

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210861Orig1s000

211710Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
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 14, 2018
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 211710
Product Name and Strength: Vitrakvi (larotrectinib) Oral Solution, 20mg/mL
Applicant/Sponsor Name: Loxo Oncology, Inc. (Loxo)
FDA Received Date: November 2, 2018^a
OSE RCM #: 2018-483-4
DMEPA Safety Evaluator: Colleen Little, PharmD
DMEPA Acting Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised Instructions for Use (IFU) for Vitrakvi (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.^b

2 CONCLUSION

The revised IFU for Vitrakvi is acceptable from a medication error perspective. We have no further recommendations at this time.

^a All container label, carton labeling, Instructions for Use, and Prescribing Information for the oral solution (NDA 211710) were only submitted under NDA 210861.

^b Little C. Label and Labeling Review Memo for Vitrakvi (NDA 211710). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 24. RCM No.: 2018-483-3.

APPENDIX A. IFU RECEIVED ON NOVEMBER 2, 2018

Available from: \\cdsesub1\evsprod\nda210861\0060\m1\us\11413-instructions-for-use.pdf

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/s/

COLLEEN L LITTLE
11/14/2018

SEVAN H KOLEJIAN
11/14/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: October 24, 2018
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 211710
Product Name and Strength: Vitrakvi (larotrectinib) Oral Solution, 20mg/mL
Applicant/Sponsor Name: Loxo Oncology, Inc. (Loxo)
FDA Received Date: October 17, 2018^a
OSE RCM #: 2018-483-4
DMEPA Safety Evaluator: Colleen Little, PharmD
DMEPA Acting Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised Instructions for Use (IFU) for Vitrakvi (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.^b

2 CONCLUSION

The revised IFU is unacceptable from a medication error perspective. We find the IFU can be improved for clarity as described in Section 3.

3 RECOMMENDATIONS FOR LOXO

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

- A. Instructions for Use

^a All container label, carton labeling, Instructions for Use, and Prescribing Information for the oral solution (NDA 211710) were only submitted under NDA 210861.

^b Little C. Label and Labeling Review Memo for Vitrakvi (NDA 201861 and NDA 211710). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 10. RCM No.: 2017-2588-2 and 2018-483-2

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/s/

COLLEEN L LITTLE
10/24/2018

SEVAN H KOLEJIAN
10/24/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: October 10, 2018

Requesting Office or Division: Division of Oncology Products 2 (DOP2)

Application Type and Number: NDA 210861 (capsules) and NDA 211710 (oral solution)

Product Name and Strength: Vitrakvi (larotrectinib) Capsules, 25 mg and 100 mg
Vitrakvi (larotrectinib) Oral Solution, 20 mg/mL

Applicant/Sponsor Name: Loxo Oncology, Inc. (Loxo)

FDA Received Date: September 18, 2018, September 25, 2018, and September 28, 2018^a

OSE RCM #: 2017-2588-2 and 2018-483-2

DMEPA Safety Evaluator: Colleen Little, PharmD

DMEPA Acting Team Leader: Sevan Kolejian, PharmD, MBA

^a All container label, carton labeling, Instructions for Use, and Prescribing Information for the oral solution (NDA 211710) were only submitted under NDA 210861.

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels for Vitrakvi (Appendix A) and Instructions for Use (IFU) for Vitrakvi oral solution (Appendix B) 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.^b

2 DISCUSSION AND CONCLUSION

The revised container labels for Vitrakvi are acceptable from a medication error perspective.

We note that Loxo has determined that human factors (HF) studies are not needed to validate the IFU for Vitrakvi oral solution and provided justification on September 28, 2018^c. We found Loxo's justification acceptable. However, we determined that the revised IFU for Vitrakvi oral solution can be improved for clarity and to promote the safe use of Vitrakvi oral solution as described in Section 3.

3 RECOMMENDATIONS FOR LOXO ONCOLOGY, INC.

We recommend the following be implemented prior to approval of NDA 211710:

A. Instructions for Use

1. Please see Appendix B for our IFU recommendations in track changes.

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^b Little C. Label and Labeling Review Memo for Vitrakvi (NDA 201861 and NDA 211710). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 10. RCM No.: 2017-2588-1 and 2018-483-1.

^c Loxo Oncology, Inc. NDA 211710 Vitrakvi Response to Information Request: DMEPA. San Francisco (CA): Loxo Oncology, Inc.; 2018 SEP 28

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/s/

COLLEEN L LITTLE
10/10/2018

SEVAN H KOLEJIAN
10/10/2018

**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: October 4, 2018

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name), Dosage Form and Route, Application Type/Number: VITRAKVI (larotrectinib) capsules, for oral use, NDA 210861
VITRAKVI (larotrectinib) solution, for oral use, NDA 211710

Applicant: Loxo Oncology, Inc.

1 INTRODUCTION

On March 26, 2018, Loxo Oncology, Inc. submitted for the Agency's review two original New Drug Applications (NDA) 210861 for VITRAKVI (larotrectinib) capsules and NDA 211710 for VITRAKVI (larotrectinib) solution, which are considered New Molecular Entities (NMEs). The purpose of these NDA's is to seek approval of VITRAKVI (larotrectinib) capsules and VITRAKVI (larotrectinib) solution, for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion.

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 Products 2 (DOP2) on May 4, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VITRAKVI (larotrectinib) capsules and VITRAKVI (larotrectinib) solution, and proposed Instructions for Use (IFU) for VITRAKVI (larotrectinib) solution.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on August 21, 2018.

2 MATERIAL REVIEWED

- Draft VITRAKVI (larotrectinib) capsules and VITRAKVI (larotrectinib) solution Patient Package Insert (PPI) received on March 26, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 27, 2018.
- Draft VITRAKVI (larotrectinib) solution Instructions for Use (IFU) received on July 9, 2018, further revised on August 9, 2018 and September 25, 2018, and received by DMPP and OPDP on September 26, 2018.
- Draft VITRAKVI (larotrectinib) capsules prescribing Information (PI) received on March 26, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 27, 2018

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 APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI using Arial font, size 10 and the IFU using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

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

4 CONCLUSIONS

The PPI and IFU are 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 and IFU 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 and IFU.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
10/04/2018

KEVIN WRIGHT
10/04/2018

LASHAWN M GRIFFITHS
10/04/2018

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

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

Memorandum

Date: September 12, 2018

To: Patricia Keegan, M.D., Director
Division of Oncology Products 2 (DOP2)

Idara Udoh, MS, Regulatory Project Manager, DOP2

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Vitrakvi™ (larotrectinib) capsules, for oral use and oral solution

NDA: 210861 and 211710

In response to Division of Oncology Products 2 (DOP2) consult request dated May 4, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Vitrakvi™ (larotrectinib) capsules, for oral use and oral solution.

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DOP2 (Idara Udoh) on August 27, 2018, and we have no comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 29, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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/s/

KEVIN WRIGHT
09/13/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: September 10, 2018

Requesting Office or Division: Division of Oncology Products 2 (DOP2)

Application Type and Number: NDA 210861 (capsules) and NDA 211710 (oral solution)

Product Name and Strength: Vitrakvi (larotrectinib) Capsules, 25 mg and 100 mg
Vitrakvi (larotrectinib) Oral Solution, 20 mg/mL

Applicant/Sponsor Name: Loxo Oncology, Inc. (Loxo)

FDA Received Date: August 29, 2018^a

OSE RCM #: 2017-2588-1 and 2018-483-1

DMEPA Safety Evaluator: Colleen Little, PharmD

DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

^a All container label, carton labeling, Instructions for Use, and Prescribing Information for the oral solution (NDA 211710) were only submitted under NDA 210861.

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Vitrakvi (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.^b

2 DISCUSSION AND CONCLUSION

Loxo previously proposed (b) (4)
(b) (4)

Loxo is proposing to change (b) (4)
(b) (4)

(b) (4). In addition, Loxo is proposing (b) (4)
(b) (4). Loxo intends to revise the Instructions for Use (IFU) to include instructions for inserting the adaptor and oral syringe cleaning instructions. We recommend that Loxo submit the proposed revised IFU for review.

The revised Vitrakvi container labels are unacceptable from a medication error perspective. We find the container labels can be improved for clarity as described in Section 3.

3 RECOMMENDATIONS FOR LOXO ONCOLOGY

We recommend the following be implemented prior to approval of this of NDA 210861 and NDA 211710:

- A. Container Labels (Capsules)
 - a. Remove the statement (b) (4) as this is not required information and adds clutter to the label. The route of administration is only required per 21 CFR 201.100(b)(3) if the product is not for oral use.
- B. Container Labels (Oral Solution)
 - a. Remove the statement (b) (4) for clarity and to decrease clutter on the label.
 - i. Ensure the (b) (4) "100 mL," remains on the principal display panel in accordance with 21 CFR 201.51.
- C. Instructions for Use (IFU)
 - a. We note you plan on revising the product IFU to include instructions for inserting the adaptor and oral syringe cleaning instructions. We recommend you submit revised IFU, including the images you intend to use, for review.

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^b Little C. Label and Labeling Review for Vitrakvi (NDA 201861 and NDA 211710). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 21. RCM No.: 2017-2588 and 2018-483.

