DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Avenue Building 51 Silver Spring, MD 20993 301-796-3150 Fax:(301)594-1204	1/20/2026-1/29/2026* FEI NUMBER 3021927419

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Prof. Bernardo Leon Rapaport, Clinical Investigator

FIRM NAME	STREET ADDRESS
Prof. Bernardo Leon Rapoport	129 Oxford Road, Corner Northwold Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Johannesburg, 2196 South Africa	Clinical Investigator

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

An investigation was not conducted in accordance with the investigational plan.

Specifically,

Your study site failed to follow the protocol and pharmacy manual instructions with respect to proper dosage and administration of the investigational product (IP).

A. The Pharmacy Manual utilized for both (b) (4) and (b) (4) studies require (b) (4) to be diluted to achieve a final concentration range of 1.1mg/mL to 3.4mg/mL. 2 of 8 (25%) subjects enrolled into (b) (4) and 3 of 11 (27%) subjects enrolled into (b) (4) received at least one dose of (b) (4) that is above the allowed concentration levels:

Study Number	Subject Number	Visit Number	Dose Concentration Administered to Subject (mg/mL)
(b) (4)	(b) (6)	C1D1	3.9
		C1D1	4.255
		C1D8	4.255
		C2D1	4.255
		C1D8	3.885
		C1D1	4.0
		C1D8	4.0
		C1D8	4.0

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EMPLOYEE(S) SIGNATURE
Richard W Berning, Investigator - Dedicated BIMO Cadre

X Richard W Berning Investigator - Dedicated BIMO Cadre Signed By: RICHARD W. BERNING -S Date Signed: 01-29-2026 08:40:02

DATE ISSUED
1/29/2026

[a] Subject (b) (6) had a grade 3 adverse event of abnormal kidney functions 3 days after C1D1.

[b] Subject (b) (6) had a grade 3 diarrhea adverse event 2 days after C1D1 as well as a grade 2 skin rash adverse event 6 days after C1D1, requiring dose interruption.

B. Both study protocols specify that the first (b) (4) infusion should be administered over 3 hours, with subsequent infusions administered over 1 to 2 hours if previous infusions were well tolerated. 3 of 11 subjects (27%) enrolled into (b) (4) received (b) (4) infusions in less than the minimum duration required for subsequent infusions:

Study	Subject	Visit	Visit Date	Required Duration	Documented Duration
(b) (4)	(b) (6)	C1D1	24 Aug 2023	3 hours	2 hours: 1100-1300, later changed to 1100-1400 on 11 Sep 2023.
		C3D8	18 May 2023	60-120 minutes	30 minutes: 1235-1305, later changed to 1235-1335 on 16 Oct 2023.
		C5D8	29 Jun 2023	60-120 minutes	30 minutes: Original start time is 1047-1117; later changed to 1057-1127 at an unknown date. [a]
		C4D1	29 Jun 2023	60-120 minutes	30 minutes: 1047-1117.[a]
		C5D8	26 Jul 2023	60-120 minutes	30 minutes: 1150-1220

[a] Subject (b) (6) C5D8 and Subject (b) (6) C4D1 both occurred on 29 Jun 2023 and feature identical (b) (4) infusion times prior to the undated and unattributed correction to Subject (b) (6) C5D8's infusion record

C. The (b) (4) study protocol requires that patients be monitored "during, and for at least 30 minutes after infusion" of (b) (4) The protocol also specifies that (b) (4) is to be administered "on Day 1 of 21-day cycles."

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i. For 3 of the 11 (27%) subjects enrolled into (b) (4), there was at least one visit where this monitoring period was not observed after (b) (4) administration was complete before beginning (b) (4) administration. Three of these instances happened on C1D1, the subjects' first exposure to (b) (4)

Subject	Visit	Observation Period Between Infusions
(b) (6)	C1D1	0 minutes
	C2D1	0 minutes
	C3D1	0 minutes
	C1D1	0 minutes
	C2D1	0 minutes
	C1D1[a]	Overlapping Administration
	C12D1	7 minutes
	C13D1	3 minutes

[a] Note: Subject (b) (6) C1D1 shows (b) (4) starting prior to completion of (b) (4) infusion.

ii. Subject (b) (6) received (b) (4) doses only 7 days apart within the same cycle: C6D1 dated 03 Jul 2024 and C6D8 dated 09 Jul 2024.

