



March 29, 2023

Joanne Kurtzberg, MD  
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Dear Dr. Kurtzberg:

This letter describes the results of a United States Food and Drug Administration (FDA) inspection that concluded on June 30, 2022. During the inspection, an FDA investigator met with you and your staff to review the conduct and oversight of a clinical study titled (b) (4) (hereinafter, the protocol). The FDA conducted this inspection under the Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational products.

At the conclusion of the inspection, the FDA investigator discussed with you and your staff their inspectional observations. We reviewed the Establishment Inspection Report (EIR), and accompanying exhibits and attachments, and we have follow-up questions regarding your evaluation and reporting of serious adverse events.

The compiled list of serious adverse events (SAEs) from all sites (exhibit 27) contains 28 serious adverse events, however 22 of 28 events listed were not reported in any annual report submitted to FDA from 2018-2022<sup>1</sup> (exhibit 28) even though those 22 events appear to meet the serious adverse event criteria defined in the protocol.

1. Please explain why the following 22 events that appear to meet the serious adverse event criteria defined in the protocol were not reported in annual reports submitted to FDA:

Subject ID	Adverse Event	Start Date	End Date	Related to Study Product	Expected Adverse Event
(b) (6)	Surgical and medical procedure – Other, specify	11/29/2017	12/8/2017	Unrelated	Expected
	Surgical and medical procedure – Other, specify	2/21/2021	2/24/2021	Unrelated	Expected
	Device related infection	3/1/2021	3/14/2021	Unrelated	Expected
	Surgical and medical procedure - Other, specify	3/1/2021	3/14/2021	Unrelated	Expected

<sup>1</sup> (b) (6) was reported in your 2020 annual report; (b) (6) (middle ear inflammation) and (b) (6) (seizure x2) were reported in your 2022 annual report.

(b) (6)	Surgical and medical procedures - Other, specify	10/22/2020	10/23/2020	Unrelated	Expected
	Surgical and medical procedures - Other, specify	3/15/2021	3/15/2021	Unrelated	Expected
	Surgical and medical procedures - Other, specify	8/22/2018	8/22/2018	Unrelated	Expected
	Surgical and medical procedures - Other, specify	4/19/2018	4/19/2018	Unrelated	Expected
	Surgical and medical procedures - Other, specify	5/17/2018	5/17/2018	Unrelated	Expected
	Seizure	8/6/2018	8/7/2018	Unrelated	Expected
	Surgical and medical procedures - Other, specify	5/16/2018	5/16/2018	Unrelated	Expected
	Surgical and medical procedures - Other, specify	4/1/2019	4/1/2019	Unrelated	Expected
	Pancreatitis	3/10/2021	<sup>2</sup>	Unrelated	Unexpected
	Sinusitis	11/1/2019	<sup>2</sup>	Unrelated	Unexpected
	Seizure	7/1/2019	10/31/2019	Unrelated	Expected
	Surgical and medical procedures - Other, specify	9/1/2019	9/1/2019	Unrelated	Expected
	Hematoma	12/19/2018	12/21/2018	Unrelated	Expected
	Movements involuntary	10/2/2020	1/1/2021	Unrelated	Expected
	Infusion related reaction	7/23/2019	7/23/2019	Definitely	Expected
	Surgical and medical procedures - Other, specify	5/29/2020	5/30/2020	Unrelated	Expected
	Infusion related reaction	2/6/2019	2/6/2019	Possibly	Expected
	Lymph gland infections	2/8/2019	2/11/2019	Unrelated	Expected

2. According to your compiled SAE list, subject (b) (6) experienced unexpected sinusitis unrelated to the study product beginning on 11/1/2019 with the comments “mastoiditis – required hospitalization; complicated by seizure”. However, your 2020 annual report states that subject (b) (6) experienced a non-serious, expected seizure unrelated to the study product. *Please clarify the criteria used to determine the adverse event type and whether it was considered serious or non-serious.*
3. Adverse events (AEs) in your annual reports from 2018 through 2021 are located under headers labeled Adverse Events: Frequent and Serious, however the reports also state: “All AEs were

<sup>2</sup> Spaces were left blank in exhibit 27.

deemed not serious”. *Please clarify what criteria were used to determine which adverse events would be reported annually, and please explain the discrepancies in your descriptions of the AEs as “serious” and “not serious.”*

4. Your annual reports from 2018-2022 listed 93 total adverse events; 28 serious adverse events were recorded on your SAE list but only 7 adverse events appear in both exhibits: (b) (6) and three occurrences of (b) (6) . *Please explain the reasons for the discrepancies in adverse events between the two exhibits.*

We remind you that as a sponsor, you are responsible for ensuring that the investigation is conducted in accordance with the protocol. We also remind you it is your responsibility to ensure a safety data monitoring committee is in place to review safety data and make determinations of study halting rules. To better assess safety for the investigational product, we recommend that you report AEs separately by protocol ID, indication, and include subject ID, adequate description of the AE, the grade, relatedness of the AE and any other pertinent information to support understanding of the AE in the context of the study. These details will aid in the understanding of the safety of the investigational product.

Please submit a written response to FDA within fifteen (15) business days of receipt of this letter. 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 240-402-8979.

We also request that you send a copy of your response to Anne Johnson, Director FDA ORA-OBIMO East, U.S. Custom House, Room 900, 200 Chestnut Street, Philadelphia, Pennsylvania 19106.

The FDA has several references available at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm> that offer information on human subject protection and the conduct of clinical research. If you have any questions about this letter or clinical studies of investigational products, you may contact:

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Sincerely,

**Melissa J. Mendoza** -S Digitally signed by Melissa J. Mendoza -S  
Date: 2023.03.29 14:18:14 -04'00'

Melissa J. Mendoza, JD  
Director, Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research