CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213312Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 9, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 213312
Product Name and Strength:	Fyarro (sirolimus protein-bound nanoparticles) For Injectable Suspension (albumin-bound), 100 mg/vial
Applicant/Sponsor Name:	Aadi Bioscience, Inc.
OSE RCM #:	2020-1336-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 5, 2021 for Fyarro. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Fyarro (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Stewart, J. Label and Labeling Review for Fyarro (NDA 213312). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 27. RCM No.: 2020-1336.

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/s/

JANINE A STEWART
11/09/2021 03:39:27 PM

ASHLEIGH V LOWERY
11/16/2021 11:38:27 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 29, 2021

To: Sharon Sickafuse, MS, Regulatory Project Manager
Division of Oncology 2 (DO2)

From: Emily Dvorsky, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for FYARRO™ (sirolimus protein-bound particles for injectable suspension) (albumin-bound), for intravenous use

NDA: 213312

In response to DO2 consult request dated June 9, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for FYARRO™ (sirolimus protein-bound particles for injectable suspension) (albumin-bound), for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO2 (Sharon Sickafuse) on October 20, 2021, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 10, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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/s/

EMILY M DVORSKY
10/29/2021 02:10:37 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 27, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 213312
Product Name, Dosage Form, and Strength:	Fyarro (sirolimus albumin-bound nanoparticles) For Injectable Suspension, 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Aadi Bioscience, Inc.
FDA Received Date:	January 15, 2021, May 28, 2021, September 10, 2021
OSE RCM #:	2020-1336
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Fyarro (sirolimus albumin-bound nanoparticles) For Injectable Suspension, the Division of Oncology 2 (DO2) requested that we review the proposed Fyarro Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B– N/A
Human Factors Study	C– N/A
ISMP Newsletters*	D –N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), container label, and carton labeling for Fyarro to identify deficiencies that may lead to medication errors and other areas of improvement.

We note the term (b) (4) appears in the PI, on the container label and labeling and we communicated with OPQ regarding the appropriateness of this package type term. We defer to OPQ to determine the appropriate package type term for this product. Additionally, our review of the PI, container label and carton labeling identified areas of vulnerability that can be modified to improve the clarity of the information presented.

4 CONCLUSION & RECOMMENDATIONS

Our review of materials found that the proposed Fyarro PI, container label, and carton labeling may be improved to promote safe use of this product. Thus, we provide related recommendations below in Section 4.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. Consider revising the title of Section [redacted] to read "*Preparation and Administration"* to reflect the order of product use.

b. Consider revising the preparation instructions in Section [redacted] *Preparation and Administration* for improved clarity and readability as follows:

Preparation:

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.

2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.

3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized powder as this will result in foaming.

4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized powder.

5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any powder occurs. Avoid shaking to vial to prevent the generation of foam.

6. If foaming or clumping occurs, let suspension stand for at least 15 minutes until foam subsides. If foaming or clumping is present after one hour, do not use the reconstituted suspension.

Each mL of the reconstituted formulation will contain 5 mg FYARRO.

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

7. [redacted].

8. Transfer the volume of FYARRO required for the calculated dose into an empty PVC or polyolefin infusion bag for administration without further dilution.

The use of medical devices containing silicone oil as a lubricant (e.g., syringes and intravenous bags) to reconstitute and administer FYARRO may result in the formation of proteinaceous strands.

Visually inspect FYARRO for particulate matter, proteinaceous strands, and discoloration prior to administration. Discard reconstituted suspension if particulate matter, proteinaceous strands, or discoloration are observed.

Administration:

Administer the reconstituted FYARRO suspension intravenously over 30 minutes.

4.2 RECOMMENDATIONS FOR AADI BIOSCIENCE, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The established name is not at least half the size of the proprietary name. Revise the size of the established name to be in accordance with 21 CFR 201.10(g)(2).
2. Consider revising the statement [redacted] (b) (4) to read "For intravenous infusion." We recommend this to minimize the risk of administering the drug as an intravenous bolus.
3. Revise the package type term [redacted] (b) (4) to the use the appropriate package type term, "Single-dose vial".
4. Remove the statement that reads [redacted] (b) (4) to reduce clutter on the principal display panel.

