CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218160Orig1s000

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)

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

Date of This Review:	March 29, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 218160 and NDA 213246/S-010
Product Name, Dosage Form, and Strength:	Retevmo (selpercatinib) Tablet, 40 mg, 80 mg, 120 mg, and 160 mg
Applicant Name:	Loxo Oncology Inc.
FDA Received Date:	March 22, 2024
TTT ID #:	2023-5151-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

Loxo Oncology Inc. submitted a revised container label received on March 22, 2024 for Retevmo. The Division of Oncology 2 (DO2) requested that we review the revised container label for Retevmo (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

Loxo Oncology Inc. implemented all of our recommendations and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON MARCH 22, 2024

Container Label(s)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Stewart, J. Label and Labeling Review for Retevmo (NDA 218160 and NDA 213246/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2024 MAR 13. TTT ID: 2023-5151.

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/s/

JANINE A STEWART
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ASHLEIGH V LOWERY
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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)

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Date of This Review:	March 13, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 218160 and NDA 213246/S-010
Product Name, Dosage Form, and Strength:	Retevmo (selpercatinib) Tablet , 40 mg, 80 mg, 120 mg, and 160 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Loxo Oncology Inc.
FDA Received Date:	June 13, 2023
TTT ID #:	2023-5151
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

NDA 218160

As part of the approval process for Retevmo (selpercatinib) Tablet , the Division of Oncology 2 (DO2) requested that we review the proposed Retevmo prescribing information (PI), patient information, and container labels for areas of vulnerability that may lead to medication errors.

NDA 213246/S-010

Loxo Oncology Inc. submitted a Labeling Supplement under NDA 213246; Retevmo (selpercatinib) capsules, which cross references NDA 218160, which was submitted to support the proposed Retevmo tablet dosage form. This supplement cross references bioequivalence data and labeling submitted under NDA 218160. Loxo seeks approval to co-label both dosage forms under a single Retevmo labeling.

2 BACKGROUND

Retevmo (selpercatinib) was originally approved under NDA 213246 on May 8, 2020 and is currently available as 40 mg and 80 mg capsules. Loxo Oncology Inc. has submitted NDA 218160 for a proposed immediate-release tablet dosage form which they developed as a product redesign in strengths of 40 mg, 80 mg, 120 mg, and 160 mg to replace the current commercial capsule formulation. Loxo expressed in the submission that this proposed redesign was intended to offer an improved experience for patients in terms of reducing the number and size of the dosage units required to achieve the prescribed dosage.

3 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed Section 2 Dosage and Administration, Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information, and Patient Information for areas of vulnerability that may lead to medication errors. We note the proposed changes to sections 3 and 16 of the PI and to the Patient Information, which involve the addition of product information related to the newly proposed tablet formulation, appear appropriate and do not introduce new risks for medication errors. We also note there a no substantive changes proposed to sections 2 or 17.

However, our review of the Retevmo container labels identified an area of needed improvement to support safe medication use.

5 CONCLUSION & RECOMMENDATIONS

The proposed Retevmo PI and Patient Information are acceptable from a medication error perspective .

The proposed Retevmo container label for the 160 mg strength can be improved to ensure safe medication use. We provide specific recommendations in Section 5.1 below.

5.1 RECOMMENDATIONS FOR LOXO ONCOLOGY INC.

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

A. Container Labels

1. The 160 mg strength is not clearly differentiated due to the (b) (4) For products with multiple strengths, a lack of differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature. We recommend revising the color scheme of the 160 mg such that the strength appears in its own unique color (b) (4) .

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 1 presents relevant product information for Retevmo received on June 13, 2023 from Loxo Oncology Inc..

Table 2. Relevant Product Information for Retevmo		
Product Name	Retevmo (NDA 218160) [proposed]	Retevmo (NDA 213246) [a]
Initial Approval Date	N/A	May 8, 2020
Active Ingredient	selpercatinib	
Indication	• Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test. • Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy. • Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). • Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.	
Route of Administration	Oral	
Dosage Form	Tablet	Capsule
Strength	40 mg, 80 mg, 120 mg, and 160 mg	40 mg and 80 mg
Dose and Frequency	In adults and pediatric patients 12 years of age or older is based on weight: • Less than 50 kg: 120 mg orally twice daily • 50 kg or greater: 160 mg orally twice daily **Recommended RETEVMO Dose Reductions for Adverse Reactions**	