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/s/

COLLEEN L LITTLE
09/10/2018

SEVAN H KOLEJIAN
09/10/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	August 21, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 210861 (capsules) and NDA 211710 (oral solution)
Product Name and Strength:	Vitakvi (larotrectinib) Capsules, 25 mg and 100 mg Vitakvi (larotrectinib) Oral Solution, 20 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Loxo Oncology, Inc. (Loxo)
FDA Received Date:	March 26, 2018, June 15, 2018, and July 9, 2018 ^a
OSE RCM #:	2017-2588 and 2018-483
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

^a All container label, carton labeling, Instructions for Use, and Prescribing Information for the oral solution (NDA 211710) were only submitted under NDA 210861.

1 REASON FOR REVIEW

As part of NDA 210861 and NDA 211710, this review evaluates the proposed Vitrakvi prescribing information (PI), container labels, carton labeling, and Instructions for Use (IFU) to identify areas of vulnerability that could 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 Label and Labeling 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 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

Loxo proposes to utilize 1 PI for both the capsules and oral solution formulation of Vitrakvi.

Our review of the materials found the proposed Vitrakvi PI, container labels, carton labeling, and IFU may be improved to promote safe use of this product.

During an internal meeting on June 21, 2018, CMC stated that based on stability data provided by the Applicant, Vitrakvi oral solution would have a ^(b)₍₄₎ day in use period. Additionally, Loxo proposed ^(b)₍₄₎. We acknowledge the proposed IFU instructs ^(b)₍₄₎ to discard unused Vitrakvi oral solution ^(b)₍₄₎ days after opening the bottle, however, the proposed PI, oral solution container labels, and oral solution carton labeling do not include this information. Therefore, we provide recommendations related to a ^(b)₍₄₎-day in use period for Vitrakvi oral solution.

(b) (4)

^(b)₍₄₎. At the time of this review, the Review Team is still under discussion

with Loxo with regards to this proposed (b) (4). DMEPA will continue to be involved in these discussions.

4 CONCLUSION & RECOMMENDATIONS

We conclude the proposed PI, container labels, carton labeling, and IFU for Vitrakvi may be improved to promote the safe use of the product as described in Section 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Please see Appendix H for our PI recommendations in track changes.

4.2 RECOMMENDATIONS FOR LOXO ONCOLOGY, INC.

We recommend the following be implemented prior to approval of NDA 210861 and NDA 211710:

A. General Comments (Capsules and Oral Solution Container labels & Carton Labeling)

1. Identify the location and header of the lot number and expiration date on the container labels and carton labeling.
 - a. Ensure the lot number and expiration date are clearly differentiated from one another and are not located in close proximity to other numbers where the numbers can be mistaken as the lot number.^{b,c}
 - b. For the expiration date, we recommend using a format such as MMMYYYY (e.g. JAN2019) or MMMDDYYYY (e.g. JAN312019) to minimize confusion and reduce the risk for deteriorated drug medication errors.^a
2. Consider revising the product code in the NDC number to ensure that the middle 3 or 4 digits are non-sequential (-0390-, -0391-, -0392-). The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the product code is not a differentiating feature. If for some reason, the middle digits cannot be revised, consider increasing the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example, XXXX-**XXXX**-XX.^d

^b Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

^c Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

B. Container Labels and Carton Labeling (Capsules)

1. Consider relocating the equivalency statement to the area of the label bearing the logo to decrease clutter and improve the readability of more important product information.

C. Container Labels (Capsules)

1. Relocate the net quantity statement away from the product strength (e.g., increase white space in between the net quantity and strength statements, or relocate to after the Rx only statement). From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.^c
2. Consider revising the statement (b) (4) (b) (4) to Usual Dosage: See prescribing information.” to ensure consistency with carton labeling and to reduce clutter.

The example layout below demonstrates our recommendations only (not to size, spacing, color, etc.).



D. Carton Labeling (Capsules)

1. Consider removing the (b) (4) on the bottom of panels. We note across Bayer's prescription oral product line, there are inconsistencies in the product information provided in this (b) (4) format (e.g., Yasmin and Stivarga).

E. Container labels & Carton Labeling (Oral Solution)

1. Include the statements "Date of first opening __/__/__. Discard unused portion (b) (4) days after first opening." in bold font under storage information on the container label and carton labeling. Additionally, the "__/__/__" statement will alert the users to write a complete date (month, day, and year) on the container label and carton labeling.
2. Consider relocating the equivalency statement to the area of the label bearing the logo to decrease clutter and improve the readability of more important product information.
3. Bold and relocate the statement "Store at 2°C to 8°C (36°F to 46° F)." to immediately follow the statement, "Keep refrigerated." to increase the prominence of all presented storage information and minimize the risk of part of the storage information being overlooked.

F. Container Labels (Oral Solution)

1. Add the net quantity statement to the principal display panel in accordance with 21 CFR 201.51. Ensure that the net quantity statement is located away from the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.^c
2. Consider revising the statement (b) (4) (b) (4) to Usual Dosage: See prescribing information." to ensure consistency with carton labeling and to reduce clutter.

The example layout below demonstrates our recommendations only (not to size, spacing, color, etc.).



G. Carton labeling (Oral Solution)

1. Consider removing the (b) (4) from the grey shaded box on the bottom of p (b) (4) cription oral product line, there are inconsistencies in the product information provided in this (b) (4) (b) (4) format (e.g., Yasmin and Stivarga).

H. Instructions for Use

1. Please see Appendix I for our IFU recommendations in track changes.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vitrakvi received on June 15, 2018 from Loxo Oncology, Inc.

Table 2. Relevant Product Information for Vitrakvi	
Initial Approval Date	N/A
Active Ingredient	Larotrectinib
Indication	For the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion.
Route of Administration	Oral
Dosage Form	Capsules and Oral solution
Strength	Capsules: 25 mg and 100 mg Oral solution: 20 mg/mL
Dose and Frequency	Adult: 100 mg taken orally, twice daily until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Pediatric (1 month to 18 years): 100 mg/m ² taken orally, twice daily with a maximum of 100 mg per dose until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.
How Supplied	Capsules: 60 count bottles Oral solution: 100 mL bottle
Storage	Capsules: at room temperature 20°C to 25°C (68° F to 77° F); temperature excursions between 15° C and 30° C (59° F to 86° F) are permitted [see USP Controlled Room Temperature]. Oral Solution: Refrigerate solution at 2° to 8° C (36° to 46° F). Do not freeze.
Container Closure	Capsules 25 mg: (b) (4) HDPE bottle with a (b) (4) cap (b) (4) 100 mg: (b) (4) HDPE bottle with a (b) (4) cap (b) (4) Oral Solution 100 mL (b) (4) Bottle, (b) (4) and capped with (b) (4) child resistant (b) (4) closure (b) (4).

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,^e along with postmarket medication error data, we reviewed the following Vitrakvi labels and labeling submitted by Loxo Oncology Inc.

- Container label received on March 26, 2018
- Carton labeling received on March 26, 2018
- Instructions for Use (Image not shown) received on July 9, 2018
- Prescribing Information (Image not shown) received on June 15, 2018
- Physical sample of oral solution container (not shown) received on July 10, 2018

G.2 Label and Labeling Images

Container Labels



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^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

COLLEEN L LITTLE
08/21/2018

CHI-MING TU
08/21/2018

Clinical Inspection Summary

Date	August 14, 2018
From	Navid Homayouni, M.D., Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Idara Udoh, M.S., Regulatory Project Manager Leigh Marcus, M.D., Clinical Reviewer Martha Donoghue, M.D., Cross Discipline Team Leader Division of Oncology Products 2
NDA #	210861 and 211710
Applicant	Loxo Oncology, Inc.
Drug	Larotrectinib
NME (Yes/No)	Yes
Therapeutic Classification	Priority
Proposed Indication(s)	Treatment of patients with unresectable or metastatic solid tumors with NTRK fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior therapy or who have no alternative therapy.
Consultation Request Date	March 26, 2018
Summary Goal Date	August 15, 2018
Action Goal Date	November 26, 2018
PDUFA Date	November 26, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study Protocol LOXO-TRK-15002 was submitted to FDA in support of a proposed indication for NDA 210861(Larotrectinib capsule) and NDA 211710 (Larotrectinib solution). This was a Phase 2, multi-center, open-label study of patients with advanced solid tumor cancer harboring NTRK fusion proteins. The data for LOXO-TRK-15002 submitted by the Sponsor to the Agency in support of NDA 210861 and NDA 211710 appear reliable based on available information from the inspections of two domestic clinical sites, the Contract Research Organization (CRO) for blinded central review and the Sponsor.

Two clinical sites, Dr. Alexander Drilon, M.D. (Site 101) and Dr. David Hong, M.D. (Site 104), the CRO, (b) (4), and the Sponsor, Loxo Oncology were selected for audit.

There were no significant inspectional observations for the clinical investigators, Dr. Alexander Drilon, M.D. and Dr. David Hong, M.D., the CRO, (b) (4) and the

Sponsor, Loxo Oncology, and the final compliance classification for these inspections is No Action Indicated (NAI).

II. BACKGROUND

Loxo Oncology Inc., as sponsor of NDA 210861 and NDA 211710 seeks priority approval for the use of larotrectinib for the treatment of patients with unresectable or metastatic solid tumors with NTRK fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments. The TRKs play a key role in central nervous system (CNS) and peripheral nervous system development as well as in cell survival. Fusions represent a class of genetic alterations involving NTRK that have known oncogenic and transforming potential. The resultant fusion protein is both aberrantly expressed and has constitutive activation of the kinase domain, resulting in activation of oncogenic downstream pathways.