B. Container Labels

1. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read "Recommended Dosage: See prescribing information."

C. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read "Recommended Dosage: See prescribing information."
2. The storage requirements for the vials before reconstitution was omitted from the proposed container label and carton labeling. Add the bolded statement "**Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).** Retain in the original carton to protect from light." We recommend this to ensure the prominence of

this important information and to minimize the risk of the storage information being overlooked.

3. The storage information for reconstituted suspension appears incomplete and inconsistent with the information provided in the Prescribing Information which includes information for storage of the reconstituted suspension in the vial and storage of the reconstituted suspension in an infusion bag. Revise the information so that the information is complete and consistent between both labeling components.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fyarro received on May 28, 2021 from Aadi Bioscience, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Fyarro and the Listed Drug		
Product Name	Fyarro	Rapamune[a]
Initial Approval Date	N/A	September 15, 1999 and August 25, 2000
Active Ingredient	sirolimus albumin-bound nanoparticles	sirolimus albumin-bound nanoparticles
Indication	For the treatment of advanced (metastatic or locally advanced) malignant perivascular epithelioid cell carcinoma (PEComa).	• As an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients aged 13 years and greater receiving renal transplants • For the treatment of patients with lymphangioleiomyomatosis.
Route of Administration	Intravenous infusion	oral
Dosage Form	For Injectable Suspension	Solution and tablets
Strength	100 mg/vial	60 mg/60 mL and 0.5 mg, 1 mg, and 2 mg
Dose and Frequency	Recommended dose is 100 mg/m^2 administered as an IV infusion over 30 minutes on days 1 and 8 of a 21-day cycle. • Dose reductions to 75 mg/m^2 and 56 mg/m^2 are recommended in patients with mild and moderate hepatic impairment, respectively.	Renal Transplant Patients: Administer once daily by mouth, consistently with or without food. Administer the initial dose as soon as possible after transplantation and 4 hours after CsA. Adjust the Rapamune maintenance dose to achieve sirolimus trough concentrations within the target-range. Hepatic impairment: Reduce maintenance dose in patients with hepatic impairment. In renal transplant patients at low-to moderate-immunologic risk: Rapamune and CsA Combination Therapy: One

[a] Rapamune [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 OCT 01. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021083s067,021110s085lbl.pdf

		loading dose of 6 mg on day 1, followed by daily maintenance doses of 2 mg. Rapamune Following CsA Withdrawal: 2–4 months post-transplantation, withdraw CsA over 4–8 weeks. In renal transplant patients at high-immunologic risk: Rapamune and CsA Combination Therapy (for the first 12 months post-transplantation): One loading dose of up to 15 mg on day 1, followed by daily maintenance doses of 5 mg. Lymphangioleiomyomatosis Patients Administer once daily by mouth, consistently with or without food . Recommended initial Rapamune dose is 2 mg/day. Adjust the Rapamune dose to achieve sirolimus trough concentrations between 5–15 ng/mL. Hepatic impairment: Reduce maintenance dose in patients with hepatic impairment.
How Supplied	Single-dose vial individually packaged in a carton	Oral Solution Carton: One 2 ounce (60 mL fill) amber glass bottle, one oral syringe adapter for fitting into the neck of the bottle, sufficient disposable oral syringes (amber color) and caps for daily dosing and a carrying case Tablets: ▪ 0.5 mg and 1 mg: Bottles of 100 tablets and Redipak cartons of 10 blister cards of 10 tablets each ▪ 2 mg: Bottles of 100 tablets
Storage	Store the vials in the original cartons at 2° to 8°C [USP Refrigerated Temperature] (36° to 46°F). Retain in the original package to protect from light.	Oral Solution: Refrigerated at 2°C to 8°C (36°F to 46°F). Tablets :20°C to 25°C [USP Controlled Room Temperature] (68°F to 77°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Fyarro labels and labeling submitted by Aadi Bioscience, Inc..

