Food and Drug Administration  
Center for Drug Evaluation and Research  

Summary Minutes of the  
Joint Pulmonary-Allergy Drugs Advisory Committee and the  
Drug Safety and Risk Management Drugs Advisory Committee Meeting  

March 19, 2015

Location: Holiday Inn Gaithersburg, 2 Montgomery Village Avenue  
Gaithersburg, MD

Topic: The committees discussed the supplemental new drug application (sNDA)  
204275-S001, for fluticasone furoate and vilanterol inhalation powder  
(tradename Breo Ellipta) submitted by GlaxoSmithKline for the once daily  
maintenance treatment of asthma in patients 12 years of age and older. The  
discussion included efficacy data, but the focus of the meeting was safety,  
including the adequacy of the safety database to support approval and whether  
a large safety trial to evaluate serious asthma outcomes is recommended.

These summary minutes for the March 19, 2015 joint meeting of the Pulmonary-Allergy  
Drugs Advisory Committee and the Drug Safety and Risk Management Drugs Advisory  
Committee of the Food and Drug Administration were approved on  
_____April 15, 2015_____.

I certify that I attended the March 19, 2015 joint meeting of the Pulmonary-Allergy Drugs  
Advisory Committee and the Drug Safety and Risk Management Drugs Advisory  
Committee and that these minutes accurately reflect what transpired.

_______/s/_______    ______/s/________
Cindy Hong, PharmD     Erik Swenson, MD  
Designated Federal Officer         Acting Chairperson, PADAC  
Pulmonary-Allergy Drugs  
Advisory Committee
Summary Minutes of the Joint Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting
March 19, 2015

The following is the final report of the joint meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) held on March 19, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Pulmonary, Allergy, and Rheumatology Products and the Office of Surveillance and Epidemiology, and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm433815.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm433818.htm.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 19, 2015 at the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and GlaxoSmithKline. The meeting was called to order by Erik Swenson, MD (Acting Chairperson). The conflict of interest statement was read into the record by Cindy Hong, PharmD (Designated Federal Officer). There were approximately 130 people in attendance. There were two Open Public Hearing speakers.

Issue: The committees discussed the supplemental new drug application (sNDA) 204275-S001, for fluticasone furoate and vilanterol inhalation powder (tradename Breo Ellipta) submitted by GlaxoSmithKline for the once daily maintenance treatment of asthma in patients 12 years of age and older. The discussion included efficacy data, but the focus of the meeting was safety, including the adequacy of the safety database to support approval and whether a large safety trial to evaluate serious asthma outcomes is recommended.

Attendance:
PADAC Members Present (Voting): John E. Connett, PhD; Steve N. Georas, MD; Elaine H. Morrato, DrPH, MPH; James M. Tracy, DO; Yanling Yu, MS, PhD (Consumer Representative)

PADAC Members Not Present (Voting): Kathryn Blake, PharmD; Mitchell Grayson, MD; Michelle Harkins, MD, FCCP; Nizar N. Jarjour, MD; Francis X. McCormack, MD; Dennis R. Ownby, MD (Chairperson)

PADAC Member Present (Non-Voting): Howard M. Druce, MD (Industry Representative)
The agenda proceeded as follows:

**Call to Order and Introduction of Committee**
Erik Swenson, MD
Acting Chairperson, PADAC

**Conflict of Interest Statement**
Cindy Hong, PharmD
Designated Federal Officer, PADAC

**FDA Opening Remarks**
Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of Drug Evaluation II (ODE-II)
Office of New Drugs (OND), CDER, FDA

**APPLICANT PRESENTATIONS**

BREO ELLIPTA 100/25 and 200/25 (Fluticasone furoate / Vilanterol)
Introduction
Katharine Knobil, MD
Senior Vice President
Research and Development
GlaxoSmithKline

BREO ELLIPTA 100/25 and 200/25
Courtney Crim, MD
(Fluticasone furoate / Vilanterol)  
Asthma: Efficacy and Safety  
Director, Project Physician Lead  
GlaxoSmithKline

