly mild to moderate in intensity, low in frequency, and balanced across arms. Among pediatric subjects, the overall incidence of ICS-related events was low, and we did not observe concerning patterns by age.

Slide 14
I will now pivot to DENALI for an abbreviated summary of results, which, again, are relevant given the higher standing dose of investigative product administered in this trial.

Slide 15
The overall incidence of adverse events was lower than in MANDALA, as expected given the smaller sample size, milder population, and shorter treatment duration. Rates of adverse events were relatively balanced between arms, and again we note the rates of adverse events attributed to randomized treatment or leading to discontinuation of randomized treatment were low and balanced. Serious adverse events were rare.

Slide 16
Among pediatric subgroups, the overall incidence of adverse events was very low, and most adverse events were mild or moderate in severity. The only adverse event attributed by investigators to randomized treatment was the same serious adverse event of asthma in an adolescent subject randomized to BDA 80/180. Based on these data, no new signals were identified.

Slide 17
In summary, our review of safety data from the BDA development program was reassuring. The safety database for adults was adequate for review. We did not find overuse of BDA or differences between BDA and albuterol use patterns to be a significant issue or common event. Based on the safety data we did not identify new or unexpected signals, and adverse events were consistent with the well-described risks of both drug classes. Furthermore, we noted that background ICS was also associated with the risk of ICS-related adverse events.

However, we do note limitations in using this data to draw definitive conclusions. For pediatric subjects, the sample size and duration of exposure were limited. The observed data also did not capture use patterns we might anticipate in the real-world, such as over-use. Finally, the trials were not designed to assess long-term effects of increased inhaled corticosteroid use, which are of greatest concern for pediatric patients.

Slide 18
I will now move on to the last section of this talk.

Slide 19
To begin the concluding section, we present this forest plot again, and recapitulate the key findings:

First, in the full analysis set combining all ages and in adult subjects only, BDA demonstrated a statistically significant delay in time to first severe acute asthma exacerbation compared to albuterol.

Slide 20
Second, the size of the treatment effect, magnitude of statistical significance, and robustness to sensitivity analyses are greater for high dose BDA compared to the low dose.

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Finally, and of central importance for the committee discussion, the efficacy results for both doses in the pediatric subgroups are inconclusive. Attempts to use Bayesian techniques only distill the need to assess whether high degree of extrapolation of adult data is appropriate.

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Although it is not within the scope of this talk to provide a comprehensive regulatory history of asthma treatments approved for pediatric patients, we think a brief context will be helpful for the discussion and will highlight the unique issues in considering BDA approval.

For BDA development, the Applicant initially proposed enrolling subjects as young as 6 in the exacerbation trial, and the Agency recommended inclusion of subjects down to 4 in both pivotal trials, since the mono-components of BDA are already approved for patients as young as 12 months old.

The Agency recommended the Applicant consider Bayesian approaches to address anticipated issues related to small sample sizes, although there was no agreement on the amount of borrowing or specific statistical model to be used.

In terms of regulatory precedent, inhaled products, which are locally acting, require clinical data to support efficacy. Extrapolation of efficacy based on PK is not appropriate. Typically, adolescents have been included in adult asthma efficacy trials, and younger children are enrolled in subsequent dedicated trials. We have not always required statistical significance in adolescent subgroups to approve a product but generally do for separate trials in younger children. There have been cases in which we've made decisions based on trends in both safety and efficacy, if consistent with results in adults, and leveraged some degree of extrapolation.

We have made this determination on a case-by-case basis since there are clinically important differences between adult and pediatric disease. Summarizing the many immunological, anatomical, and environmental factors that may contribute to these differences is not within the scope of this talk, but we invite the committee to discuss such issues during the meeting.

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Finally, a key distinction is that, to date, most products approved for pediatrics have been for an established indication for the drug class (e.g., an ICS as controller therapy) or even an established indication for the drug itself (e.g., reformulation of an ICS). BDA would represent a novel combination, indication, and intended use.

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As previously mentioned, the decision to leverage extrapolation requires thoughtful consideration of clinical and pharmacologic factors. As shown in this figure from the recent FDA guidance, the right sides, or green zones, of the top two arrows indicate conditions in which high degree of extrapolation is appropriate: first, the disease and response to treatment are the same in adults and pediatrics. Second, there is a high degree of confidence in the available evidence. When these two conditions are met, the bottom arrow shows that appropriate pathways for pediatric drug development can include strong extrapolation of adult data, supported only by exposure matching facilitated by either a separate PK study or enrollment for PK analysis of a small cohort of pediatric subjects in the adult trials.

However, the left sides, or red zones, of the three arrows indicate that under conditions in which the diseases and response to treatment are different and there are more significant knowledge gaps, the more appropriate plan is to obtain clinical data in pediatric subjects through dedicated adequate and well-controlled trials.

The middle section of the bottom arrow lists some techniques for diseases that fall within this spectrum, such as Bayesian analyses. As presented earlier, in the case of the BDA, the degree of borrowing from adult data to achieve meaningful results (that is, statistical significance) in the *post-hoc* Bayesian analyses renders the question at hand to be one of extrapolation. Finally, we note that this schema is intended to guide drug development programs a priori, but we believe this remains a useful framework for the anticipated meeting discussion.

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Before presenting the questions to the committee, I will conclude this talk with an abbreviated preliminary benefit-risk summary. Three detailed benefit-risk frameworks, broken down by age cohort and including broader clinical considerations, appear at the end of the briefing document. The Agency will incorporate feedback and discussion from the advisory committee before finalizing our benefit risk assessment for BDA.

At this time, we identify the following issues: in adults, both pivotal trials met the FDA-agreed upon primary endpoints. High dose BDA demonstrated benefit in reducing severe exacerbations and systemic corticosteroid use. In terms of safety, no new signals were identified that were unexpected for the drug classes and population, and we anticipate labeling and routine pharmacovigilance will be appropriate risk mitigation strategies. Lingering clinical uncertainties pertain to the novel indication and intended use, the absence of statistically significant benefit demonstrated for the secondary endpoints assessing asthma control and quality of life, and residual risks of ICS-related adverse events with real world use.

For patients 12 to 18, the efficacy of the proposed dose, BDA 160/180 is inconclusive. Safety findings were comparable with those in adults; however, uncertainties include not only those already identified in adults above, but also the following issues: whether and how much extrapolation of adult data is appropriate, the small size and duration of the safety database for this age group, and the lack of information on long-term risks, to which we expect adolescents to be more vulnerable than adults.

Similarly, for patients 4 to 11, the efficacy of the proposed dose, BDA 80/180 is inconclusive. Safety findings were reassuring but also limited in scope and do not include long-term risks, to which younger children may be the most vulnerable. Finally, extrapolation of adult data remains a key uncertainty.

We invite the committee to identify other areas of uncertainty or concern.

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In conclusion, we present 5 questions to the advisory committee.

The first two are non-voting discussion questions and are:

1. Discuss the data to support the efficacy of BDA for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older. Specifically address available data in adolescents and young children and the appropriate degree of extrapolation in these age groups.

2. Discuss the safety data for BDA for the proposed indication. Discuss any specific pediatric safety concerns.

The final three questions we will put to a vote:

Do the data support a favorable benefit risk assessment for use of BDA in patients with asthma within each respective age cohort listed here. If not, what additional data are needed?