- Container label received on September 10, 2021
- Carton labeling received on September 10, 2021
- Prescribing Information (Image not shown) received on May 28, 2021, available from \\CDSESUB1\evsprod\nda213312\0008\m1\us\1-14-1-3-draft-labeling-text-clean.docx

G.2 Label and Labeling Images

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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JANINE A STEWART
10/27/2021 03:41:59 PM

ASHLEIGH V LOWERY
10/27/2021 08:33:32 PM

Clinical Inspection Summary

Date	6/3/2021
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Amy Barone, MD, Clinical Reviewer Gautam Mehta, MD, Clinical Reviewer Diana Bradford, MD, Clinical Team Leader Harpreet Singh, MD, Division Director Sharon Sickafuse, Regulatory Project Manager Division of Oncology 2 (DO2)
NDA #	213312
Applicant	Aadi Bioscience Inc.
Drug	sirolimus albumin-bound nanoparticles for injectable suspension (*nab*-sirolimus)
NME (Yes/No)	Yes
Therapeutic Classification	mTOR inhibitor
Proposed Indication	Treatment of patients with advanced (metastatic or locally advanced) malignant Perivascular Epithelioid Cell carcinoma (PEComa)
Consultation Request Date	December 8, 2020
Summary Goal Date	June 15, 2021
Action Goal Date	TBD
PDUFA Date	TBD

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study PEC-0001 were submitted to the Agency in support of a New Drug Application (NDA 213312) for sirolimus albumin-bound nanoparticles for injectable suspension (*nab*-sirolimus) for the treatment of patients with advanced (metastatic or locally advanced) malignant Perivascular Epithelioid Cell carcinoma (PEComa). Three clinical investigators Drs. Wagner (Site 001), Ravi (Site 004), and Ganjoo (Site 007), and the central radiology imaging center (b) (4) were selected for on-site clinical inspections.

The inspections revealed no significant findings. There was no evidence of underreporting of serious adverse events or significant protocol deviations. Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of the NDA.

II. BACKGROUND

Aadi Bioscience Inc. seeks approval of *nab*-sirolimus for the above proposed indication. In support of the NDA, the Applicant submitted clinical data from Study **PEC-001** (NCT 02494570), titled **"**A Phase 2 Multi-center Investigation of Efficacy of ABI-009 (*nab*-rapamycin) in Patients with Advanced Malignant Perivascular Epithelioid Cell Tumors (PEComa)."

Study Design:
Study PEC-001 is an on-going phase 2, single-arm, open-label, multi-center study of *nab*-sirolimus in patients with advanced malignant PEComa.

Major inclusion criteria include adult subjects with

- histologically confirmed diagnosis of malignant PEComa that was advanced (either metastatic or locally) and for which surgery was not a recommended option;
- available tumor specimen to allow retrospective centralized confirmation of malignant PEComa and for mTOR pathway analysis and biomarker analysis;
- measurable disease per RECIST 1.1;
- no prior treatment with an mTOR inhibitor;
- prior treatment (chemotherapy, radiotherapy, surgery, or other therapeutic agents) occurring greater than 5 half-lives or $\geq$ 28 days before enrollment

Subjects were to receive the study drug, *nab*-sirolimus, at a dose of 100 mg/m^2 IV infusion (over 30 minutes) weekly for 2 weeks followed by a week of rest (cycle was 21 days total). Subjects were to continue on treatment until disease progression or unacceptable toxicity, death, withdrawal of consent, initiation of another anticancer therapy, or their physician felt it was no longer in their best interest to continue treatment. End of treatment (EOT) evaluations were to be completed at that time.

The primary objective was to investigate the efficacy of *nab*-sirolimus in advanced malignant PEComa. The primary endpoint was overall response rate (ORR) at 6 months, assessed by independent review. ORR is defined as the proportion of patients who achieve a confirmed partial response (PR) or complete response (CR) per RECIST 1.1. The key secondary endpoints were duration of response (DOR), progression-free survival (PFS), PFS at 6 months (PFS6), and overall survival (OS).

Tumor evaluation by contrast-enhanced CT or MRI of the chest, abdomen, and pelvis was to be performed during screening, within 28 days prior to start; then every 6 weeks after Cycle 1, Day 1 for the first year, then every 12 weeks thereafter until disease progression. If an initial observation of objective response (CR or PR) was made, a confirmation scan was to be done at 6 weeks after initial observation.