LOXO-TRK-15002 is an ongoing Phase 2 basket study of the oral TRK inhibitor larotrectinib in subjects with NTRK fusion positive tumors. The study included a screening period, a treatment period, a safety follow-up visit, and long-term follow-up (LTFU) assessments. Safety, survival, and subsequent anticancer therapies were tracked in the LTFU period.

The first patient was enrolled on October 13, 2015. The data cut-off for interim analysis was July 17, 2017. The study included 8 cohorts of patients with tumors bearing NTRK fusions, including non-small cell lung cancer (NSCLC), thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, and primary CNS tumor, and a cohort that enrolled patients of all other histologic types or patients without measurable disease. To allow for consistency in the collection and analysis of data across the development program for larotrectinib, the Sponsor harmonized key eligibility, safety, and efficacy assessments for Studies LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003, while making provisions for centralized review of radiology scans and collection of tumor specimens for all patients with NTRK fusion cancers.

Patients must have had at least one measurable lesion as defined by RECIST v1.1 or RANO criteria for primary CNS tumors. Patients without measurable disease (evaluable disease only) were eligible for enrollment to Cohort 8, regardless of tumor type.

Larotrectinib was administered to patients at 100 mg twice daily and cycles were in 28-day increments. The only dose modifications allowed were reductions for management of toxicities, and dose re-escalation was allowed. No dose escalation above 100 mg BID was permitted. Patients were evaluated radiographically at the end of Cycle 2, and every other cycle for the first 12 months and every 3 cycles thereafter; additional assessments could be ordered by the Investigator. Patients with primary CNS disease underwent radiographic evaluation of their disease at the end of each cycle between Cycle 1 to Cycle 4, and every 2 cycles between Cycle 5 to Cycle 12, and every 3 cycles thereafter. Patients continued dosing of larotrectinib until disease progression, unacceptable toxicity, patient withdrawal of consent, or death. Patients with progressive disease could continue larotrectinib if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study drug, and continuation of treatment was approved by the Sponsor.

The primary endpoint was overall response rate (ORR) by independent radiology review and measured by the proportion of subjects with best overall confirmed response of complete response (CR) or partial response (PR) by RECIST or RANO criteria, as appropriate, following treatment with larotrectinib for each tumor-specific disease cohorts.

LOXO-TRK-15002 was conducted at 37 sites worldwide. As of the interim data cut-off date, a total of 47 patients had been enrolled and received at least 1 dose of the study drug. Patients were enrolled to 1 of 8 tumor-defined cohorts, as categorized by the Investigator: NSCLC (3 patients), thyroid cancer (5 patients), sarcoma (11 patients), colorectal (6 patients), salivary gland cancer (10 patients), biliary cancer (2 patients), primary CNS cancer (2 patients), and a collective group of other cancers (8 patients) comprising patients with cancer of the appendix (1), breast (1), melanoma (4), pancreas (1), and non-measurable salivary gland cancer (1). Study drug had been discontinued in 17 patients. Of these, the majority discontinued treatment for the reason of disease progression

GCP inspection was conducted at two clinical investigator (CI) sites, the CRO and the Sponsor. The CI sites for inspection were chosen because of high enrollment and high study drug efficacy rates.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # # of Subjects	Inspection Dates	Classification
Alexander Drilon, M.D. Site Number: 101 1275 York Avenue New York, NY 10065	Study: LOXO-TRK-15002 Enrolled: 18	May 14-17, 2018	NAI
David Hong, M.D. Site Number: 104 1515 Holcombe Blvd Houston, TX 77030	Study: LOXO-TRK-15002 Enrolled: 8	May 2-4 and 7, 2018	NAI
CRO: (b) (4) (b) (4)	Study: LOXO-TRK-15002	June 4-7, 2018	NAI
Sponsor: Loxo Oncology, Inc. 701 Gateway Blvd Suite 420 South San Francisco, CA 94080	Study: LOXO-TRK-15002	April 25-27 and May 2, 2018	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Alexander Drilon, M.D. (Site 101)

The site screened 23 subjects and 18 were enrolled into the study. Nine (9) subjects completed the study and 1 withdrew consent. Eight (8) subjects were in follow up. An inspection of all enrolled subject's records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, the inspection included review of IRB approvals, subject eligibility, study monitoring, concomitant medications, case report forms, drug accountability, staff training logs, protocol deviations, primary endpoint, safety data and adverse events reporting to determine overall protocol compliance. Study source documents and records of the inspected subjects were compared to the data listings and the electronic Case Report Forms (eCRF) and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The primary efficacy endpoint data, ORR, as determined by the Investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 101 appear reliable based on available information.

2. David Hong, M.D. (Site 104)

The site screened 9 subjects and 8 were enrolled into the study. One (1) subject completed the study and 7 were in active treatment. An audit of all enrolled subject's records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, the inspection included review of study subject eligibility criteria, safety and data monitoring, test article accountability, institutional review board/institutional ethics committee (IRB/IEC) and sponsor correspondence, protocol deviations, primary endpoints, safety data and adverse event reports to determine the site's adherence with the applicable regulations for the investigational products as well as overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and eCRF and found to be the same.

There were no significant inspectional observations noted and no Form FDA-483, Inspectional Observations, was issued. The primary efficacy endpoint data, ORR, as determined by the Investigator, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 104 appear reliable based on available information.

3. (b) (4) (CRO)

(b) (4) had been contracted to perform central reads per RECIST v1.1 or RANO criteria for NTRK fusion patients enrolled in Study Protocol LOXO-TRK-15002 with evaluable solid tumors. The central reviews were conducted per (b) (4) (b) (4) to support the primary endpoint of confirmed objective response (CR, PR).

The inspection included a review of the firm's training program, standard operating procedures

and policies, data collection and handling, the firm's Trial Master Files (TMF) and primary endpoint verification. Twenty-five (25) subject's records from three clinical sites (101, 104 and 114) were reviewed for the best overall response for each cycle against the data listings and found to be the same.

The inspection revealed no evidence of CRO non-compliance with the Charter/investigational plan and no Form FDA-483, Inspectional Observations, was issued. The primary efficacy endpoint data, ORR, as determined by the IRC assessment, were verifiable. The overall conduct of the CRO appeared to be in compliance with good clinical practice. The data from [REDACTED]^{(b) (4)}, associated with Study Protocol LOXO-TRK-15002 appear reliable based on available information.

4. Loxo Oncology, Inc. (Sponsor)

The inspection was issued to review the conduct of Study Protocol LOXO-TRK-15002 performed in support of the application. The inspection included a review of the financial disclosures, standard operation procedures and policies, training and monitoring records, safety and adverse event reporting, data collection and handling, and electronic records management.

The inspection found no major deficiencies that would impact data integrity or subject safety. A form FDA 483, Inspectional Observation was not issued. There was appropriate oversight and management of the clinical trial. There was no evidence of under reporting of AEs. For sites 101 and 104, the primary endpoint data was compared to the Sponsor submitted data listings and found to be the same.

Overall, the Sponsor appeared to adequately verify that the clinical investigation was conducted in accordance with the investigational plan and that responsibilities of the clinical investigators were carried out. The data from Loxo Oncology, Inc., associated with Study Protocol LOXO-TRK-15002, appear reliable based on available information.

{See appended electronic signature page}

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

CONCURRENCE:

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OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Navid Homayouni
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

NAVID R HOMAYOUNI
08/14/2018

PHILLIP D KRONSTEIN
08/14/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	NDA 210861
Brand Name	
Generic Name	Larotrectinib (LOXO-101)
Sponsor	Loxo Oncology, Inc.
Indication	Treatment of patients with unresectable or metastatic solid tumors
Dosage Form	Capsule
Drug Class	Tropomyosin-related kinase (TRK) inhibitor
Therapeutic Dosing Regimen	100 mg BID
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Unknown (maximum dose studied 200 mg QD)
Submission Number and Date	004, 1/22/2018
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolonging effect of larotrectinib (100 to 900 mg single dose) was detected in this QT study.

The effect of larotrectinib has been evaluated in healthy adult male subject over a wide dose range (100 to 900 mg). This study did not include a positive control, however the requirement for inclusion of a positive control can be waived if the study includes doses resulting in exposures that are 2-fold higher than the worst-case exposure scenario (ICH E14 Q&A (R3) 5.1). The highest dose in this study (900 mg) resulted in a C_{max} that is ~7.8-fold higher than the C_{max} for the highest recommended therapeutic dose (100 mg BID) and ~2.8-fold higher than the suprathreshold exposure scenario (co-administration with a strong CYP3A4 and P-gp inhibitor).

Concentration-QTc analysis of the healthy volunteer study showed an absence of relationship between larotrectinib concentration and QTc with a two-sided upper 90% confidence interval below 10 ms (section 5.3). These findings are further supported by preclinical data (hERG assay and preclinical CV safety studies).

2 PROPOSED LABEL

The Sponsor included the following language in the proposed label:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

The following is QT-IRT's proposed labeling language based on the clinical pharmacology labeling guidance, which is a suggestion only. We defer final labeling decisions to the Division.

At a dose 9 times the maximum approved recommended dose, [TRADENAME] does not prolong the QT to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Larotrectinib is a potent and highly selective inhibitor of tropomyosin receptor kinases (TRK), with activity against the TRK family of proteins TRKA, TRKB, and TRKC. Chromosomal rearrangements involving the genes NTRK1, NTRK2, and NTRK3 which encode these TRK proteins, result in the formation of oncogenic TRK fusion proteins. These chimeric proteins activate downstream signaling pathways and have transformative oncogenic potential. In both purified enzyme and cellular assays, larotrectinib demonstrated potent inhibitory activity against TRKA, TRKB, and TRKC at low nanomolar concentrations (IC₅₀ 1-59 nM).