<table>
<tr><td></td><td>
<table>
<tr><th>Dose Reduction</th><th>Patients Weighing Less Than 50 kg</th><th>Patients Weighing 50 kg or Greater</th></tr>
<tr><td>First</td><td>80 mg orally twice daily</td><td>120 mg orally twice daily</td></tr>
<tr><td>Second</td><td>40 mg orally twice daily</td><td>80 mg orally twice daily</td></tr>
<tr><td>Third</td><td>40 mg orally once daily</td><td>40 mg orally twice daily</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>film-coated tablets in strengths of 40 mg, 80 mg, 120 mg, and 160 mg; each in a 60-count bottle</td><td>40 mg capsules: 60-count bottle
80 mg capsules: 60-count and 120 count bottles</td></tr>
<tr><td>Storage</td><td colspan="2">Store at 20˚C to 25˚C (68˚F to 77˚F), excursions permitted between 15˚C and 30˚C (59°F to 86°F)</td></tr>
<tr><td>Container Closure</td><td colspan="2">White, HDPE bottles with closures containing an aluminum foil induction heat seal liner (b) (4) and HDPE (b) (4) closures.</td></tr>
</table>

[a] Retevmo [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 NOV 06. Available from: https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=7fa848ba-a59c-4144-9f52-64d090f4d828&type=pdf .

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 6, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Retevmo. Our search identified 4 previous reviews[b,c,d,e], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Stewart, J. Label and Labeling Review for Retevmo (selpercatinib) (NDA 213246/S-08). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 SEP 20. RCM No.: 2022-1281

[c]. Mahmoud, S. Label and Labeling Review for Retevmo (selpercatinib) (NDA 213246). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 MAY 18. RCM No.: 2021-31

[d] Stewart, J. Label and Labeling Review for Retevmo (selpercatinib) (NDA 213246). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 15. RCM No.: 2019-2472-1

[e] Stewart, J. Label and Labeling Review for Retevmo (selpercatinib) (NDA 213246). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 02. RCM No.: 2019-2472

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Retevmo labels and labeling submitted by Loxo Oncology Inc..

- Container label received on June 13, 2023
- Prescribing Information (Image not shown) received on June 13, 2023, available from \\CDSESUB1\EVSPROD\nda218160\0001\m1\us\proposed-uspi-clean.docx
- Patient Information received on June 13, 2023, available from \\CDSESUB1\EVSPROD\nda218160\0001\m1\us\proposed-ppi-clean.docx

F.2 Label and Labeling Images

(b) (4)

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

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ASHLEIGH V LOWERY
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****Pre-decisional Agency Information****

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

Memorandum

Date: **2/28/2024**

To: Jeffrey Ingalls, Regulatory Project Manager, Division of Oncology 2 (DO2)

From: Courtney Leach, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for RETEVMO® (selpercatinib) tablets, for oral use and RETEVMO® (selpercatinib) capsules, for oral use

NDA/BLA: 218160; 213246-S010

Background:
In response to DO2's consult requests dated June 26, 2023 and February 5, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI) and carton and container labeling for the original NDA submission for RETEVMO® (selpercatinib) tablets, for oral use and for supplement 010 for RETEVMO® (selpercatinib) capsules, for oral use. NDA 213246-S010 is a labeling supplement to update the parent NDA 213246 with the new RETEVMO tablets formulation under NDA 218160.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 20, 2024, and we do not have any comments at this time.

PPI:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on February 27, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on February 26, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Courtney Leach at (301) 796-1044 or Courtney.Leach@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 27, 2024
To:	Jeffrey Ingalls, PharmD Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Courtney Leach, PharmD, BCCCP, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route, Application Type/Number:	RETEVMO (selpercatinib) tablets, for oral use; NDA 218160 RETEVMO (selpercatinib) capsules, for oral use; NDA 213246/S-010
Applicant:	Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company

1 INTRODUCTION

On June 13, 2023, Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company submitted for the Agency's review an original New Drug Application (NDA) 218160 for RETEVMO (selpercatinib) tablets. With this submission, the Applicant proposes a new tablet formulation for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged drug transfection (RET) gene fusion.

On October 26, 2023, Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company submitted for the Agency's review a Prior Approval Supplement (PAS) – Labeling to their approved New Drug Application (NDA) 213246/S-010 for RETEVMO (selpercatinib) capsules. The purpose of this submission is to amend the labeling via cross-reference to the selpercatinib tablet bioequivalence data to include both capsules and tablets.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on June 26, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RETEVMO (selpercatinib) tablets, and on February 5, 2024, for DMPP and OPDP to review the Applicant's proposed PPI for RETEVMO (selpercatinib) capsules.