Subjects were to undergo safety assessments and procedures at the End of Treatment (EOT) visit (at least 4 weeks ± 7 days after the last dose of study drug). After the EOT visit, subjects that had not withdrawn consent were to continue in follow up for survival and anticancer therapy approximately every 12 weeks (± 3 weeks).

As of the cutoff date, 35 subjects were enrolled and 34 had received at least one dose of study drug. The study is being conducted across 9 study centers, all in the United States. The data cutoff for the current submission is May 22, 2019 and the study is ongoing.

III. RESULTS

1. Dr. Vinod Ravi (CI Site 004)

MD Anderson Cancer Center
1515 Holcombe Blvd
Houston Texas 77030
Inspection dates: February 9 – 12, 2021

This investigator was inspected as a surveillance inspection for Study PEC-001. This was the first FDA inspection for this investigator.

The enrollment logs inspected at the site were consistent with the data listings. At the time of the data cutoff, the investigator site had screened 7 subjects and enrolled five. One subject had died (Subject # (b) (6)), 3 subjects were off treatment due to disease progression (Subject #s (b) (6)), and 2 subjects remained on treatment (Subject #s (b) (6)

The source records for all 5 enrolled subjects were reviewed and compared to the subject data line listings. Reviewed records included imaging records, eligibility criteria, informed consent, adverse events and SAEs, and protocol deviations. Also reviewed were study records including Form FDA 1572s, financial disclosures, site training records, IRB communications, investigational product accountability records and the study protocol with amendments at the site.

The primary endpoint of ORR and the secondary endpoint of DOR were based on independent central review of imaging. All imaging studies performed at the site for study scheduled assessments were performed according to the protocol and correctly submitted to the central radiology facility. The secondary endpoint of overall survival was verified with the source records.

There was no observation of underreporting of protocol deviations or adverse events. No Form FDA 483 was issued to Dr. Ravi at the conclusion of the inspection.

2. Dr. Andrew J. Wagner (CI Site 001)

450 Brookline Ave,
Boston, MA 02215-5418
Inspection Dates: February 22 – 26 and March 1-4, 2021

This investigator was inspected as a surveillance inspection for Study PEC-001. This was the first FDA inspection for this investigator.

All subjects met eligibility criteria and the enrollment logs were consistent with the data listings. At the time of data cutoff, nine subjects were enrolled; 2 withdrew consent before treatment and seven subjects were treated. At the time of the inspection, three subjects had died (Subject #s (b) (6)), one subject withdrew consent and follow up (Subject # (b) (6)) and 2 subjects withdrew due to disease progression and are on follow up (Subject #s (b) (6)). Subject # (b) (6) is still on treatment.

The source documents for the seven enrolled subjects were reviewed and compared to the subject data line listings. The reviewed subject records included paper and electronic medical records, including imaging records, informed consent, eligibility criteria, investigational product administration records, adverse events and SAEs, and protocol deviations. Study records were also reviewed including Form FDA 1572s, financial disclosures, delegation of authority log, site monitoring records, IRB communications, Sponsor communications, investigational product accountability records, site protocol with amendments, and the electronic data capture system audit trails.

The key primary and secondary endpoint data were based on independent central review of imaging. All imaging was performed and sent to the central imaging facility as per the protocol. All required imaging submission dates were verified. The secondary endpoint of OS was verified against the source data at the site.

An unreported protocol deviation was identified at the site. Subject # (b) (6) was enrolled into the study despite having met the exclusion criteria regarding use of fentanyl within 14 days prior to receiving the first dose of ABI-009. On the day prior to the initiation of the study drug, Subject # (b) (6) was treated with 7 doses of fentanyl injection, intravenously, during an outpatient procedure. This was not reported as a protocol deviation either to the sponsor or to the IRB.

Reviewer's Comments:
Subject # (b) (6) should not have been enrolled in the study given that he met the exclusion criteria regarding fentanyl. Dr. Wagner and the study staff reported that they were unaware that Subject # (b) (6) had received fentanyl and that they had not reviewed the electronic medical record which recorded the fentanyl administration. Although Dr. Wagner failed to review the EMR, the observation is isolated. He provided adequate response to the finding in a letter dated, March 25, 2021. Dr. Wagner acknowledged the error and his responsibility in his response to the FDA Form 483. His preventive action

plan includes training the study team regarding the need to review recent procedures for medication administrations in addition to subjects' on-going medication lists. There is no evidence of harm to this subject from the protocol deviation. The preventive action plan is acceptable. This protocol deviation was not reported in the subject line listings submitted to FDA by the sponsor.

