WARNING LETTER

Melanie M. Hoppers, M.D./Physicians Quality Care

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WARNING LETTER

FDA Ref. No.: 24-HFD-45-11-01

Dear Dr. Hoppers:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between December 6 and 15, 2022. Investigator Ann B. Borromeo, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)**, "**(b)(4)**,"[1] of the investigational drug **(b)(4)**, performed for **(b)(4)**
- Protocol MV40618, "A Phase IIIb, Multicenter, Randomized, Double-blind, Placebo-controlled, Clinical Efficacy Study of Baloxavir Marboxil for the Reduction of Direct Transmission of Influenza from Otherwise Healthy Patients to Household Contacts," of the investigational drug baloxavir marboxil (RO7191686), performed for Genentech, Inc., a subsidiary of F. Hoffmann-La Roche Ltd.

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Investigator Borromeo presented and discussed with you the Form FDA 483, Inspectional Observations. We acknowledge receipt of your January 6, 2023, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your January 6, 2023, written response, it appears that you did not adhere to the applicable statutory requirements in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and applicable regulations contained in Title 21 of the Code of Federal Regulations, part 312 [21 CFR 312] governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** required you to ensure that subjects met all eligibility requirements before their enrollment into the study. Specifically, Protocol **(b)(4)** required you to ensure that subjects had a laboratory-confirmed **(b)(4)** at the local study laboratory, to be eligible for inclusion in the study. In addition, the protocol required the subject to be within **(b)(4)** test result from the local study lab at the time of study randomization, to be eligible for inclusion in the study.

You failed to adhere to this requirement. Examples of this failure include, but are not limited to, the following:

1. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a **(b)(4)** test result on **(b)(6)**.

2. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a negative **(b)(4)** test result on **(b)(6)**.

3. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization.

4. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization.

5. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a **(b)(4)** test result on **(b)(6)**.

6. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a **(b)(4)** test result on **(b)(6)**.

In your January 6, 2023, written response to the Form FDA 483, you stated that you take full responsibility for all study-related activities conducted under your supervision. You also acknowledged that subjects should not have been enrolled in the protocol because they did not have a **(b)(4)** test result as required by the protocol.

You stated that the issues found at your site were attributed to a clinical research coordinator for this study. You stated that before the FDA inspection, you had self-reported this issue to the Institutional Review Board, the state nursing board, and the sponsor's medical monitor.

In your written response, you stated that upon learning about your clinical research coordinator's misconduct, **(b)(4)**, the site management organization that you had partnered with to perform the clinical study, hired a clinical research director who was tasked with developing a quality management system and updating internal processes and standard operating procedures (SOPs), which included the Responsibilities of the Principal Investigator SOP and the Diagnostic and Lab Report Review Process SOP. You also noted that in July 2022, all **(b)(4)** staff received training on the new SOPs and process guidance. You further stated that, since the FDA inspection, you have determined there are additional SOPs and internal processes that need to be further developed.

While we acknowledge the actions that you have taken and plan to take, your response is inadequate because you have not provided sufficient details on how you, as a clinical investigator, will ensure adequate supervision and oversight of study personnel to whom you have delegated study procedures and tasks (for example, verifying that study activities performed by study personnel adhere to the protocol requirements), and how you plan to prevent similar violations from occurring in the future. Further, your Responsibilities of the Principal Investigator SOP does not identify subject eligibility determinations as a task that must be performed by the principal investigator. In addition, your SOPs describing the creation and maintenance of source documentation and management of study regulatory files do not include the clinical investigator as a responsible party for these study procedures. Without these details, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

Additionally, we request documentation of the additional SOPs and internal processes that you have further developed, and documentation of trainings that you and your staff have taken and plan to take. We also request that you explain how these additional SOPs and internal processes and trainings will ensure that ongoing and future clinical investigations will be conducted in compliance with applicable FDA regulations.

We emphasize that as the clinical investigator, you were ultimately responsible to ensure that your clinical study was conducted properly and in compliance with FDA regulations, both to protect the rights, safety, and welfare of study subjects and to ensure the integrity of study data. Your failure to ensure that subjects met protocol-required inclusion criteria, and your lack of oversight and supervision of the clinical study, raise significant concerns about the safety of study subjects enrolled at your site, and about the integrity of the data generated at your site.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address any deficiencies and establish procedures to ensure that any ongoing or future studies comply with FDA regulations.

This letter notifies you of our findings and provides you with an opportunity to address the above deficiencies. Within 15 business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address this matter adequately may lead to regulatory action. If you believe that you have complied with the FD&C Act and relevant regulations, please include your reasoning and any supporting information for our consideration.

If you have any questions, please call Miah Jung, Pharm.D., M.S., at 240-402-3728. Alternatively, you may e-mail FDA at CDER-OSI-Communications@fda.hhs.gov. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,
{See appended electronic signature page}
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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1 Coronavirus Disease 2019 (COVID-19) is the respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).