3.2 MARKET APPROVAL STATUS

Larotrectinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Larotrectinib had an IC₅₀ value of 147 µM in the human ether-à-go-go-related gene (hERG) assay (Module 2.6.2.4.1.2), which is approximately 230-fold higher than the maximum unbound concentration (C_{max}(unbound) = 640 nM) in patients administered 100 mg BID. No changes were noted in ECG parameters, including corrected QT interval (QTc), in any of the non-clinical studies (Module 2.6.2.4.2.1). Together, these data indicate that larotrectinib has a low risk.

3.4 CLINICAL EXPERIENCE

Overall, almost all patients experienced at least 1 treatment-emergent AE during the study. Those reported in ≥ 5% of patients are presented in Table 15, by maximum severity (Grades 1-4), for each of the analysis sets. The most common AEs for the overall analysis set were fatigue (37%), nausea (28%), dizziness (26%), anemia, vomiting (both 25%), and AST increase (24%). Differences > 10% between the Efficacy-evaluable NTRK fusion analysis set and the overall analysis set of any grade were seen for AST

increase (36% vs 24%), ALT increase (36% vs 21%), diarrhea (29% vs 19%) and weight increase (24% vs 13%).

Mean values and changes from baseline for ECG measurements are summarized in Table 14.4.24.04 and shifts from baseline are summarized in Table 14.4.25.2. There were no clinically important mean changes for ECG measurements from baseline to last postbaseline value.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of larotrectinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 121211 (DARRTS [01/03/2017](#)). The protocol review recommended inclusion of a 24 h time-point and noted that insufficient information had been provided to comment on the dose selection and raised concerns about study interpretability if the study was terminated after the 3rd cohort (cohorts 4 through 6 were previously listed as optional). As noted later, the study report addresses all these concerns.

The sponsor submitted the study report for larotrectinib, including electronic datasets and waveforms to the ECG warehouse.

4.2 QT STUDY

4.2.1 Title

A Phase 1, Single Ascending Dose, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Cardiac Effect, and Pharmacokinetics of LOXO-101 in Healthy Adult Subjects.

4.2.2 Protocol Number

LOXO-TRK-16009

4.2.3 Study Dates

April-01-2017 to July-25-2017

4.2.4 Objectives

Primary:

- To assess the safety and tolerability of single oral doses of LOXO-101 when administered to healthy adult subjects.
- To evaluate the effects of single oral doses of LOXO-101 on the heart rate (HR) corrected QT (QTc) interval by assessing concentration-QT (C-QT) relationship using exposure-response modelling.

Secondary:

- To assess the pharmacokinetics (PK) of single oral doses of LOXO-101 when administered to healthy adult subjects.

- To assess the effect of single oral doses of LOXO-101 on other electrocardiogram (ECG) parameters including QTc (time based), QT, PR, and RR intervals, QRS duration, and HR.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, double-blind, placebo-controlled, SAD study conducted at 1 study center in the US. Screening of subjects occurred within 28 days prior to dosing. There were 6 cohorts of 8 subjects (6 active and 2 placebo in each cohort) dosed for evaluation. There were at least 2 females in each cohort, at least one of whom was assigned to receive the active drug.

4.2.5.2 Controls

The sponsor used a placebo control.

4.2.5.3 Blinding

This was a double-blind, placebo controlled study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Each planned dose level included 8 subjects with 2 subjects randomized to receive placebo and 6 subjects randomized to receive the active drug. The planned dose levels were as follows:

- Cohort 1: 100 mg LOXO-101 (1 x 100 mg capsule) or matching placebo (1 matching placebo capsule).
- Cohort 2: 200 mg LOXO-101 (2 x 100 mg capsules) or matching placebo (2 matching placebo capsules).
- Cohort 3: 400 mg LOXO-101 (4 x 100 mg capsules) or matching placebo (4 matching placebo capsules).
- Cohort 4: 600 mg LOXO-101 (6 x 100 mg capsules) or matching placebo (6 matching placebo capsules).
- Cohort 5: 900 mg LOXO-101 (9 x 100 mg capsules) or matching placebo (9 matching placebo capsules).
- Cohort 6: 1300 mg LOXO-101 (13 x 100 mg capsules) or matching placebo (13 matching placebo capsules).

Based on the data from 100, 200, 400, and 600 mg, it was estimated that the target C_{max} could be achieved with a dose of 900 mg. To avoid exposing patients to unnecessarily high doses of study drug, the decision was made not to administer the 1300 mg dose and thus 900 mg was selected as the highest dose for this study. The dose level of 1300 mg in Cohort 6 was replaced by a 700 mg dose to provide additional data at high LOXO-101 plasma levels to further define the dose-response.

Reviewer's Comment: Both LOXO-101 and placebo subjects in cohorts 5 and 6 received palonosetron to reduce any nausea and vomiting that may be caused by high doses of

LOXO-101 and/or due to swallowing a large pill. Based on a previous TQT study of palonosetron (DARRTS 08/06/2007), which included doses up to 2.25 mg of palonosetron, no QTc interval changes of 0.25 mg palonosetron are expected. Lastly, based on the label for palonosetron no PK interaction between palonosetron and larotrectinib is expected.

4.2.6.2 Sponsor's Justification for Doses

A 100 mg dose of LOXO-101 was selected as the starting dose in this single ascending dose (SAD) study as it is the clinical dose intended to be used in future studies and as the intended clinical therapeutic dose to be administered BID. At a minimum, single doses of up to 600 mg of LOXO-101 were planned to be administered to obtain a wide range of exposures for the C-QT response relationship analysis unless one of the Study Stopping Rules (refer to Section 10.5.5 of the protocol [Appendix 16.1.1]) were met that would prevent further dose escalation. By the time of completion of the 600 mg cohort, data were available that defined the potential increase in C_{max} with concomitant administration of 100 mg of LOXO-101 with a strong inhibitor of CYP3A4 in Study LOXO-TRK-16010, which was 2.81 fold (GMR, 90% CI 2.26 to 3.49 fold). Furthermore the C_{max} of LOXO-101 with steady-state dosing of 100 mg BID in cancer patients was determined to be 908 ng/mL (n=29). To explore the concentration-responses relationship of LOXO-101 plasma level and changes in QTc, doses greater than 600 mg were considered necessary to reach C_{max} that was two-fold greater than the “worst case” clinical exposure. This C_{max} was estimated by multiplying the cancer patient C_{max} under normal conditions (908 ng/mL) by the fold increase with a strong CYP3A4 inhibitor (2.81-fold) by an additional safety factor of 2, to obtain a target C_{max} in this study of approximately 5100 ng/mL (908 * 2.81 * 2). To obtain data on plasma concentration-versus-QT effect at these higher exposures that may be achieved in clinical use of LOXO-101, dosing up to 1300 mg was allowed per protocol, to obtain a sufficiently high multiple of the highest clinically relevant exposure (of at least approximately 2-fold the population-based C_{max} that would be expected in patients with cancer receiving a potent CYP 3A4 inhibitor), however based on the data from 100, 200, 400, and 600 mg, it was estimated that the target C_{max} could be achieved with a dose of 900 mg. To avoid exposing patients to unnecessarily high doses of study drug, the decision was made not to administer the 1300 mg dose and thus 900 mg was selected as the highest dose for this study. The dose level of 700 mg provided additional data at high LOXO-101 plasma levels to further define the dose-response.

Reviewer's Comment: Acceptable. The therapeutic C_{max} is ~908 ng/mL and the worst-case exposure scenario is co-administration with a strong CYP3A4 and P-gp inhibitor (2.81-fold increase in exposure) and the supratherapeutic exposure is therefore ~2551 ng/mL. The highest dose in this study is 900 mg, which resulted in exposures more than 2x supratherapeutic exposure and therefore supports waiving the requirement for inclusion of a positive control per ICH E14 Q&A (R3) section 5.1. Lastly, a major metabolite of LOXO-101 was observed in the mass balance study (~26% of plasma AUC), which appears to be renally eliminated and was observed to have a half-life of 5.6 h. Based on the mass balance study, the highest dose in this study (900 mg) is expected to cover the clinically relevant exposures at steady-state of this metabolite.

4.2.6.3 Instructions with Regard to Meals

A single oral dose was administered following an overnight fast on the morning of Day 1 at Hour 0 by the blinded clinic staff. Subjects fasted overnight for at least 10 hours prior to study drug administration, and continued the fast for at least 4 hours postdose. All study drugs were administered with approximately 240 mL of water.

Reviewer's Comment: Acceptable, food has not been observed to impact larotrectinib exposure.

4.2.6.4 ECG and PK Assessments

ECG: Predose (-0.66, -0.5 and -0.25 h) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post-dose

PK: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose

Reviewer's Comment: Acceptable, the ECG/PK collection includes T_{max} of larotrectinib (~1 h), the major metabolite M14 (~1 to 2 h) and up to 24 h post-dose to allow for detection of delayed effects as previously recommended (DARRTS [01/03/2017](#)).

4.2.6.5 Baseline

The average value of the 9 predose measurements was used as baseline.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 48 subjects entered the study and were randomized to study treatment; all 48 subjects completed the study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Assay Sensitivity

Sponsor did not provide any data or analysis on assay sensitivity.

