Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
November 8, 2022

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed the new drug application 214070, for a fixed dose combination of budesonide and albuterol sulfate metered dose inhaler, submitted by AstraZeneca and Bond Avillion 2 Development LP. The proposed indication is as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older.

These summary minutes for the November 8, 2022 meeting of the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration were approved on 1/9/2023.

I certify that I attended the November 8, 2022 meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Takyiah Stevenson, PharmD
Designated Federal Officer, PADAC

/s/
David H. Au, MD, MS
Chairperson, PADAC

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
November 8, 2022

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 8, 2022. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials and pre-recorded presentations from the FDA, AstraZeneca and Bond Avillion 2 Development LP. The meeting was called to order by David H. Au, MD, MS (Chairperson). The conflict of interest statement was read into the record by Takyiah Stevenson, PharmD (Designated Federal Officer). There were approximately 288 people online. There was one Open Public Hearing (OPH) speaker presentation.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:
The committee discussed the new drug application 214070, for a fixed dose combination of budesonide and albuterol sulfate metered dose inhaler, submitted by AstraZeneca and Bond Avillion 2 Development LP. The proposed indication is as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older.

Attendance:
PADAC Members Present (Voting): David H. Au, MD, MS (*Chairperson*); Scott E. Evans, MD, FCCP, ATSF; Fernando Holguin, MD, MPH; Edwin H. Kim, MD, MS; Susanne May, PhD; James M. Tracy, DO

PADAC Members Not Present (Voting): Leonard B. Bacharier, MD; Emma H. D'Agostino, PhD (Consumer Representative); Brian T. Garibaldi, MD, PhD; John M. Kelso, MD; Janet S. Lee, MD, ATSF

PADAC Member Present (Non-Voting): Dawn M. Carlson, MD, MPH (*Industry Representative*)

Temporary Members (Voting): Michael D. Cabana, MD, MPH; Mary Cataletto, MD; Michelle M. Cloutier, MD; Mark S. Dykewicz, MD; Paul A. Greenberger, MD; Sally Hunsberger, PhD; Bridgette L. Jones, MD, MSc, FAAAAI, FAAP; Alex Kaizer, PhD; Randi Oster, MBA (*Acting Consumer Representative*); Jennifer A. Schwartzott, MS (*Patient Representative*); James K. Stoller, MD, MS

FDA Participants (Non-Voting): Sally Seymour, MD; Kelly Stone, MD, PhD; Elisabeth Boulos, MD; Yongman Kim, PhD; Dong-Hyun Ahn, PhD

Designated Federal Officer (Non-Voting): Takyiah Stevenson, PharmD

Open Public Hearing Speaker: Michelle Dickens

The agenda was as follows:

Call to Order	**David H. Au, MD, MS** Chairperson, PADAC
Introduction of Committee and Conflict of Interest Statement	**Takyiah Stevenson, PharmD** Designated Federal Officer, PADAC
FDA Introductory Remarks	**Kelly Stone, MD, PhD** Associate Director for Therapeutic Review Division of Pulmonology, Allergy, and Critical Care Office of Immunology and Inflammation Office of New Drugs, CDER, FDA
APPLICANT PRESENTATION	**Bond Avillion 2 Development LP/AstraZeneca**
Summary	**Ed Piper, MBBS** Global Franchise Head Core Inhaled Products AstraZeneca
Clinical Perspective	**Neil Skolnik, MD** Professor of Family and Community Medicine Sidney Kimmel Medical College Thomas Jefferson University Jefferson Health
Clarifying Questions to the Applicant	
FDA PRESENTATION	
FDA Summary Presentation	**Kelly Stone, MD, PhD**
Clarifying Questions to the FDA	
LUNCH	
Open Public Hearing	
FDA Charge to the Committee	**Kelly Stone, MD, PhD**
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Discuss the data to support the efficacy of fixed dose combination of budesonide and albuterol sulfate metered dose inhaler (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.
    a. For adolescents (12 to <18) and young children (4 to <12), discuss if extrapolation of adult data to pediatric subjects is appropriate and, if so, discuss the appropriate degree of extrapolation in these age groups.