D. The Pharmacy Manual used for both studies states: "Calculate the prescribed dose in mg based on the subject's body weight at Cycle 1, Day 1 (C1D1). The dose is to remain constant throughout the study unless there is a >10% change in body weight from C1D1. Modifications to the study drug doses

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administered should be made for a > 10% change in body weight from C1D1 and according to local and regional prescribing standards. Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines."

Both study protocols state: "The dose of (b) (4) will be calculated based on actual weight at [enrollment/randomization] (using weight obtained either at screening or on C1D1) and remains constant throughout the study, unless there is a > 10% change in body weight from baseline. Modifications to the study treatment doses administered should be made for a > 10% change in body weight from baseline and according to local and regional prescribing standards. Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines."

Your site routinely changed the reference weight used for (b) (4) dose calculations in a manner inconsistent with the protocol and pharmacy manual requirements.

In my review of these studies at your site, I observed:

- Doses were recalculated based on current visit weights for subjects with <10% body weight changes from baseline, with no documentation that these changes were made according to institutional guidelines.
- When doses were reduced due to toxicity (not body weight change), your site inappropriately established new baseline weights using current visit weights rather than maintaining the original baseline weight.
- Your site failed to maintain consistency in approach, with some subjects having doses correctly calculated from baseline weight while others did not.

This impacted 3 of 8 subjects (37.5%) across approximately 25 total visits for (b) (4), and 5 of 11

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subjects (45.5%) across approximately 35 total visits for (b) (4).

Examples include:

- Subject (b) (6) ((b) (4)): toxicity dose adjustments made using current visit weight at C4D1 through C6D8; C7D8 through last dose at C16D8.
- Subject (b) (6) ((b) (4)): toxicity dose adjustments made using current visit weight at C3D1 through last dose at C9D1.
- (b) (4) Subjects (b) (6) and (b) (6) had dose reductions per protocol using the baseline weight for reductions due to toxicity at C2D1 and C3D1, respectively.

OBSERVATION 2

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

A. Modifications were made to IP preparation documentation for the dilution volume for (b) (4) dosing. The original value would result in a dose concentration outside of the protocol-specified range of 1.1 mg/mL to 3.4 mg/mL. Many of these were not attributable to a person or date, as there was no initials or dates documented by the changes.

Study	Subject	Visit	Apparent Original (b) (4) oncentration	Is Modification Attributable?
(b) (4)	(b) (6)	C1D1	4.12 mg/mL	No
		C1D8[a]	4.12 mg/mL	No
		C2D1[b]	4.12 mg/mL	No

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(b) (4)	(b) (6)	C2D1[c]	4.12 mg/mL	No
		C2D8[d]	Unknown, original entry obscured	Yes
		C2D1	4.00 mg/mL	No
		C2D1[e]	3.885 mg/mL	No
		C2D8[e]	Unknown. Original entry obscured	Yes

[a] Subject (b) (6) C1D8 (01 Aug 2023) occurred on the same day as Subject (b) (6) C1D1 visit, which had a confirmed overconcentration of (b) (4)

[b] Subject (b) (6) C2D1 dose prepared but not administered due to subject experiencing a hypoglycemic event prior to administration, so C2D1 was repeated.

[c] During Subject (b) (6)'s C2D1 infusion, she felt hot and developed a rash and the dose was interrupted.

[d] Subject (b) (6) discontinued treatment after C2D8, as more than 3 weeks had elapsed between C1D8 and C2D1 due to adverse events/toxicities, which met protocol stopping criteria for study treatment.

[e] Subject (b) (6) C1D1 is a confirmed overconcentration of (b) (4) with a dose of 777mg and a total dilution volume of 200mL. Refer to Observation 1, sub-item B.