There was no observation of underreporting of adverse events.

3. Dr. Kristen Ganjoo (CI Site 007)

Stanford University
269 Campus Dr
Stanford, CA 94305-5101
Inspection dates: February 1-8, 2021

This investigator was inspected as a surveillance inspection for Study PEC-001. This investigator was inspected previously with an inspectional classification of voluntary action indicated (VAI) for inadequate case histories and not adhering to the protocol.

The enrollment logs inspected at the site were consistent with the data listings. At the time of data-cutoff, the investigator had screened 5 subjects and enrolled four. Two subjects had died (Subject #s (b) (6)) and one subject had discontinued treatment due to disease progression (Subject # (b) (6)). At the time of inspection, one subject was still active in the study (Subject # (b) (6)).

The eligibility criteria for all 5 screened subjects and the source data for the enrolled subjects were reviewed and compared to the subject data line listings. The reviewed subject records included medical records, informed consents, eligibility criteria, protocol deviations, and adverse events. The study records were also reviewed including Form FDA 1572s, financial disclosures, site training logs, delegation of authority logs, monitoring visits, IRB communications, site protocol with amendments, investigational product storage and accountability records, and EDC functionality and audit records.

The primary endpoint was based on independent review of imaging. The imaging studies at the site were acquired according to the protocol and sent to the central radiology facility. The secondary endpoint of overall survival was confirmed with the source data. There was no observation of underreporting of adverse events.

Informed consent was inadequate for two study subjects. Subject # (b) (6) signed a (b) (6)-language short form. Information was presented to the subject verbally in the subject's native language, (b) (6). There is no record of what information was presented verbally to the subject during the consent process. Subject # (b) (6) signed a (b) (6) language short form. There is no record of whether a translator was present during the consent process, nor is there a record of what information was presented verbally to the subject. In both cases, there was no IRB-approved written summary of what is to be said to the subject during the consent process.

Reviewer's Comments: Informed consent was inadequate for Subjects # (b) (6) *. Dr. Ganjoo should have obtained an IRB approved written summary of what is to be said to subjects who are non-English speakers during the consent process, according to 21 CFR 50.27(b)(2).*

There were seven protocol deviations involving three subjects that were found at the site, but not reported in the subject data line listings submitted to the Agency. These included five post infusion ECGs for 4 subjects performed out of the protocol-required window of 30 min +/- 10 minutes. The out of window ECGs occurred between 2 minutes up to 24 hours out of window. Additionally, two CTs in two different subjects were performed 3 days out of window. These deviations were reported in the site's electronic system for recording protocol deviations (OnCore), however they were not transferred to the eCRF.

Reviewer's Comments: Although the unreported protocol deviations were not reported to the sponsor by Dr. Ganjoo or other site staff, none of the unreported protocol deviations would have impacted the safety or efficacy data generated by the site. The findings do not appear to be clinically significant .

4. (b) (4)

This CRO was inspected as a surveillance inspection for Study PEC-001; the previous FDA inspection for this establishment was conducted 10/2019 with an inspectional classification of NAI.

(b) (4) was responsible for determining the radiologic tumor response according to RECIST 1.1, which determined the primary endpoint data and certain secondary endpoint data (PFS, DOR), for study PEC-001. Records reviewed included the firm's standard operating procedures (SOPs) and the Imaging Review Charter (IRC). The inspection reviewed the imaging data for disease response for all subjects and there were no discrepancies. The central imaging was conducted in compliance with the study's IRC and protocol. No Form FDA 483 was issued at the end of the inspection

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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cc:

Review Division /Division Director/Harpreet Singh, MD
Review Division /Project Manager/ Sharon Sickafuse
Review Division/Cross Discipline Team Lead/Diana Bradford, MD
Review Division/Clinical Reviewer/ Amy Barone, MD
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OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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