    Committee Discussion*: The majority of the committee members agreed that more data are needed to determine the efficacy of fixed dose combination of budesonide and albuterol sulfate metered dose inhaler (BDA) for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in adolescents (12 to <18) and young children (4 to <12) with asthma. Several members stated that the study was not adequately powered to assess the efficacy of BDA in patients younger than 18 years of age, given the small subgroup sample size. Members added that the data are unreliable and inconclusive due to the small sample size and the highly variable outcomes in adolescents and young children in the clinical trials. Some members acknowledged that there is a large degree of heterogeneity in asthma and its treatment between young children, adolescents, and adults. Therefore, the majority of the committee members agreed that extrapolation of adult data to pediatric subjects would not be appropriate. The members recommended additional studies with larger sample sizes of young children (4 to <12) and adolescents (12 to <18). Please see the transcript for details of the Committee's discussion.*

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

    Committee Discussion: *Committee members expressed concern that similarly as the data from the small sample sizes of pediatric patients were deemed unreliable to assess efficacy, the data are also inadequate to determine pediatric safety of BDA. Members expressed concern for the long-term effects on bone density and highlighted the single adverse event of anxiety and depressive disorder that occurred in the MANDALA study. Several committee members acknowledged there are short-term and long-term data of albuterol and budesonide products on the market. However, members agreed that the data regarding long-term safety of using BDA as rescue therapy are unknown. In addition, members mentioned their concerns for adverse events due to overexposure to inhaled corticosteroids (ICS) if used excessively for this indication. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Do the data support a favorable benefit risk assessment for use of BDA in patients ≥18 years of age with asthma?

    a. If not, what additional data are needed?

    Vote Result: Yes: 16 No: 1 Abstain: 0

Committee Discussion: *The majority of the committee members voted "Yes," reflecting agreement that the data supports a favorable benefit risk assessment for use of BDA in patients ≥18 years of age with asthma. Several members noted the robust efficacy signal and the minimal safety concerns of BDA use in this age group. One member who voted "No" noted the need for analysis of asthma triggers. In addition, this member expressed concerns that there were no data collected about the impact of BDA on the growth of patients who are 18 years old, young men especially. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Do the data support a favorable benefit risk assessment for use of BDA in patients ≥12 to <18 years of age with asthma?

    a. If not, what additional data are needed?

    Vote Result: Yes: 8 No: 9 Abstain: 0

    Committee Discussion: *A slight majority of the committee members voted "No" agreeing that the data do not support a favorable benefit risk assessment for use of BDA in patients ≥12 to <18 years of age with asthma. Several members noted the heterogeneity of the efficacy and safety data and the small sample sizes made it challenging to extrapolate adult data to pediatric subjects in this age group. Members expressed concern that though the risks are known and manageable, the data presented are not reliable to confidently support efficacy in this age group. It was also noted by several members that the data regarding the high-dose formulation of BDA in this age group were inconclusive for efficacy and safety. These members recommended additional studies that include large sample sizes and a detailed analysis of demographics be conducted.*

    Committee members who voted "Yes" agreed that the short-term data presented do demonstrate a favorable benefit risk assessment. While these members acknowledged that there are differences between the patient populations, asthma and its treatment in adolescents (≥12 to <18) are similar to adults. These members agreed that it is reasonable to extrapolate the efficacy data from adults to this age group and expect a similar level of efficacy. In addition, several members agreed there were no significant safety signals identified in this age group. A couple of members recognized the potential for abuse of BDA as a rescue inhaler and highlighted the need for real-world evidence about how the product would be used. They also recommended that new education be created to prevent abuse among pediatric patients. Members also recommended that additional studies be conducted to assess the effects of long-term exposure of BDA and ICS accumulation. Please see the transcript for details of the Committee's discussion.

5. **VOTE:** Do the data support a favorable benefit risk assessment for use of BDA in patients ≥4 to <12 years of age with asthma?

    a. If not, what additional data are needed?

Vote Result: Yes: 1 No: 16 Abstain: 0

Committee Discussion: *The majority of the committee members voted "No" agreeing that the data does not support a favorable benefit risk assessment for use of BDA in patients ≥4 to <12 years of age with asthma. Several members mentioned they had similar concerns for the lack of data in this age group as they did with adolescents. Members again expressed concern that though the risks are known and manageable, the data presented are not reliable to confidently support efficacy in this age group. A couple of members stated that it was not appropriate to extrapolate the data from adults to the small subgroup of patients in this age group due to significant differences in disease pathophysiology between adults and young children. These members recommended that larger studies in patients ≥4 to <12 years need to be conducted in order to better assess efficacy and safety, especially the potential long-term effects on growth. One member who voted "Yes" commented that due to the similarities in asthma among the age groups, in addition to the reassuring safety profile, extrapolation of adult data to pediatric subjects are appropriate. This member also mentioned there could be children in this age group that would likely benefit from BDA. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:05 p.m. ET.