March 22, 2021

VIA E-MAIL & UPS EXPRESS MAIL

Michael L. Levin, M.D.
1012 East Sahara Avenue
Las Vegas, Nevada 89104-3218

Dear Dr. Levin:

This letter informs you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted between November 16, 2020 and November 25, 2020. The FDA investigators met with you during the inspection to review your conduct as a clinical investigator of the following clinical study:

(b) (4)

The FDA conducted this inspection under the Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational products. At the end of the inspection, the FDA investigators presented a Form FDA 483, Inspectional Observations, for your review and discussed the listed observations with you.

Based on our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated December 16, 2020 to the Form FDA 483 ("Response Letter"), we determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR) Part 312 (available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312). The violations include, but are not limited to, the following:

1. **Failure to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and applicable regulations; failure to protect the rights, safety, and welfare of subjects under your care [21 CFR § 312.60].**

   A. Study protocol (b) (4), Schedules of Events, Tables 14 and 15 includes follow-up safety calls on study Days 8, 15, 22, 36, 43, 50 and 85. Safety calls on Days 8, 15, and 22 occur after the administration of the (b) (4). Safety calls on Days 36, 43, 50 and 85 occur after the administration of the (b) (4).

   A review of 103 subject records[1] during the inspection showed that at least one follow-up safety call was not performed for 47 of 103 subjects after they received the investigational (b) (4). Twenty subject records showed two or more safety follow up calls were missed. The table below provides examples of missed follow-up safety calls.

Subject	Missed Safety Call Day	(b) (4)	(b) (4)
(b) (6)	15	(b) (6)	
	15 and 50		
	15 and 85		
	43		
	15, 22, 43, and 85		
	8		
	85		
	85		
	8 and 85		
	8		
	22		
	22		
	8 and 15		
	8, 15, and 22		
	36		
	15		
	15		
	85		
	8		
	8, 15, and 22		
	15		
	15		
	15		
	8		
	8		
	8 and 15		
	8, 15, and 50		

[1] The Form FDA 483 incorrectly referenced 102 rather than 103 subject records.

(b) (6)	8, 15, and 36	(b) (6)	(b) (6)
	8		(b) (4) not administered
	8 and 50		(b) (6)
	8, 15, 22, 36, 43, and 85		(b) (6)
	8		(b) (6)
	36, 43, and 50		(b) (4) not administered
	15		(b) (6)
	50		
	8		
	8, 36		
	50		
	36, 43, and 50		(b) (4) not administered
	36, 43, and 50		(b) (4) not administered
	8 and 22		(b) (6)
	36, 43, and 50		(b) (4) not administered
	22, 36, 43, and 50		(b) (4) not administered
	50		(b) (6)
	8		(b) (6)
	36, 43, and 50		(b) (4) not administered
	8		(b) (6)

Your Response Letter explains that the impact of rapid enrollment and the complexity of the safety calls was not adequately anticipated and stretched available resources. Your corrective action plan included dedicated time for staff to complete safety calls, hiring additional staff delegated to completing safety calls after training, revision of source documents to capture attempted safety calls, training on the new source documents, re-education of staff, and pausing enrollment on September 11, 2020,[2] to allow the staff to address the backlog for enrolled subjects and improve compliance.

According to your corrective and preventive actions (CAPA) worksheet, dated November 19, 2020, you had intended to resolve the issue of safety calls not completed or completed out of window by September 30, 2020. However, during the inspection, the FDA investigators noted that safety calls continued to be missed after the intended resolution date, including, for example, multiple missed safety calls for subject (b) (6) .

[2] We note that the materials collected during the inspection do not reflect a notification to the institutional review board (IRB) regarding this pause in enrollment. We remind you that under 21 CFR 312.66, an investigator must assure that he or she will promptly report to the IRB all changes in the research activity.

We acknowledge that in your Response Letter, you committed to instituting certain corrective actions in addition to those you had already implemented at the time of FDA's inspection. However, your response did not provide sufficient detail to fully assess the adequacy of your corrective actions. Specifically, your response did not explain the continued occurrence of missed safety calls after the intended resolution date referenced in your November 2020 CAPA worksheet or provide adequate assurance that your corrective actions have been successfully implemented.

B. Protocol Version 3 section 5.2, Exclusion Criterion 11 states: "(b) (4) ." You failed to review the (b) (4) results to determine eligibility for subjects (b) (6) when you randomized these subjects into protocol (b) (4) on September 9, 2020.

In your Response Letter, you explain that you "entered the two subjects into the trial based on Protocol Amendment #2 criteria which allowed (b) (4) subjects to be included in the study as well as [your] medical judgement of the subjects being medically stable and on appropriate medication to maintain that stability for an extended period of time." However, Protocol Amendment #3, which was in place when these subjects were screened, included limitations on the (b) (4) . Protocol Amendment #3, dated August 20, 2020, received IRB approval on August 24, 2020 and was signed by you on August 26, 2020.

Your corrective actions referenced in your Response Letter included contacting the subjects and obtaining and reviewing their b) (4) results. Your Response Letter also stated that, by January 31, 2021, you would create an internal guidance on implementation of protocol amendments and applicable changes to source documents regarding protocol amendment changes. However, your response cannot be evaluated due to a lack of supporting documentation. Specifically, you have not provided details regarding what is included in the internal guidance.

C. Protocol Section 11.2.8, Protocol Deviations, states: "It is the responsibility of the site Investigator to use continuous vigilance to identify and report deviations to the Sponsor or its designee. All deviations must be addressed in study source documents, reported to study monitor." During the inspection, it was noted that your site did not identify certain protocol deviations and did not enter identified protocol deviations in the Electronic Data Capture (EDC) to notify the sponsor. Your site relied on the study monitor to track protocol deviations. A protocol deviation page was generally included in each subject chart, however, the FDA investigators noted multiple instances of missing or blank protocol deviation logs in subject charts for subjects who experienced protocol deviations such as missed safety calls or out of window visits.

We acknowledge that this finding was not included on the FDA Form 483 you received. Therefore, your Response Letter does not address it.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational new drugs. It is your responsibility to ensure adherence to each requirement of the law, including the Federal Food, Drug, and Cosmetic Act (FD&C Act) and all applicable FDA regulations.

We request a written response within fifteen (15) business days of your receipt of this letter. In your response, please provide written documentation of the actions you have taken or will take to correct any violations and to prevent the recurrence of similar violations in current and future studies for which you are the clinical investigator. If you believe that you have complied with the FD&C Act and FDA regulations, please include your reasoning and any supporting information for our consideration.

Your response should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., WO71-G112, Silver Spring, MD 20993-0002. If you have any questions regarding this letter, please contact the Division of Inspections and Surveillance, CBER at 240-402-8928.

We also request that you send a copy of your response to Eric Pittman, Director, FDA ORA-BIMO West, 55 West Jackson Street, Suite 1500, Chicago, Illinois 60661.

Sincerely,

Mary A. Malarkey -S

Digitally signed by Mary A. Malarkey -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054353, cn=Mary A. Malarkey -S
Date: 2021.03.22 10:05:55 -04'00'

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Eric Pittman, Director
FDA ORA-BIMO West
550 West Jackson Street, Suite 1500
Chicago, Illinois 60661

(b) (4)