CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218550Orig1s000

OTHER REVIEW(S)

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 6, 2023
To:	Raniya Al-Matari, PhD Regulatory Health 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:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kelle Caruso, PharmD, BCPS 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 (non-proprietary name), Dosage Form and Route, Application Type/ Number, Supplement Number:	• ROZLYTREK (entrectinib) oral pellets, NDA 218550 • ROZLYTREK (entrectinib) capsules, for oral use, NDA 212725/S-009
Applicant:	Genentech, Inc.

1 INTRODUCTION

On April 28, 2023, Genentech, Inc. submitted for the Agency's review an original New Drug Application (NDA) 218550 for ROZLYTREK (entrectinib) oral pellets and a Prior Approval Supplement (PAS) – Efficacy to their approved NDA 212725/S-009 for ROZLYTREK (entrectinib) capsules. With these submissions, the Applicant proposes:

NDA 218550

- the indication for treatment of adult [redacted] (b) (4) with solid tumors that have an neurotrophic tyrosine receptor kinases (NTRK) gene fusion without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have progressed following treatment or have no satisfactory alternative therapy.

NDA 212725/S-009

- to expand the indication to include [redacted] (b) (4) with NTRK fusion-positive, locally advanced or metastatic solid tumor and to support the new route and method of administration for entrectinib capsule suspension.

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 Division of Oncology II (DO2) on May 23, 2023 to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFUs) for ROZLYTREK (entrectinib) capsules and ROZLYTREK (entrectinib) oral pellets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs was completed on September 27, 2023.

2 MATERIAL REVIEWED

- Draft ROZLYTREK (entrectinib) capsules and ROZLYTREK (entrectinib) oral pellets PPI received on April 28, 2023, revised throughout the review cycle, and received by DMPP and OPDP on October 2, 2023.
- Draft ROZLYTREK (entrectinib) capsules and ROZLYTREK (entrectinib) oral pellets IFUs received on April 28, 2023, revised throughout the review cycle, and received by DMPP and OPDP on October 2, 2023.
- Draft ROZLYTREK (entrectinib) capsules and ROZLYTREK (entrectinib) oral pellets Prescribing Information (PI) received on April 28, 2023, revised throughout the review cycle, and received by DMPP and OPDP as an electronic copy on October 2, 2023, and further revised by the RD on October 4, 2023 and October 5, 2023.
- Approved ROZLYTREK (entrectinib) capsules labeling dated July 18, 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. In our review of the IFUs, the target reading level is at or below an 8th grade 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 and IFUs we:

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

4 CONCLUSIONS

The PPI and IFUs 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 IFUs 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 IFUs.

Please let us know if you have any questions.

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MEMORANDUM

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

Date of This Memorandum:	October 5, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 218550 and NDA 212725/S-009
Product Name, Dosage Form, and Strength:	Rozlytrek (entrectinib) Oral Pellets, 50 mg per stick pack Rozlytrek (entrectinib) Capsules, 50 mg per stick pack
Applicant/Sponsor Name:	Genentech, Inc.
TTT ID #:	2023-4852-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on October 2, 2023 for Rozlytrek. The Division of Oncology 2 (DO2) requested that we review the revised carton labeling for Rozlytrek (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]

We acknowledge that the Applicant, citing limited space on the Rozlytrek capsule container label, did not add the recommended statements to the container label. However, the recommended statements were implemented on the Rozlytrek capsule carton labeling for the 100 mg and the 200 mg strength configurations.

2 CONCLUSION

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

[a] Stewart, J. Label and Labeling Review for Rozlytrek (NDA 218550 and NDA 212725/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 SEP 26. TTT ID No.: 2023-4852.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 2, 2023

NDA 218550 Carton labeling

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

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

Memorandum

Date: October 5, 2023

To: Raniya Al-Matari, Regulatory Project Manager
Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, DO2

From: Kelle Caruso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for ROZLYTREK® (entrectinib) capsules, for oral use; ROZLYTREK® (entrectinib) oral pellets

NDA: 212725 S-009; 218550

Background:
In response to DO2's consult request dated May 23, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for ROZLYTREK® (entrectinib) oral pellets, and for S-009 for ROZLYTREK® (entrectinib) capsules, for oral use, which extends the currently approved indication to include patients (b) (4) years of age and also introduces a new route and method of administration.