B. Source records related to administration of IP to study subjects has discrepant information or implausible timepoints, were changed without justification, and/or are missing pertinent information:

Study	Subject	Visit	Visit or Document Date	Document Issues
(b) (4)	(b) (6)	C6D1	03 Jul 2024	An initial infusion form was completed with pre-dose vitals, but no infusion documentation. The form states that no adverse events or interruptions/delays occurred during infusions. A new infusion form was generated for this date, also dated 03 Jul 2024.

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(b) (4)	(b) (6)	C4D1	03 Apr 2024	Original infusion record completed through to post-dose vitals wit (b) (4) administered 1035-1105, flush from 1137-1132, and post-dose vitals at 1137. The changes to this document state the infusion was 1035-1135, flush 1137-1207, and post-dose vitals at 1215.
		C4D8	06 Apr 2023	Infusion record does not indicate what product is infused at this visit. Infusion times originally written as 1300-1330 with post dose vitals taken at 1400; corrected to 1300-1400 and post-dose vitals at 1430.
		C7D8	30 Jul 2024	Original complete infusion record states (b) (4) administered 1125-1225 and flush from 1226-1256 with no (b) (4). Post dose vitals at 1300. A new infusion document was made and signed 22 Aug 2024 that includes (b) (4) administration and was signed 22 Aug 2024 but dated 30 Jul 2024.
		C14D8	07 Jan 2025	Doctor signed off on prescription at 1052 and IP mixing time is stated as 1058; infusion record states that (b) (4) infusion started at 1020 before both of those signoffs.
		C3D8	18 May 2023	Infusion record updated almost 5 months later to change (b) (4) infusion from 30 minutes (1235-1305) to 60 minutes (1235-1335). Post-dose vital time stated to be 1310, which contradicts the changes.
		C5D8	29 Jun 2023	Changes made to (b) (4) infusion times with no date of correction; changes still indicate (b) (4) administered over improper duration of 30 minutes.
		C11D1	25 Oct 2023	Visit records state the IP was not handed over for

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				infusion until 1315; infusion record states infusion began at 1310.
(b) (4)	(b) (6)	C4D1	29 Jun 2023	Visit records state the IP was not handed over for infusion until 1050, while infusion records state the infusion began at 1047. Corrections were made to change the handover time to a time of 1043.
		C4D1	20 Dec 2023	Post-dose vitals stated to occur at 1216; this is in the middle of stated infusion times of (b) (4) 1107-1207) and (b) (4) (1240-1310).
		C5D1	09 Jan 2024	Original infusion record entry states (b) (4) infusion from 1050-1250 and (b) (4) from 1322-1352, with post dose vitals done 1303, in the middle of the infusions. The infusion document was changed to show (b) (4) infusion 1050-1150, (b) (4) infusion 1222-1252, and post-dose vitals remain 1303.
		C15D1	22 Jan 2025	IP mixing time is 1054, prior to study doctor signoff at 1100.
		C15D8	30 Jan 2025	Original mix time occurs before investigator signoff. (b) (4) infusion stop time modified to meet 60-minute requirement. IP mixing time originally 1014 and handoff time 1018, but study doctor did not sign off until 1015; those times were corrected to 1018 and 1025 respectively.
		C2D1	17 Apr 2024	(b) (4) infusion not on original infusion record with post dose vitals recorded (but no time of this activity). A new copy of this infusion record was generated with (b) (4) infusion documented.

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(b) (4)	(b) (6)			
		C7D1	18 Jan 2024	Study doctor requested 425.5mg of (b) (4) IP preparation states 38.3mL dose prepared, indicative of a 383mg dose given.
		C1D1	24 Mar 2023	No dilution volume documented to determine concentration administered at this visit. (b) (4)
		C6D1	10 May 2023	No dilution volume documented to determine concentration administered at this visit.
		C4D8	13 Nov 2023	No dilution volume documented to determine concentration administered at this visit.
		C12D1	14 Nov 2024	No dilution volume documented to determine concentration administered at this visit.

***DATES OF INSPECTION**
1/20/2026(Tue), 1/21/2026(Wed), 1/22/2026(Thu), 1/23/2026(Fri), 1/26/2026(Mon), 1/27/2026(Tue), 1/28/2026(Wed), 1/29/2026(Thu)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."