2 MATERIAL REVIEWED

- Draft RETEVMO (selpercatinib) tablets PPI received on June 13, 2023, and draft RETEVEMO (selpercatinib) capsules PPI received on October 26, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 20, 2024.
- Draft RETEVMO (selpercatinib) tablets Prescribing Information (PI) received on June 13, 2023, and draft RETEVMO (selpercatinib) capsules Prescribing Information (PI) received on October 26, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 20, 2024.
- Approved RETEVMO (selpercatinib) capsules labeling dated September 21, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Amendment: This review is amended to include attachments.

DATE: January 19, 2024

TO: Harpreet Singh, M.D.
Director
Division of Oncology 2 (D02)
Office of Oncologic Diseases (OOD)
Office of New Drugs (OND)

FROM: Sri Rama Krishnaiah Yellela, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
DNDSI, OSIS

SUBJECT: Inspection of clinical site Lilly Center for Clinical Pharmacology Pte., Ltd., Synapse, Singapore

1. Inspection Summary

OSIS arranged an inspection of one clinical study (#J2G-MC-JZPA) conducted by Dr. Noel M. Varghese, MBBS at Lilly Center for Clinical Pharmacology Pte., Ltd., Synapse, Singapore and submitted in support of NDA 218160 (Retevmo® [selpercatinib or LY3527723] tablets 40 mg, 80 mg, 120 mg, and 160 mg). The study was conducted under IND 133193.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out meeting. However, the ORA Investigator discussed one finding regarding a late (9-day delay) follow-up phone call made to one subject who withdrew consent after receiving the last dose of investigational product (IP). The study protocol required a follow-up phone call within 7 to 10 days after administering last IP dose, and thus the finding is a protocol deviation and regulatory violation of 21 CFR 312.60. However, after reviewing the establishment inspection report and available source records, I conclude the finding did not affect subject safety because subject # (b) (6) discontinued due to personal reasons and not because of adverse

events (AEs). In addition, the late follow-up phone call confirmed that subject # (b) (6) was doing well.

2. Inspected Study:

NDA 218160

Study Number: J2G-MC-JZPA
Study Title: *"An open-label, randomized, two-period crossover study to investigate the effect of food on the pharmacokinetics of selpercatinib in healthy participants"*
Dates of study conduct: 04/19/2022 – 06/23/2022

Clinical Investigator: Noel M. Varghese, M.B.B.S.
3 Biopolis Drive #02-11
Synapse, Singapore 138623
FEI #3027615692

Clinical site: Lilly Center for Clinical Pharmacology Pte., Ltd.
3 Biopolis Drive #02-11
Synapse, Singapore 138623
FEI #3014479753

3. Inspectional Findings

ORA Investigator Tawny L. Colling inspected Lilly Center for Clinical Pharmacology Pte., Ltd., Synapse, Singapore from December 11, 2023 to December 15, 2023.

3.1 Previous Inspection

The clinical investigator (CI) has no FDA inspection history. In contrast, the clinical site had an onsite BA/BE inspection from 2/3/2020 to 2/7/2020. Form FDA 483 was not issued during the previous inspection. However, one finding was discussed regarding failure of clinical investigator Ronan P. Kelly, M.D. to document an AE for one subject. A similar finding was not observed during the current inspection. The OSIS final classification of the site was NAI.

3.2 Current Inspection

The records reviewed during the current inspection included but were not limited to ethics committee approvals, staff training records, subject eligibility, informed consent (IC), test article dosing, PK sample centrifugation, AEs and protocol deviations.

At the conclusion of the inspection, Investigator Colling did not observe any objectionable conditions and Form FDA 483 was not issued. However, she discussed one finding at the inspection closeout meeting. The discussion item, clinical investigator's response during the inspection and my evaluation are presented below.

3.2.1. Discussion Item

Discussion item 1: Follow-up phone call to subject # (b) (6) was not performed within protocol-specified window of 7-10 days after administering the last dose.

OSIS Evaluation: The finding is true. Subject # (b) (6) received his last dose of IP on (b) (6) and withdrew from the study due to personal reasons on (b) (6) [***Attachment #1***]. The study protocol required a follow-up phone call within 7 to 10 days after the last dose of IP [***Attachment #2***]. However, the follow-up phone call occurred on (b) (6) which is 9 days outside the protocol-allowed timeframe. Thus, the finding is a protocol deviation and regulatory violation of 21 CFR 312.60 [***Attachment #3***].