4.2.8.2.2 Categorical Analysis

QTcF Interval

QTcF was classified into the following categories: > 450 to ≤ 480 msec; > 480 to ≤ 500 msec; and > 500 msec; and change from time-matched baseline for QTcF was classified as > 30 msec to ≤ 60 msec and > 60 msec. There were no QTcF values > 450 msec observed at baseline or post treatment on this study and no QTcF change from baseline greater than 30 msec.

QTcP Interval

QTcP was classified into the following categories: > 450 to ≤ 480 msec; > 480 to ≤ 500 msec; and > 500 msec; and change from time-matched baseline for QTcP was classified

as > 30 msec to ≤ 60 msec and > 60 msec. There were no QTcP values > 450 msec observed at baseline or post treatment on this study and no QTcF change from baseline greater than 30 msec.

PR Interval

PR interval was classified into the following category: increase-from-baseline $> 25\%$ resulting in PR > 220 msec. There were no PR interval values increase-from-baseline $> 25\%$ resulting in PR > 220 msec during the study.

QRS Interval

QRS interval was classified into the following category: increase-from-baseline $> 25\%$ resulting in QRS > 120 msec. There were no QRS interval values increased-from-baseline $> 25\%$ resulting in QRS > 120 msec during the study.

Heart Rate

HR was classified into the following categories: HR change-from-baseline $> 25\%$ decrease resulting in a HR < 50 bpm and HR change-from-baseline $> 25\%$ increase resulting in a HR > 100 bpm. There were no HR values that fell into the above categories during the study.

4.2.8.3 Safety Analysis

There were no deaths, SAEs, or subject discontinuations due to AEs in this study. Overall, a total of 30 TEAEs were reported by 12 (33%) active treatment subjects and 2 (17%) placebo subjects in this study. There was generally a higher incidence of TEAEs in the higher dose groups, and no AEs were reported following palonosetron alone when given as premedication prior to dosing with 700 mg LOXO-101 or 900 mg LOXO-101. One (1) AE of headache following 700 mg LOXO-101 was Grade 2 (moderate) in severity, and the remaining AEs were Grade 1 (mild). The PI considered 12 AEs related to LOXO-101/Placebo, 14 AEs related to LOXO-101/Placebo and palonosetron, and 4 AEs not related to LOXO-101/Placebo or palonosetron.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 1. C_{\max} for the highest dose (900 mg) is ~ 7.8 -fold higher than the anticipated clinically C_{\max} (908 ng/mL) and ~ 2.8 -fold higher than the expected supratherapeutic exposure (2551 ng/mL).

Table 1: Summary of larotrectinib PK following single doses of 100 to 900 mg

Pharmacokinetic Parameters	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Treatment F
AUC _{0-t} (ng*hr/mL)	1502 (47.1) [n=6]	2700 (56.3) [n=6]	6693 (38.0) [n=6]	16640 (27.7) [n=6]	23830 (37.8) [n=6]	18820 (14.1) [n=6]
AUC _{0-inf} (ng*hr/mL)	1511 (47.1) [n=6]	2728 (55.6) [n=6]	6730 (38.1) [n=6]	16720 (27.7) [n=6]	23900 (37.7) [n=6]	18890 (14.0) [n=6]
AUC%extrap	0.6017 ± 0.21306 [n=6]	1.033 ± 1.4724 [n=6]	0.5462 ± 0.44729 [n=6]	0.4857 ± 0.31042 [n=6]	0.2536 ± 0.19213 [n=6]	0.3752 ± 0.20201 [n=6]
C _{max} (ng/mL)	460.4 (67.6) [n=6]	1097 (45.5) [n=6]	2308 (52.4) [n=6]	4557 (41.2) [n=6]	7133 (31.9) [n=6]	4608 (23.0) [n=6]
T _{max} (hr)	1.050 (0.56, 2.05) [n=6]	1.053 (0.55, 2.06) [n=6]	0.806 (0.55, 1.07) [n=6]	1.058 (1.05, 1.55) [n=6]	1.079 (0.56, 2.06) [n=6]	1.052 (1.05, 1.57) [n=6]
K _{el} (1/hr)	0.2261 ± 0.10295 [n=6]	0.2064 ± 0.082634 [n=6]	0.1985 ± 0.048117 [n=6]	0.2133 ± 0.019149 [n=6]	0.2498 ± 0.043436 [n=6]	0.2290 ± 0.053281 [n=6]
T _{1/2} (hr)	3.428 ± 0.9828 [n=6]	4.106 ± 2.4964 [n=6]	3.636 ± 0.7165 [n=6]	3.275 ± 0.3240 [n=6]	2.841 ± 0.4681 [n=6]	3.200 ± 0.9094 [n=6]
Treatment A: Single Oral Dose of 100 mg LOXO-101 Treatment B: Single Oral Dose of 200 mg LOXO-101 Treatment C: Single Oral Dose of 400 mg LOXO-101 Treatment D: Single Oral Dose of 600 mg LOXO-101 Treatment E: Single Oral Dose of 900 mg LOXO-101 and 30-second intravenous infusion of 0.25 mg palonosetron Treatment F: Single Oral Dose of 700 mg LOXO-101 and 30-second intravenous infusion of 0.25 mg palonosetron AUCs and C _{max} are presented as geometric mean and geometric CV%. T _{max} values are presented as Median (Minimum, Maximum). Other parameters are presented as arithmetic mean ± SD. Source: Tables 14.2.2.1.8 through 14.2.2.1.13 Program: /CA19103/sas_prg/pksas/adam_intext_pkparam.sas 10OCT2017 12:21						

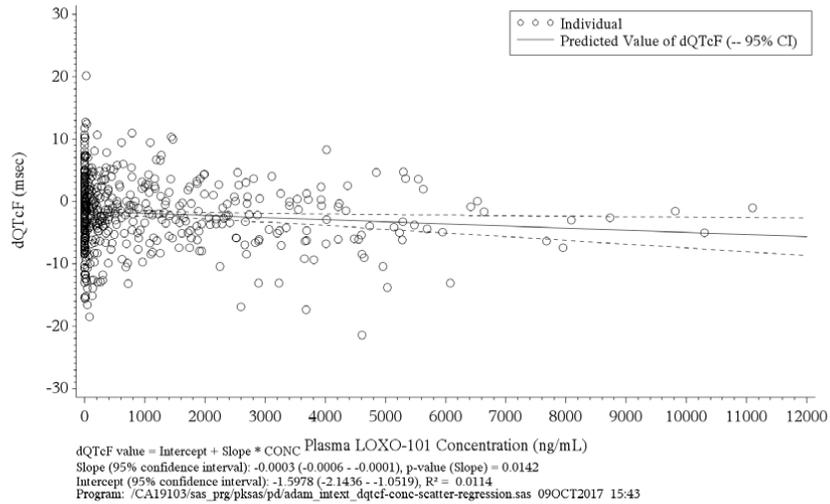
Source: CSR, Table 11-4, Page 62

4.2.8.4.2 Exposure-Response Analysis

Twelve (12) pre-specified exposure-response models were tested and the results were listed in Table 14.2.1.1.4. The final model (model with random intercept) was selected based on the smallest AIC.

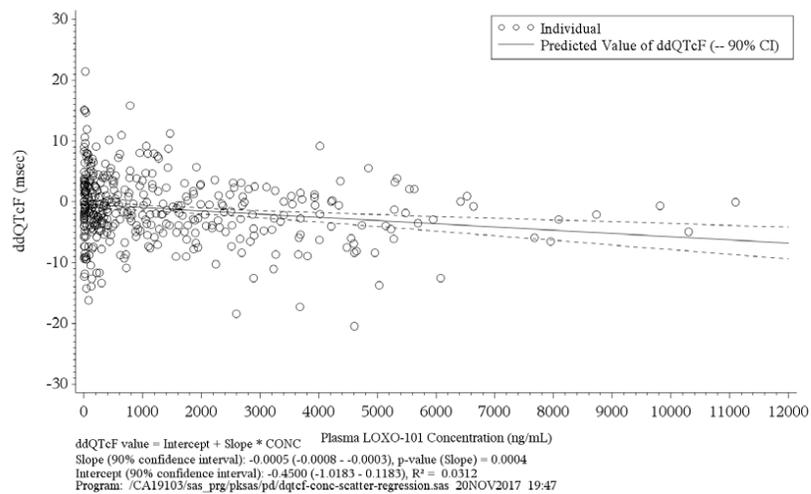
The change from baseline in QTcF (dQTcF) versus time-matched plasma LOXO-101 concentrations using the selected exposure-response model with a random intercept is presented in Figures 11-4. The model-based placebo-adjusted change from baseline in QTcF (ddQTcF) versus time-matched plasma LOXO-101 concentrations is presented in Figure 11-5.

Figure 1: Change From Baseline in QTcF (dQTcF) Versus Time-Matched Plasma LOXO-101 Concentrations



Source: CSR, Figure 11-4, Page 55

Figure 2: ddQTcF Versus Time-Matched Plasma LOXO-101 Concentrations (Scatterplot) (C-QT Population)



Source: CSR, Figure 11-5, Page 56

The model-based parameter estimates of slope and intercept for ddQTcF versus plasma LOXO-101 concentration are listed in the following table:

Table 2: Parameter Estimates for Intercept and Slope for ddQTcF Versus Plasma LOXO-101 concentration

Parameter	Estimate (90% CI)	P-Value
Intercept (msec)	-0.4500 (-1.0183, 0.1183)	0.1924
Slope (msec per ng/ml)	-0.0005 (-0.0008, -0.0003)	0.0004
Residual Variability (msec)	5.45688*	

* Mean square error from the model.