Clinical Perspectives on Asthma Management  
Eugene Bleecker, MD  
Director  
Center for Genomics and Personalized Medicine Research  
Professor of Medicine  
Wake Forest Baptist Health

Closing Remarks  
Katharine Knobil, MD

Clarifying Questions to the Presenters

BREAK

FDA PRESENTATIONS

Utilization Patterns of Breo Ellipta and Long-Acting Beta₂-Adrenergic Agonists (LABAs)  
Tracy Pham, PharmD  
Drug Utilization Analyst  
Division of Epidemiology II  
Office of Surveillance and Epidemiology  
CDER, FDA

Clinical Review of Efficacy  
Banu Karimi-Shah, MD  
Clinical Team Leader  
DPARP, ODE II, OND, CDER, FDA

Meta-analysis of Asthma Related Serious Adverse Events  
Janelle K. Charles, PhD  
Mathematical Statistician  
Division of Biometrics VII  
Office of Biostatistics  
Office of Translational Sciences, CDER, FDA

Efficacy in Subgroups and Risk- Benefit Considerations  
Banu Karimi-Shah, MD

Pediatric Perspective on the Efficacy and Safety of Breo Ellipta in Patients 12 to 17 Years of Age  
Ann McMahon, MD, MS  
Deputy Director of Science  
Office of Pediatric Therapeutics  
Office of the Commissioner, FDA

Clarifying Questions to the Presenters

LUNCH
Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy data for fluticasone furoate/vilanterol (FF/VI) 100/25 and 200/25 to support the proposed indication of the once daily maintenance treatment of asthma in patients 12 years of age and older. Include a discussion of the efficacy findings in children 12-17 years of age.

**Committee Discussion:** The majority of the members agreed that the efficacy data for adults is evident for fluticasone furoate/vilanterol. The members commented that for patients 12-17 years and older the data compared to placebo showed that efficacy is present; however there appears to be no superiority and possible inferiority when compared to fluticasone alone. Members also expressed concern, noting that the point estimates are varying and inconsistent across various endpoints in data for children. Please see the transcript for details of the committee discussion.

2. **VOTE:** Do the efficacy data provide substantial evidence of a clinically meaningful benefit of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma in adults 18 years of age and older?
   - If not, what further data should be obtained?
   
   **YES**= 18  **NO**=2  **ABSTAIN**=0

**Committee Discussion:** The majority of the members agreed that the efficacy data provide substantial evidence of a clinically meaningful benefit of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma in adults 18 years of age and older. Members who voted “YES”, commented that the data was evident for adults in the exacerbation and bronchodilator studies and noted the decrease in rescue medication use. Members who voted “NO”, noted that the addition of vilanterol did not demonstrate added value and commented on the lack of data in African Americans. Please see the transcript for details of the committee discussion.

3. **VOTE:** Are the efficacy data sufficient to demonstrate benefit of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma in adolescents 12 to 17 years of age?
   - If not, what further data should be obtained?
Committee Discussion: The majority of the committee members agreed that the efficacy data was not sufficient to demonstrate benefit of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma in adolescents 12 to 17 years of age. Members who voted “NO”, commented on the inconsistent data and the lack of a trend in the positive direction. Members noted the need for trials with larger number of subjects 12 to 17 years of age. Members who voted “YES”, noted less exacerbation in this patient age group and commented that although the current data is problematic, it will be very challenging to obtain better data than what is currently available. Please see the transcript for details of the committee discussion.

4. DISCUSSION: Discuss the safety data for FF/VI 100/25 and 200/25 once daily. Include the following in your discussion: size of overall database and findings in children 12-17 years of age.

Committee Discussion: Committee members commented on issues with extrapolating safety findings from fluticasone/salmeterol (Advair®) to apply to FF/VI. Members noted the difficulty in obtaining post-marketing adverse effect/safety data and expressed the need to obtain data pre-approval. Members also noted the need to evaluate hospitalization data, including death and intubation from the large safety studies. Please see the transcript for details of the committee discussion.

5. VOTE: Has the safety of FF/VI 100/25 and 200/25 once daily been adequately demonstrated for the proposed indication

   a. in adults 18 years and older? (VOTE)
      - If not, what further data should be obtained?