According to available records, the late follow-up phone call showed that subject # (b) (6) was doing well. In addition, subject # (b) (6) discontinued from study due to personal reasons and early discontinuation assessments did not identify any adverse events [***Attachment #3***]. Therefore, the finding did not impact the safety of subject # (b) (6) The finding is a protocol deviation and regulatory violation that did not exceed the threshold for further action.

Clinical Investigator's Response: Dr. Varghese agreed with the finding but stated that there were no safety concerns with the subject. He did not propose any corrective/ preventive actions.

Attachments

Attachment #1: Narrative of withdrawal reasons for subject # (b) (6) who discontinued from study
Attachment #2: Follow-up phone call requirement in study protocol #J2G-MC-JZPA

Attachment #3: Source record for subject # (b) (6) on dosing, discontinuation and follow-up phone call

Sri Rama Krishnaiah Yellela, Ph.D.
Pharmacologist

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza/Pham
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Yellela
OTS/OSIS/DGDSI/Cho/Benson/Ou/Skelly/Au
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov
ORA/OMPTO/OBIMO/Colling

Draft: SRKY, 01/15/2024, 1/16/2024, 1/17/2024, 1/19/2024
Edit: RCA 1/16/2024, 1/17/2024; CB 1/19/2024

OSIS File #: BE 9986 (NDA 218160)

eNSpect Assignment ID: 227627
eNSpect OpID: 258435

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/s/

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RUBEN C AYALA
01/19/2024 11:02:23 AM

CHARLES R BONAPACE
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10/10/2023

TO: Division of Oncology II (DO II)
Office of Oncologic Diseases (OOD)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 218160

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

Fortrea, Daytona Beach: The Office of Regulatory Affairs (ORA) conducted an inspection for the site in November 2022. The inspection was conducted under the following submission: BLA NON-RESPONSIVE

OSIS concluded that data from the reviewed studies were reliable.

Fortrea, Madison: The ORA conducted an inspection for the site in October 2022. The inspection was conducted under the following submission: BLA NON-RESPONSIVE

The following objectionable condition was observed:

- Failure to report to the sponsor autoinjector device defects or deficiencies identified during the study.

After review of the objectionable condition and the written response from the site, OSIS concluded that data from the reviewed studies were reliable (OSIS Final Review – October 2022).

Fortrea, Dallas: ORA conducted an inspection for the site in November 2022. The inspection was conducted under the following submission: BLA NON-RESPONSIVE

The following discussion item was discussed:

- Clinical laboratory reports for some subject visits were not documented as reviewed by the clinical investigator.

After review of the inspection findings and the response from the site, OSIS recommended that the review division consider evaluating the clinical laboratory reports from the impacted subjects to determine if their reported safety assessments are accurate.

Anaheim Clinical Trials, Anaheim: ORA conducted a Remote Regulatory Assessment (RRA) for the site in February 2022. The RRA was conducted under the following submission: BLA NON-RESPONSIVE .

The following items were discussed with the site:

1. Failure to report adverse events and concomitant medications for multiple subjects.
2. Sporadic data transcription errors and concerns regarding legibility of progress notes.
3. One subject was enrolled and dosed prior to completing all screening assessments.

After review of the inspection findings and the site's response, OSIS concluded that data from the reviewed study were reliable. However, OSIS recommended that the review division evaluate the impact of the unreported adverse events on subject safety, the inclusion of data from one ineligible subject on pharmacokinetic and immunogenicity assessments, and the use of concomitant medications by three subjects on the reliability of study data (OSIS Review - February 2022 RRA).

(b) (4): OSIS conducted an RRA for the site in (b) (4). The RRA was conducted under the following submissions: NON-RESPONSIVE.

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Fortrea, Inc.	1900 Mason Avenue, Suite 140, Daytona Beach, FL
Clinical	Fortrea, Inc.	3402 Kinsman Boulevard, Madison, WI
Clinical	Fortrea, Inc.	1341 West Mockingbird Lane, Suite 200E, 700E, and 800E, Dallas, TX
Clinical	Anaheim Clinical Trials, LLC.	2441 West La Palma Avenue, Suite 140, Anaheim, CA
Analytical	(b) (4)	

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