Source: CSR, Table 11-2, Page 56

The slope of the regressions of ddQTcF on LOXO-101 was negative and was statistically significant with p-value of 0.0004. The intercept was about -0.45 and the 90% CIs contain 0. Due to the small negative slopes, and the relatively narrow confidence intervals, placebo-adjusted changes from baseline in QTcF would not be expected to reach the regulatory threshold of concern.

The model predicted results at geometric mean C_{max} for LOXO-101 for placebo-adjusted change from baseline for QTcF (ddQTcF) are presented in Table 11-3. The predicted values for ddQTcF at geometric mean C_{max} for each treatment level were minimal, ranging from -4.21 to -0.693 msec.

At therapeutic exposures (mean C_{max} of approximately 908 ng/mL), model-based estimated value for ddQTcF is -0.929 msec and upper 90% CI for the prolongation is -0.460 msec. In cancer patients treated with 100 mg BID LOXO-101, twice the “worst case” C_{max} is considered to be approximately 5100 ng/mL, calculated by multiplying the cancer patient C_{max} under normal conditions (908 ng/mL) by the fold increase with a strong CYP3A4 inhibitor (2.81-fold, Study LOXO-TRK-16010) and by an additional safety factor of 2, to obtain 5100 ng/mL (908 * 2.81 * 2). The modeled value for ddQTcF at 5100 ng/mL is -3.318 msec with 90% upper CI -2.127 msec.

Table 3: Model Predicted ddQTcF and 90% CI at Mean C_{max} by Treatment

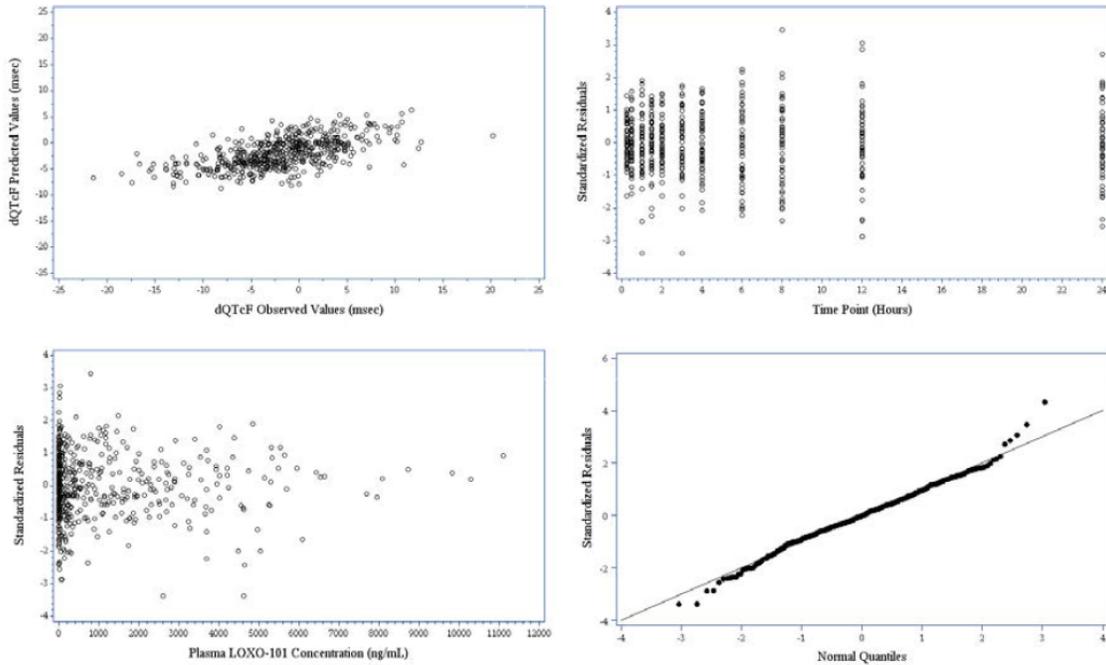
Treatment	Geometric Mean C _{max} (ng/mL)	Predicted Maximum ddQTcF (msec)	90% Confidence Interval (msec)
A	460.40	-0.693	-1.201 - -0.184
B	1097.1	-1.028	-1.488 - -0.569
C	2307.6	-1.666	-2.171 - -1.162
D	4557.1	-2.852	-3.746 - -1.958
E	7132.9	-4.210	-5.682 - -2.738
F	4608.0	-2.879	-3.784 - -1.974
*	5100.0	-3.138	-4.149 - -2.127
#	908.00	-0.929	-1.398 - -0.460

Treatment A: Single Oral Dose of 100 mg LOXO-101
 Treatment B: Single Oral Dose of 200 mg LOXO-101
 Treatment C: Single Oral Dose of 400 mg LOXO-101
 Treatment D: Single Oral Dose of 600 mg LOXO-101
 Treatment E: Single Oral Dose of 900 mg LOXO-101 and 30-second intravenous infusion of 0.25 mg palonosetron
 Treatment F: Single Oral Dose of 700 mg LOXO-101 and 30-second intravenous infusion of 0.25 mg palonosetron
 * 5100 ng/mL is the twice the worst case C_{max} in cancer patients treated with 100 mg BID LOXO-101.
 # 908 ng/mL is approximately mean C_{max} of the therapeutic exposures.
 Source: Table 14.2.1.1.5
 Program: /CA19103/sas_prg/pksas/pd/adam_intext_ddqtcf_stats.sas 22NOV2017 10:26

Source: CSR, Table 11-3, Page 57

The GoF plot of the final model is shown in Figure 11-6.

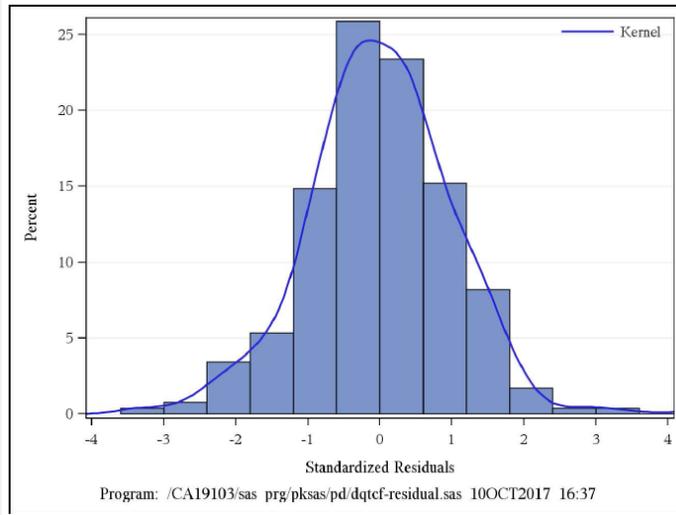
Figure 3: Goodness-of-Fit Plot of the Final Model



Source: CSR, Figure 11-6, Page 58

QTcF histograms of density versus standardized residuals for plasma LOXO-101 concentrations are presented in Figure 11-7.

Figure 4: dQTcF Histogram of Density Versus Standardized Residuals



Source: CSR, Figure 11-7, Page 59

The GoF plot and the distribution of the standardized residuals when plotted for plasma LOXO-101 concentrations showed homogeneous variance and were normally distributed which satisfied the model assumptions.

Hysteresis assessments for LOXO-101 are presented in Figure 14.2.1.2.5 and Figures 14.2.1.2.6.1 through 14.2.1.2.6.6, respectively.

Overall, there was no evidence of a hysteresis effect for ddQTcF for LOXO-101 postdose across all treatments.

Reviewer’s Analysis: The reviewer analyzed the relationship between larotrectinib concentration and QTc using the linear prespecified model and obtained similar results as the sponsor (5.3).

5 REVIEWERS’ ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate were observed, i.e. mean changes ≤ 10 bpm (section 5.3). Therefore, no assessment of the QT/RR correction methodology is necessary and QTcF should be the correction method.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject’s QTcF was above 450 ms.

Table 4: Categorical Analysis for QTcF

Treatment Group	Total (N)		Value \leq 450 ms	
	# Subj.	# Obs.	# Subj.	# Obs.
100 mg LOXO-101	6	66	6 (100%)	66 (100%)
200 mg LOXO-101	6	66	6 (100%)	66 (100%)
400 mg LOXO-101	6	66	6 (100%)	66 (100%)
600 mg LOXO-101	6	66	6 (100%)	66 (100%)
700 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)
900 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)
Placebo (Pooled)	12	132	12 (100%)	132 (100%)

Table 5 lists the categorical analysis results for Δ QTcF. No subject’s change from baseline was above 30 ms.

Table 5: Categorical Analysis of Δ QTcF

Treatment Group	Total (N)		Value \leq 30 ms	
	# Subj.	# Obs.	# Subj.	# Obs.
100 mg LOXO-101	6	66	6 (100%)	66 (100%)
200 mg LOXO-101	6	66	6 (100%)	66 (100%)
400 mg LOXO-101	6	66	6 (100%)	66 (100%)

Treatment Group	Total (N)		Value<=30 ms	
	# Subj.	# Obs.	# Subj.	# Obs.
600 mg LOXO-101	6	66	6 (100%)	66 (100%)
700 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)
900 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)
Placebo (Pooled)	12	132	12 (100%)	132 (100%)

5.2.2 HR Analysis

Table 6 lists the categorical analysis results for HR. No subject's change from baseline was above 100 bpm.