   YES= 17    NO=3    ABSTAIN=0

Committee Discussion: The majority of the members agreed that the safety of FF/VI 100/25 and 200/25 once daily has been adequately demonstrated for the proposed indication. Members who voted “YES”, commented that the data is reasonably reassuring for adults and demonstrate adequate safety, but did note the need for additional data in African Americans. Members who voted “NO”, commented that safety data cannot be extrapolated from other drug databases of long acting beta agonists to VI.

   b. in children 12-17 years of age? (VOTE)
      - If not, what further data should be obtained?

   YES= 1    NO=19    ABSTAIN=0

Committee Discussion: The majority of the members agreed that the safety of FF/VI 100/25 and 200/25 once daily has not been adequately demonstrated for the proposed indication in children 12 to 17 years of age. Members who voted “NO”, commented on the need for studies similar to
current long-acting beta agonist (LABA) studies. The member who voted “YES”, commented on the acute event rate being lower in adolescents than adults. Please see the transcript for details of the committee discussion.

6. **VOTE**: Do the efficacy and safety data support approval of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma

   a. in adults 18 years and older? **(VOTE)**
      - If not, what further data should be obtained?

      **YES= 16**  **NO=4**  **ABSTAIN=0**

   **Committee Discussion**: The majority of the members agreed that the efficacy and safety data do support approval of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma in adults 18 years and older. Members who voted “YES”, noted the advantage of once daily dosing offered by FF/VI and its positive risk-benefit profile. Members who voted “NO”, commented that data in the 65 years and older, African American, and Asian population is less understood. Please see the transcript for details of the committee discussion.

   b. in children 12-17 years of age? **(VOTE)**
      - If not, what further data should be obtained?

      **YES= 2**  **NO=18**  **ABSTAIN=0**

   **Committee Discussion**: The majority of the members agreed that the efficacy and safety data does not support the approval of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma in children 12 to 17 years of age. One member who voted “YES”, commented that the medication meets an unmet need. Members who voted “NO”, commented on the need for additional data for efficacy and safety. One member who originally voted “YES”, subsequently noted, during the explanation of the vote, that he is not in support of the indication and meant for his vote to be “NO”. Please see the transcript for details of the committee discussion.

7. **VOTE**: Do you recommend requiring a large LABA safety trial with FF/VI similar to the ongoing LABA safety trials

   a. in adults 18 years and older? **(VOTE)**
      - If yes, comment on the rationale for the trial and the timing of the trial, e.g. pre-approval, post-approval without waiting for results of pending LABA trials, post-approval pending results of ongoing LABA safety trials.

      **YES= 13**  **NO=7**  **ABSTAIN=0**
Committee Discussion: The majority of the members recommended requiring a large LABA safety trial with FF/VI similar to the ongoing LABA safety trials in adults 18 years and older. The members who voted “NO”, commented on the prematurity in requiring another prospective study and were reassured by the safety data for FF/VI and the future availability of additional data from current LABA studies. The members who voted “YES”, noted the need for a post-marketing safety study, but there were mixed opinions as to whether the results of current LABA trials would influence the need to start or continue a safety trial for FF/VI. Members also commented on the need for more information in minorities. Please see the transcript for details of the committee discussion.

b. in children 12-17 years of age? (VOTE)
   - If yes, comment on the rationale for the trial and the timing of the trial, e.g. pre-approval, post-approval without waiting for results of pending LABA trials, post-approval pending results of ongoing LABA safety trials.

YES= 17  NO=2  ABSTAIN=0  No-Voting=1

Committee Discussion: The majority of the members recommended requiring a large LABA safety trial with FF/VI similar to the ongoing LABA safety trials in children 12 to 17 years of age. The members who voted “YES”, commented on the presence of safety signals and the need to define the etiology of those signals in pre-marketing studies. The members who voted “NO”, noted that safety study is needed, but efficacy needs to be demonstrated first. The possible difficulty in enrolling a large number of pediatric subjects was also noted as a concern. One committee member was not present to vote as noted for the record. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 5:00 p.m.