Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

January 9, 2023

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

Topic: The committee discussed supplemental biologics license application (sBLA) 125387, aflibercept solution for intravitreal injection, submitted by Regeneron Pharmaceuticals, Inc. The supplement was submitted in response to FDA's pediatric written request. FDA's written request was for studies of aflibercept in the treatment of retinopathy of prematurity.

These summary minutes for January 9, 2023 of the Dermatologic and Ophthalmic Drugs Advisory Committee meeting of the Food and Drug Administration were approved on March 8, 2023.

I certify that I attended the January 9, 2023 meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

LaToya Bonner, PharmD
Designated Federal Officer, DODAC

/s/

James Chodosh, MD, MPH
Chairperson, DODAC

Summary Minutes of the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting
January 9, 2023

The Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on January 9, 2023. 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 from the FDA and Regeneron Pharmaceutical, Inc. The meeting was called to order by James Chodosh, MD (Chairperson). The conflict-of-interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 191 people online. There was a total of five 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 biologics license application (sBLA) 125387, aflibercept solution for intravitreal injection, submitted by Regeneron Pharmaceuticals, Inc. The supplement was submitted in response to FDA's pediatric written request. FDA's written request was for studies of aflibercept in the treatment of retinopathy of prematurity.

Attendance:
Dermatologic and Ophthalmic Drugs Advisory Committee Members Present (Voting): James Chodosh, MD, MPH (*Chairperson*); Todd Durham, MS, PhD (*Consumer Representative*); Timothy Murray, MD, MBA, FACS

Dermatologic and Ophthalmic Drugs Advisory Committee Members Not Present (Voting): Brian Green, DO, MS, FAAD; Mary Elizabeth Hartnett, MD, FACS, FARVO; Ken Katz, MD, MSc, MCSE; Megha Tollefson, MD; Christina Y. Weng, MD, MBA; Maria A. Woodward, MD, MSc

Dermatologic and Ophthalmic Drugs Advisory Committee Member Present (Non-Voting): Ercem Atillasoy, MD (*Industry Representative*)

Temporary Members (Voting): Michael F. Chiang, MD; Janine A. Clayton, MD, FARVO; Elizabeth Joniak-Grant, PhD (*Patient Representative*); Michael Lai, MD, PhD

FDA Participants (Non-Voting): Charles J. Ganley, MD; Wiley A. Chambers, MD; William M. Boyd, MD

Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers Present: Nicole Pratt; Jennifer Dunbar, MD; R.V. Paul Chan, MD (Prevent Blindness); Kathy Cundiff; Tim Cleland, MD

The agenda was as follows:

Call to Order	**James Chodosh MD** Chairperson, DODAC
Introduction of Committee and Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, DODAC
FDA Opening Remarks	**Wiley Chambers, MD** Director Division of Ophthalmology Office of Specialty Medicine Office of New Drugs, CDER, FDA
APPLICANT PRESENTATIONS	**Regeneron Pharmaceuticals, Inc.**
EYLEA® (aflibercept) for the Treatment of Retinopathy of Prematurity Introduction	**Boaz Hirshberg MD, MBA** Senior Vice President (VP) Clinical Sciences General Medicine Regeneron Pharmaceuticals, Inc.
Disease Background and Unmet Need	**Faruk Örge, MD** Professor of Ophthalmology and Pediatrics Case Western Reserve University Director of Pediatric Ophthalmology and Adult Strabismus Rainbow Babies and Children's Hospital
Efficacy	**Robert Vitti, MD, MBA** VP, Clinical Sciences Ophthalmology Regeneron Pharmaceuticals, Inc.
Safety	**Suzanne Green, MBChB** Therapy Area Head, Global Patient Safety Regeneron Pharmaceuticals, Inc.
Clinical Perspective	**Steven Donn, MD, FAAP, FAARC** Professor Emeritus of Pediatrics Division of Neonatal-Perinatal Medicine C.S. Mott Children's Hospital University of Michigan Medical School
Clarifying Questions	

FDA PRESENTATIONS

EYLEA (aflibercept) Wiley Chambers, MD
Treatment of Retinopathy of Prematurity

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss how the studied use of aflibercept in the treatment of retinopathy of prematurity can best be communicated to physicians and the caregivers of these premature infants.
   Committee Discussion*: The committee members acknowledged the nominal failure of the trials and believe that those results may affect the confidence of the community at-large. However, the committee did acknowledge the benefits of using anti-vascular endothelial growth factor (anti-VEGF) for the treatment of retinopathy of prematurity (ROP), which is evident by the efficacy shown in the submitted trials and by another product in aflibercept's class, bevacizumab, which has been used off-label for the last ten years in the ophthalmology community. The panel stressed the need for clear administrative instructions in the package insert as the decision to treat must often be made relatively quickly, and that decision is commonly made in the neonatal intensive care unit (NICU). Conclusively, the panel members recommended that the labeling should note that multiple treatments are often needed and that continued close follow-up is required. Lastly, one of the members suggested a drug information pamphlet catered towards parents/guardians to appropriately inform the caregivers about the drug and what to expect. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss potential labeling including:
   a. Wording of Indications and Usage

      Committee Discussion*: Altogether, the committee agreed that the broad indication "Treatment of Retinopathy of Prematurity" already in the package insert, is appropriate*

for the indication. The committee members stressed that providing specifications may complicate things, leading to the possible failure to treat. One member noted that adding a threshold to the indication can limit the physician's clinical judgement and withhold warranted therapy. Please see the transcript for details of the Committee's discussion.

b. Wording of Warnings/Precautions

***Committee Discussion**: The committee members agreed that the long-term systemic effect of aflibercept is unknown. Also, the members emphasized that the idea of systemic toxicity provoked by multiple injections and retreatment within a shorter interval (25 days) is not supported by the data shown. Therefore, the committee members stressed the need for more post surveillance data to support the safety of aflibercept for the treatment of ROP. Please see the transcript for details of the Committee's discussion.*

c. Wording of Dosing and Administration

***Committee Discussion**: When it comes to dosing, the committee members recommended that the normal protocol for dosing, "up to 3 injections may be administered", is arbitrary, as dosing regimens are often influenced by the patient's condition and age. In addition, the committee advised that the Applicant should propose flexibility in their scheduling, as retreatment and shorter intervals (less than 25 days) may be required depending on the clinical efficacy (regression or improvement) of the retinopathy. Please see the transcript for details of the Committee's discussion.*

d. Wording of Pediatric Use

***Committee Discussion**: The committee recommended that the instructions associated with dose administration should be consolidated to one section of the package insert for easy find and use. The panel members advised that the prefilled syringes should not be used in neonates and a vial is most preferred to avoid overdosing. Lastly, the site of injection for neonates is different than adults due to the anatomy of the eye. The retina specialists on the panel, advised that the site of injection should be 1 mm from the limbus and the needle should be aimed at the posterior vitreous, away from the optic nerve, lens, and retina. Please see the transcript for details of the Committee's discussion.*

e. Wording of the Clinical Trials section

***Committee Discussion**: One committee member suggested to identify the trials as two studies in the first sentence of the clinical description portion of the insert, as readers may not interpret the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT trials as two separate studies. Another panel member suggested to describe the trials as randomized treatments of EYLEA versus laser therapy, with the option of additional treatment if needed (investigators discretion). Although it is not standard to include secondary*

outcomes in the labeling, the same member noted that it would be beneficial for the public to know that there were favorable outcomes when retreatments were implemented in the trials. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 4:25 p.m. EST.