Table 6: Categorical Analysis for HR

Treatment Group	Total N		Value<=100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.
100 mg LOXO-101	6	66	6 (100%)	66 (100%)
200 mg LOXO-101	6	66	6 (100%)	66 (100%)
400 mg LOXO-101	6	66	6 (100%)	66 (100%)
600 mg LOXO-101	6	66	6 (100%)	66 (100%)
700 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)
900 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)
Placebo (Pooled)	12	132	12 (100%)	132 (100%)

5.2.3 PR Analysis

The outlier analysis results for PR are presented in Table 7. There are six subjects who experienced PR interval between 200 ms and 220 ms. There are no subjects who experienced PR interval greater than 220 ms among LOXO-101 groups.

Table 7: Categorical Analysis for PR

Treatment Group	Total (N)		Value<=200 ms		200 ms<Value<=220 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg LOXO-101	6	66	5 (83.3%)	61 (92.4%)	1 (16.7%)	5 (7.6%)
200 mg LOXO-101	6	66	6 (100%)	66 (100%)	0 (0.0%)	0 (0.0%)
400 mg LOXO-101	6	66	5 (83.3%)	62 (93.9%)	1 (16.7%)	4 (6.1%)
600 mg LOXO-101	6	66	4 (66.7%)	46 (69.7%)	2 (33.3%)	20 (30.3%)
700 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	4 (66.7%)	57 (86.4%)	2 (33.3%)	9 (13.6%)

Treatment Group	Total (N)		Value<=200 ms		200 ms<Value<=220 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
900 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)	0 (0.0%)	0 (0.0%)
Placebo (Pooled)	12	132	12 (100%)	132 (100%)	0 (0.0%)	0 (0.0%)

5.2.4 QRS Analysis

The outlier analysis results for QRS are presented in Table 8. There are no subjects who experienced QRS interval greater than 110 ms among LOXO-101 groups.

Table 8: Categorical Analysis for QRS

Treatment Group	Total (N)		Value<=100 ms		100 ms<Value<=110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg LOXO-101	6	66	6 (100%)	66 (100%)	0 (0.0%)	0 (0.0%)
200 mg LOXO-101	6	66	6 (100%)	66 (100%)	0 (0.0%)	0 (0.0%)
400 mg LOXO-101	6	66	6 (100%)	66 (100%)	0 (0.0%)	0 (0.0%)
600 mg LOXO-101	6	66	6 (100%)	66 (100%)	0 (0.0%)	0 (0.0%)
700 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	5 (83.3%)	65 (98.5%)	1 (16.7%)	1 (1.5%)
900 mg LOXO-101 and 0.25 mg Palonosetron IV	6	66	6 (100%)	66 (100%)	0 (0.0%)	0 (0.0%)
Placebo (Pooled)	12	132	12 (100%)	132 (100%)	0 (0.0%)	0 (0.0%)

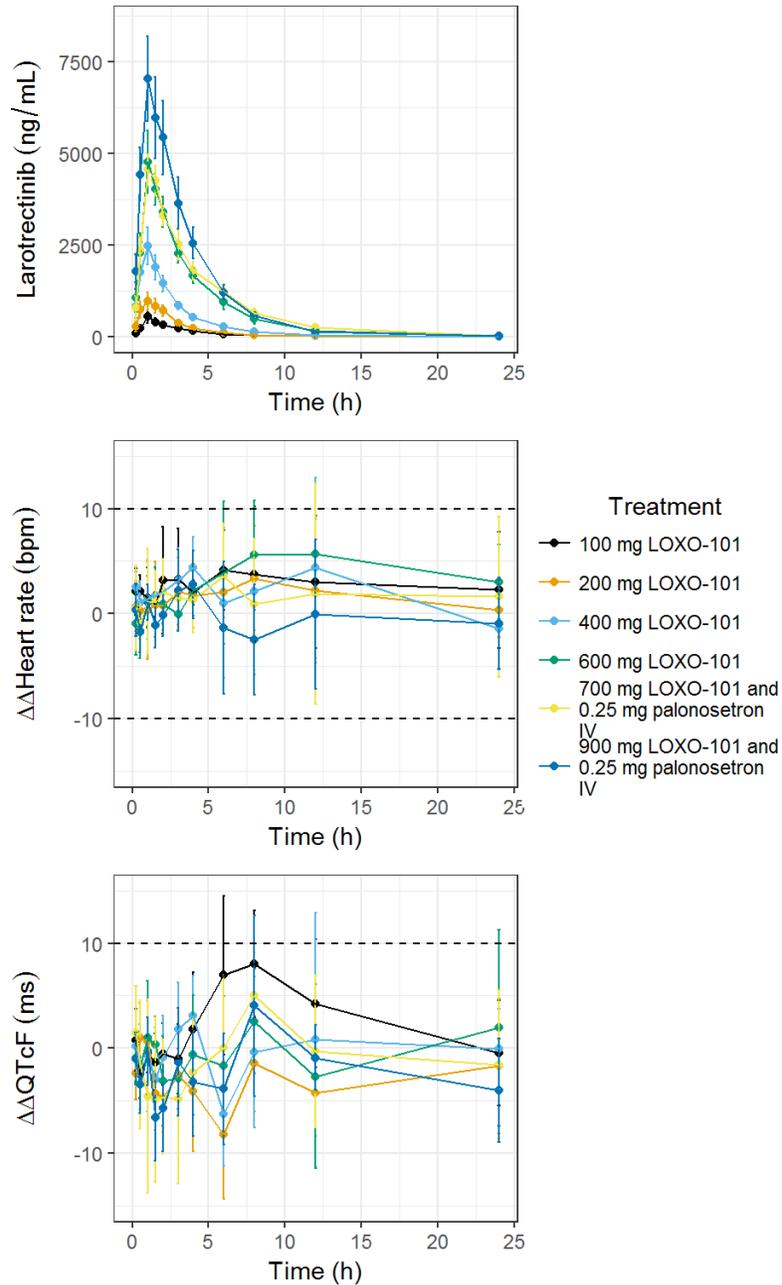
5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The objective of the clinical pharmacology analysis is to assess the relationship between larotrectinib concentration and $\Delta\Delta\text{QTcF}$ using the linear prespecified mixed effects model.

Prior to applying the prespecified model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and $\Delta\Delta\text{QTcF}$ and 3) presence of non-linear relationship.

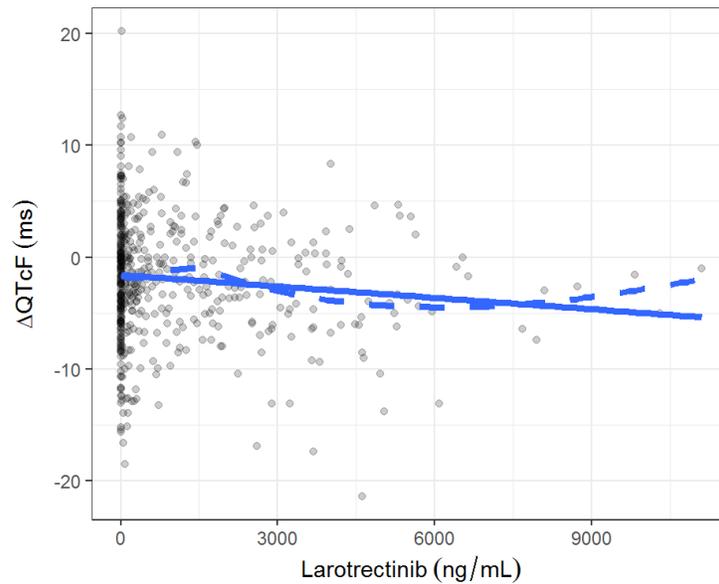
An evaluation of the time-course of larotrectinib pharmacokinetics and changes in $\Delta\Delta\text{HR}$ and $\Delta\Delta\text{QTcF}$ is shown in Figure 5, which shows an absence of significant changes in HR and do not appear to show significant hysteresis.

Figure 5: Time-course of larotrectinib (top), $\Delta\Delta$ HR (middle) and $\Delta\Delta$ QTcF (bottom)



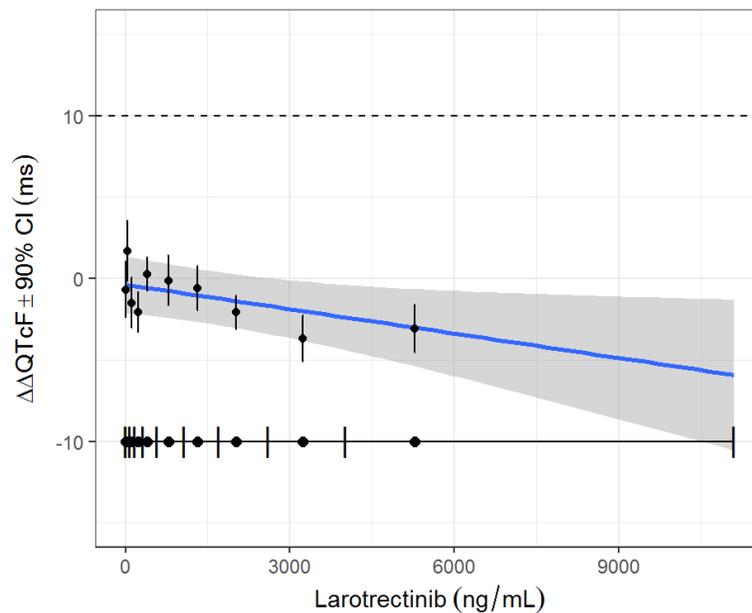
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between larotrectinib concentration and Δ QTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between larotrectinib concentration and Δ QTcF and supports the appropriateness of a linear model.

