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July 2, 2024

RESPONSE TO PREA NON-COMPLIANCE LETTER

Wendy Carter, DO
Director (Acting)
Division of Antivirals
Office of Infectious Diseases
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **NDA 210854**
NDA 214410/ Original 1
Baloxavir Marboxil (S-033188; RO7191686)
Response to PREA Non-Compliance letter

Dear Dr. Carter:

Reference is made to the following:

- Genentech Inc's Investigational New Drug Application, IND 126653 for baloxavir marboxil (S-033188; RO7191686) for the treatment of influenza, submitted to the Division of Antivirals on January 15, 2016 as Serial No. 0000.

- Genentech Inc.'s New Drug Application (NDA) 210854 approved on October 24, 2018 for the use of XOFLUZA® (baloxavir marboxil) for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

- Genentech Inc.'s NDA 214410/Original 1 approved on November 23, 2020 for the treatment (oral suspension, 2 mg/mL) and post-exposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older.

- Amendment Version 6 protocol of Study CP40559 entitled, "A Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients from Birth to < 1 Year with Influenza-Like Symptoms", submitted on May 4, 2022 (Serial No. 0261).

- The Sponsor's Deferral Extension request for PMR 3503-1 and PMR 3961-1 submitted to the FDA on August 22, 2022 and the Deferral Extension Granted letter received via email on October 3, 2022 (Reference ID: 5052805)

- The Sponsor's Deferral Extension request for PMR 3984-1 and PMR 3961-1 submitted to the FDA on August 22, 2022 and the Deferral Extension Granted letter received via email on October 3, 2022 (Reference ID: 5052799)

- The Sponsor's Clinical Study Report of Study CP40559 submitted to the FDA on December 20, 2023 as a submission of the required Pediatric Assessment

- The Notification of Non-Compliance with PREA letter received on May 22, 2024 (Reference ID: 5385378)

- Email Correspondence: Information Request/ Advice received from the FDA on May 22, 2024 with Additional Comments on the Non-Compliance letter (Reference ID: 5385476)

PMR 3503-1 as per NDA 210854 approval letter received on October 24, 2018:
Conduct a single-arm, open-label clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.
Current timelines are shown below.
Trial Completion: 08/2023
Final Report Submission: 12/2023

PMR 3984-1 as per NDA 214410/ Original 1 approval letter received on November 23, 2020:
Conduct a single-arm, open-label clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.
Current timelines are shown below.
Trial Completion: 08/2023
Final Report Submission: 12/2023

In response to PMR 3503-1 and 3984-1, the Sponsor submitted the Clinical Study Report for Study CP40559 of baloxavir marboxil treatment in infants < 1 years, prior to the milestone deadline on December 20, 2023 as a required pediatric assessment. However, no label update was proposed with the submission, as the currently approved indication in the US is for patients 5 years and older, thus the Sponsor determined that

the results from Study CP40559 did not warrant a label change for patients under 12 months of age.

The data from Study CP40559 did not adversely impact the safety or the resistance profile of the drug, and the overall benefit-risk was unaltered.

A cross-reference letter has been submitted to IND 126653.

In the Non-Compliance letter, the Agency acknowledged the submission of the final study report and requested the Sponsor provide draft labeling as a prior approval supplement (PAS) to NDAs 214410 and 210854, incorporating changes since the last approval of the Prescribing Information and FDA-approved patient labeling.

Accordingly, the Sponsor will submit the requested PAS to NDA 214410 and NDA 210854, incorporating the below proposed updates as recommended by FDA, on July 2 2024:

1. Section 8.4, Pediatric Use, Pediatric Subjects (< 5 years of age).
   See proposed edits shown in red below:

   The safety and effectiveness of XOFLUZA for treatment and post-exposure prophylaxis of influenza in pediatric subjects less than 5 years of age, including neonates, have not been established.

2. Section 12.4, Microbiology, Resistance, Clinical studies in pediatric subjects < 5 years of age.

   This section has been updated to include the treatment-emergent resistance frequencies for subjects < 5 years of age by including all subjects evaluated for treatment-emergent resistance in trial CP40559.

Additionally, the Sponsor has also updated Section 5.2 Increased Incidence of Treatment-Emergent Resistance in Patients Less Than 5 Years of Age to include all subjects evaluated for treatment-emergent resistance in trial CP40559.

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If you have any questions or need additional information regarding this submission, please contact the undersigned.

Sincerely,

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