Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting August 31, 2020

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

Topic: The Committee discussed supplemental new drug application 209482/S-008, for TRELEGY ELLIPTA, a fixed-dose combination (fluticasone furoate, umeclidinium, and vilanterol inhalation powder oral inhalation), submitted by GlaxoSmithKline, for the following proposed labeling claim: Reduction in all-cause mortality in patients with chronic obstructive pulmonary disease (COPD). The focus of the discussion was on the efficacy data submitted to support the proposed labeling claim, including the results from the Informing the Pathway of COPD Treatment (IMPACT) trial and the influence of inhaled corticosteroid (ICS) withdrawal on the results.

These summary minutes for the August 31, 2020 meeting of the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration were approved on November 17, 2020.

I certify that I attended the August 31, 2020 meeting of the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Philip Bautista, PharmD	James Stoller, MD
Acting Designated Federal Officer, PADAC	Acting Chairperson, PADAC

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting August 31, 2020

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on August 31, 2020. 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 and GlaxoSmithKline. The meeting was called to order by James K. Stoller, MD, MS (Acting Chairperson). The conflict of interest statement was read into the record by Philip Bautista, PharmD (Acting Designated Federal Officer). There were approximately 350 people online. There were a total of two Open Public Hearing (OPH) speaker presentations.

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

Agenda: The Committee discussed supplemental new drug application 209482/S-008, for TRELEGY ELLIPTA, a fixed-dose combination (fluticasone furoate, umeclidinium, and vilanterol inhalation powder oral inhalation), submitted by GlaxoSmithKline, for the following proposed labeling claim: Reduction in all-cause mortality in patients with chronic obstructive pulmonary disease (COPD). The focus of the discussion was on the efficacy data submitted to support the proposed labeling claim, including the results from the Informing the Pathway of COPD Treatment (IMPACT) trial and the influence of inhaled corticosteroid (ICS) withdrawal on the results.

Attendance:
PADAC Members Present (Voting): Emma H. D'Agostino, BS (Consumer Representative); Scott E. Evans, MD, FCCP, ATSF; John M. Kelso, MD; Gailen D. Marshall Jr., MD, PhD, FACP; Susanne May, PhD; Carrie A. Redlich, MD, MPH; James M. Tracy, DO

PADAC Members Not Present (Voting): David H. Au, MD, MS; Brian T. Garibaldi, MD, PhD; Edwin H. Kim, MD; Loretta G. Que, MD

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

Temporary Members (Voting): Paula Carvalho, MD, FCCP; Lori E. Dodd, PhD; Susan S. Ellenberg, PhD; Patricia Lupole (Patient Representative); Francis X. McCormack, MD; Benjamin Medoff, MD; Steven D. Shapiro, MD; James K. Stoller, MD, MS (Acting Chairperson)

FDA Participants (Non-Voting): Sally Seymour, MD; Banu Karimi-Shah, MD; Robert Busch, MD, MMSC; Yongman Kim, PhD; Susan Duke, MS, MS

Acting Designated Federal Officer (Non-Voting): Philip Bautista, PharmD

Open Public Hearing Speakers: MeiLan Han, MD; Meg Seymour, PhD (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	**James K. Stoller, MD, MS** Acting Chairperson, PADAC
Conflict of Interest Statement	**Philip Bautista, PharmD** Acting Designated Federal Officer, PADAC
FDA Introductory Remarks	**Banu A. Karimi-Shah, MD** Deputy Director Division of Pulmonology, Allergy, and Critical Care, Office of Immunology and Inflammation Office of New Drugs, CDER, FDA
APPLICANT PRESENTATION	**GlaxoSmithKline**
Request to Amend the TRELEGY™ ELLIPTA® Label to Include Data on the Reduction in Risk of All-Cause Mortality in Patients with COPD	**C. Elaine Jones, PhD** Medicine Development Leader Trelegy COPD GlaxoSmithKline
Clarifying Questions to the Applicant	
FDA PRESENTATION	
FDA Summary Presentation	**Banu A. Karimi-Shah, MD**
Clarifying Questions to the FDA	
LUNCH	
Open Public Hearing	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Discuss the persuasiveness of the data in the IMPACT trial to support the claim that fluticasone furoate, as a component of TRELEGY ELLIPTA, improves all-cause mortality in chronic obstructive pulmonary disease (COPD). Include the following elements in your discussion:

    a. The exploratory nature of the all-cause mortality (ACM) analysis, the lack of Type I error control, and the strength of evidence in IMPACT
    b. Whether the ACM results from IMPACT are persuasive in light of the additional ACM data from fluticasone comparisons provided by SUMMIT and TORCH
    c. The observed timeframe of the IMPACT results, i.e., the early separation in survival

    Committee Discussion: *Overall, the Committee agreed that the IMPACT trial data were not persuasive enough to support the claim that fluticasone furoate, as a component of TRELEGY ELLIPTA, improves all-cause mortality (ACM) in chronic obstructive pulmonary disease. Some of the committee members re-emphasized the exploratory nature of the ACM analysis given that IMPACT was not specifically designed to evaluate ACM. The committee members agreed that the nominal p-value of 0.042 was not persuasive as there was a large number of exploratory endpoints and a lack of type I error (multiplicity) control. The Committee agreed that the additional ACM data from fluticasone comparisons provided by SUMMIT and TORCH were not supportive of a mortality benefit attributable to the addition of fluticasone products from the comparisons that isolated the contribution of the ICS. Many of the committee members supported the contention that the observed difference in mortality within approximately 90 days was likely due to harm from ICS removal rather than a benefit of TRELEGY ELLIPTA. However, the Committee was divided on whether this observed separation could also suggest a hypothesis that a subset of patients with uncontrolled COPD might receive a benefit from the addition of ICS drugs (i.e., the contention that harm after the removal of the drug class would inform the hypothesis of benefit after addition of the drug class). The Committee expressed difficulty in hypothesizing a potential mechanism behind this observed separation that would justify a claim of benefit from TRELEGY ELLIPTA rather than a negative effect of ICS removal in the trial. One committee member emphasized that there are many phenotypes in COPD and this separation may be due to different effects in different subgroups. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss the implications of pre-study inhaled corticosteroid (ICS) use and ICS-removal on the interpretation of the ACM data in the IMPACT trial. Include the following elements in your discussion:

    a. The clinical understanding of the contribution of ICS to COPD therapy and the effects of ICS removal in patients with uncontrolled COPD and frequent exacerbations
    b. The implications of randomization to study drugs that do not contain ICS among patients with uncontrolled COPD despite pre-study ICS therapy

c. The observed timeframe of the IMPACT results, i.e., the early separation in survival
d. The pre-study ICS subgroup data from SUMMIT and TORCH, in light of the differences from IMPACT in study design and patient population

Committee Discussion: *The Committee agreed that, in current practice, clinicians would not typically remove ICS from the treatment regimens of patients with uncontrolled COPD with a history of exacerbations as was done in the IMPACT study. As such, it was noted that randomization to a study arm that did not contain ICS in this patient population should not have happened given current knowledge and practice. The committee members acknowledged that at the time that this study was designed, this design may have seemed acceptable. Regarding the early separation in survival, the Committee noted that the data were not conclusive as to whether this was ascribable to withdrawal of ICS. However, one committee member noted that it was hard to identify any other plausible mechanism for the observed results; furthermore, another committee member noted that it was very difficult to discount the possibility that this separation was attributable to anything other than the adverse impact of ICS removal. Some committee members also suggested that the observed results might generate a hypothesis for a benefit of FF/UMEC/VI triple therapy in a certain subset of patients with uncontrolled COPD. Multiple committee members also noted that harm after withdrawing ICS may not be tantamount to a benefit after adding ICS, and that the data from IMPACT are limited in their ability to show a benefit after adding ICS. Multiple members also noted that making the leap from TRELEGY ELLIPTA's labeled severe exacerbation benefit to a claim of mortality benefit must be approached with caution and supported by substantial data. Committee members acknowledged that the pre-study medication subgroup data from SUMMIT and TORCH were very material to these concerns regarding ICS removal. In addition, one committee member emphasized the difference in treatment comparisons between IMPACT, SUMMIT, and TORCH, and highlighted that fluticasone furoate and fluticasone propionate have differing levels of potency. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Discuss the generalizability of the IMPACT ACM data to relevant clinical practice decisions about fluticasone furoate (FF) as add-on therapy in COPD. Include the following elements in your discussion:

   a. The clinical relevance and persuasiveness of the ACM results from fluticasone comparisons among the ICS-naïve subgroups of IMPACT, SUMMIT, and TORCH
   b. The clinical relevance of data from the pre-study ICS subgroup to inform decisions regarding the addition of FF
   c. The clinical relevance of the IMPACT trial design and its ability to assess the benefit of adding FF
   d. The clinical implications of the proposed labeling claim in light of the submitted data

Committee Discussion: *The committee members agreed that the majority of the patients who entered the study may have already been appropriately prescribed pre-study ICS (i.e. at baseline). It was noted that those patients who were previously prescribed ICS before entering the study had worse outcomes when ICS was removed, and that those patients who were not previously on ICS did not have better outcomes. The Committee stated that the data from the pre-study ICS subgroup could not be used to inform decisions regarding the benefit of adding of FF. Regarding the clinical relevance of the IMPACT trial design, the Committee agreed that IMPACT was not adequately designed to isolate the benefit of adding FF in this patient population since many were already prescribed ICS at baseline. When addressing the clinical implication of the proposed labeling claim, some members stated that the proposed labeling would create the impression that there is a survival benefit conferred by TRELEGY ELLIPTA when there is still uncertainty about whether the study results are due to the withdrawal of ICS or due to TRELEGY ELLIPTA. Some members expressed concern that the labeling could lead to inappropriate use. Given this, another member added their concern about the risk for pneumonia with TRELEGY ELLIPTA due to the potency of the ICS component. One member stated that if the proposed labeling were to move forward, the last sentence of the proposed labeling should be edited to emphasize that there was no demonstrable difference in the non-ICS subgroup rather than that "the evaluation of all-cause mortality was limited by the small sample size." Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Do the data from the IMPACT trial provide substantial evidence of efficacy to support the claim that TRELEGY ELLIPTA improves all-cause mortality in patients with COPD?

    a. If no, what further data are needed?

Vote Result: **Yes: 1** **No: 14** **Abstain: 0**

Committee Discussion: *An overwhelming majority of the committee members agreed that the data from the IMPACT trial did not provide substantial evidence of efficacy to support the claim that TRELEGY ELLIPTA improves all-cause mortality in patients with COPD. Some members stated that the data were suggestive but not definitive. The members who voted "No" agreed that the survival difference was likely due to the adverse impact of ICS withdrawal rather than the addition of TRELEGY ELLIPTA and that the data did not meet the evidentiary standard. Many of these committee members also noted concerns regarding type I error control (multiplicity) of the all-cause mortality analyses. Some members reiterated that a step-up therapy trial would be the ideal design but they re-acknowledged the difficulty of such a trial. The member who voted "Yes" noted the benefit of the compliance with this combination product and the difficulties enrolling ICS naïve patients in this study. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 3:55 p.m. Eastern Time.