Figure 6: Evaluation of the relationship between larotrectinib concentration and Δ QTcF. The blue lines represent a linear fit (solid) and loess fit (dashed)



Finally, the linear prespecified mixed effects model was applied to the data and the goodness-of-fit plot is shown in Figure 7, which shows an absence of a relationship between larotrectinib concentration and $\Delta\Delta$ QTcF.

Figure 7: Goodness-of-fit plot for final model



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant changes in the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure in patients	<p>Adult Dose: 100 mg BID Steady-state geomean (geo %CV) C_{max} 788 ng/mL (81%), n = 37 Steady-state geomean (geo %CV) AUC_{0-24} 4350 ng*h/mL (97%), n = 37</p> <p>Pediatric Dose: 100 mg/m² (maximum 100 mg) BID Day 1 geomean (geo %CV) C_{max} 867 ng/mL (51%), n = 15 Day 1 geomean (geo %CV) AUC_{0-24} 4290 ng*h/mL (67%), n = 15</p>	
Maximum tolerated dose	Not determined, ≥ 200 mg BID	
Principal adverse events	The most common reported in $\geq 5\%$ of patients (n = 144) are dizziness n = 29 (20%), ALT increase, AST increase (both n = 27 (19%)), fatigue n = 25 (17%), and nausea n = 24 (17%)	
Maximum dose tested	Single Dose	900 mg (healthy volunteers)
	Multiple Dose	200 mg BID continuous dosing for 28-day cycles (adult cancer patients)
Exposures Achieved at Maximum Tested Dose	Single Dose	900 mg geomean (geo %CV) C_{max} 7133 ng/mL (32%) 900 mg geomean (geo %CV) AUC_{inf} 23900 ng*h/mL (38%)
	Multiple Dose	200 mg BID geo mean C_{max} (geo %CV) 929 ng/mL (175%) 200 mg BID geomean AUC_{0-24} (geo %CV) 6070 ng*h/mL (155%)
Range of linear PK	50 mg QD to 200 mg BID (cancer patients) 100 mg to 400 mg single-dose (healthy volunteers); slightly supra-proportional at doses >400 mg	
Accumulation at steady state	<p>Cancer patients (100 mg BID): Geomean $AUC_{Day 8} / AUC_{Day 1}$: 1.1-fold (geo %CV 58%)</p> <p>Healthy volunteers (100 mg BID): Geomean $C_{max, Day 10} / C_{max, Day 1}$ is ~1.6-fold Geomean $AUC_{Day 10} / AUC_{Day 1}$ is ~1.6-fold</p>	
Metabolites	<p>One major metabolite, termed M14, which is a glucuronide conjugate formed following loss of the hydroxypyrrolidine-urea moiety of larotrectinib, is present in human plasma and accounts for approximately 26% of total-derived material (unchanged larotrectinib accounts for approximately 19%). The remainder is due to other metabolites, each of which contribute to < 10% of total drug-derived material.</p> <p>In vitro data from human tissues demonstrated that larotrectinib is metabolized primarily by CYP3A4.</p> <p>The major as well as minor human metabolites of larotrectinib are present in the plasma of species used for non-clinical safety testing. None have been tested for primary pharmacology (TRK) inhibition, but based on structure-activity analysis, the probability of them being active is remote.</p>	

Absorption	Absolute/Relative Bioavailability	Absolute bioavailability, oral capsule Geomean (geo %CV): 34% (6.7%) Relative bioavailability, Solution/Capsule C _{max} : 1.36 (95% CI 1.18 – 1.57) AUC _{inf} : 1.05-fold (95% CI 0.96 – 1.14)
	T _{max}	Healthy volunteers Median (range), 100 mg oral dose <ul style="list-style-type: none"> • Capsule (fasted): 0.76 h (0.46, 2.00) • Capsule (fed): 3.00 h (2.00, 4.08) • Solution (fasted): 0.44 (0.21, 1.01) Cancer patients Median (range), 100 mg BID dose <ul style="list-style-type: none"> • Capsule (fasted): 1 h (0.5 to 9 h)
Distribution	V _d /F or V _d	V _{ss} geomean (geo %CV): 48.3 L (38%), IV dose (~7.58 µg)
	% bound	Mean plasma protein binding (%CV): Approximately 70% bound (1%)
Elimination	Route	<ul style="list-style-type: none"> • 8%-13% of oral dose excreted unchanged in urine • 29% of IV dose excreted unchanged in urine • Metabolism by CYP3A4 based on in vitro and in vivo data
	Terminal t _{1/2}	Multiple, depending on time frame of sampling. Typical values of arithmetic mean (±SD) half-life <ul style="list-style-type: none"> • 4.1 (± 2.3) hours for parent • 12.8 (± 4.7) hours for total radioactivity
	CL/F or CL	CL geomean (geo %CV): 33.6 (42%) L/h, IV dose (~7.58 µg)
Intrinsic Factors	Age	In progress
	Sex	In progress
	Race	In progress
	Renal Impairment (in progress) 100 mg single oral dose	C _{max} ↑1.25x AUC _{0-last} ↑1.40x AUC _{0-inf} ↑1.46x
	Hepatic Impairment (in progress) 100 mg single oral dose	Geomean AUC _{0-t} Healthy match (n = 7), 1220 ng*h/mL Mild (n = 8), 1430 ng*h/mL Moderate (n = 8), 2360 ng*h/mL Severe (n = 6), 3150 ng*h/mL
	Population PK studies and special population studies are in progress to address the effect of these factors on pharmacokinetics of larotrectinib	

Extrinsic Factors	Drug interactions	<p>100 mg single oral dose</p> <p>Strong CYP3A4 inhibition (MD itraconazole) C_{max} change 2.81-fold (95% CI 2.25 – 3.49) AUC_{inf} change 4.31-fold (95% CI 3.76 – 4.95)</p> <p>Strong CYP3A4 inducer (MD rifampin) C_{max} change 0.29-fold (95% CI 0.23 – 0.37) AUC_{inf} change 0.19-fold (95% CI 0.15 – 0.24)</p> <p>P-gp CYP3A4 inhibitor (SD rifampin) C_{max} change 1.79-fold (95% CI 1.47 – 2.19) AUC_{inf} change 1.67-fold (95% CI 1.52 – 1.84)</p> <p>(MD = multiple-dose; SD = single dose)</p>
	Food Effects	<p>100 mg single oral dose, effect of food: C_{max} change 0.65-fold (95% CI 0.57 – 0.76) AUC_{inf} change 1.06-fold (95% CI 0.97 – 1.16)</p>
Expected High Clinical Exposure Scenario	<p>Alterations in exposure based on drug interactions or special populations (e.g. hepatic impairment and renal impairment) are in progress. Treatment with the strong CYP3A4 and P-gp inhibitor itraconazole was used as the “worst case” high clinical exposure scenario and C_{max} and AUC were increased 2.81-fold and 4.31-fold, respectively.</p>	
Preclinical Cardiac Safety	<p>In vitro inhibitory effects of larotrectinib on hERG potassium currents was 147 μM [62,900 ng/mL], which is approximately 70-fold higher than the maximum total (bound+unbound) arithmetic mean plasma concentration (914 ng/mL) at the human dose regimen of 100 mg BID, and approximately 230-fold higher than the clinical unbound concentration of larotrectinib in plasma. No adverse cardiovascular (CV) effects were noted in telemetry-instrumented rats or monkeys at doses up to 300 mg/kg and 100 mg/kg, respectively. One noteworthy finding was in one telemetry-instrumented monkey given 200 mg/kg of larotrectinib which had an adverse decrease (> 45%) in diastolic arterial blood pressure at an approximate maximal exposure of 16000 ng/mL which corresponded to approximately 18-fold higher than the C_{max} (914 ng/mL) at the human dose of 100 mg BID. No adverse CV effects were observed in the anesthetized dog given larotrectinib intravenously up to 13 mg/kg or in monkeys following repeat administration up to 100 mg/kg/day for 28 days.</p>	

Clinical Cardiac Safety	<p>A concentration-response QTc study conducted in human volunteers at doses of 100 mg, 200 mg, 400 mg, 600 mg, 700 mg, and 900 mg. At therapeutic exposures (anticipated arithmetic mean C_{max} of approximately 908 ng/mL at the time of study conduct), model-based estimated value for ddQTcF was -0.929 msec and upper 90% CI for the prolongation is -0.460 msec. In cancer patients treated with 100 mg BID larotrectinib, twice the “worst case” C_{max} is considered to be approximately 5100 ng/mL, calculated by multiplying the arithmetic mean cancer patient C_{max} under normal conditions (908 ng/mL, n = 29, at the time of the QT study [currently 914 ng/mL, n = 37]) by the fold increase with a strong CYP3A4 inhibitor, multiple-dose itraconazole (2.81-fold) and by an additional safety factor of 2, to obtain 5100 ng/mL (908 * 2.81 * 2). The modeled value for ddQTcF at 5100 ng/mL was -3.318 msec with 90% upper CI -2.127 msec.</p> <p>Overall, the exposure-response modeling demonstrated a small effect of larotrectinib to shorten the QTcF interval. This mild shortening was not of clinical significance. There was no meaningful effect on the other ECG parameters</p>
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