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on October 4, 2023, and our comments are provided below.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from DARRTS on October 4, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Kelle Caruso at 301-796-5044 or Kelle.Caruso@fda.hhs.gov.

PI:

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION	"The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders. (6.1)"	OPDP notes that Section 6.1 of the PI contains new data on the safety of Rozlytrek in pediatric patients. Does the data in Table 10 need to be presented in the highlights as the most common adverse reactions in pediatric patients? We note that the following adverse reactions that occurred in ≥ 20% of pediatric patients did not occur at rates of ≥ 20% in the original study population: pain in extremity (26%), skeletal fracture (25%), decreased appetite (24%), headache (22%), abdominal pain (20%), upper respiratory tract infection (20%), urinary tract infection (20%), and nasal congestion (20%). We defer to DO2 on whether inclusion of the data from Table 10 in the highlights would be appropriate.
5.3 Skeletal Fractures	(b) (4)	Consistent with the Labeling Review Tool, (b) (4) should be avoided. These terms minimize the risks associated with Rozlytrek and if left in the label, can be used in promotion. OPDP recommends using the (b) (4) to describe these events.

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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)

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

Date of This Review:	September 26, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 218550 and NDA 212725/S-009
Product Name, Dosage Form, and Strength:	Rozlytrek (entrectinib) Oral Pellets, 50 mg per stick pack Rozlytrek (entrectinib) Capsules, 100 mg and 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	April 28, 2023, August 28, 2023
TTT ID #:	2023-4852
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

NDA 218550

As part of the approval process for Rozlytrek (entrectinib) Oral Pellets, a new formulation to support pediatric oral dosing and administration (NDA 218550), the Division of Oncology 2 (DO2) requested that we review the proposed Rozlytrek prescribing information (PI), container labels, and carton labeling , and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

NDA 212725/S-009

Genentech, Inc. submitted a Efficacy Supplement for Rozlytrek (entrectinib) Capsules (NDA 212725/S-009) to support new routes of administration and a new method for preparing an oral suspension using Rozlytrek capsules. Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Rozlytrek prescribing information (PI), container labels, and carton labeling , and IFU for areas of vulnerability that may lead to medication errors.

Both submissions propose options that expand the Rozlytrek dose range for the treatment younger pediatric patients with solid tumors and allow administration to adult and pediatric patients who have difficulty or are unable to swallow whole capsules.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C
FDA Adverse Event Reporting System (FAERS)*	D
Labeling Recommendations (PI and IFU)	E
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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed PI changes to Section 2 Dosage and Administration, Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information; all involving the addition of the newly proposed pellet formulation and new information regarding the option to prepare the capsules as an oral

suspension. We found the proposed revisions in Sections 3, 16, and 17 acceptable from a medication error perspective. However, given the caveats associated with the indication, the age of the patient, whether the patient can swallow, and the prescribed dosage, and the appropriate dosage form, we found the proposed language throughout Section 2 could be revised for improved order, clarity, and completeness.

We also reviewed the proposed IFU for the pellet formulation and the IFU for preparing Rozlytrek capsules as an oral suspension. We found the proposed language throughout both IFUs could be revised for improved order, clarity, and completeness. We communicated with DMPP to propose revisions for consistency with the PI. Thus, we provide related recommendations in Section 4.1 below.

Our review of the container label and carton labeling for Rozlytrek oral pellets identified a (b) (4) on the carton labeling that could contribute to wrong technique errors. Our review of the container label and carton labeling for Rozlytrek oral capsules identified the need to include product information that would inform the pharmacist and users that the capsules can now be used to prepare an oral suspension. Thus, we provide recommendations for Genentech in Section 4.2 below.

Finally, our search of the FDA Adverse Event Reporting System identified reports of patients who were unable to swallow Rozlytrek capsules and who tried various techniques to take or give Rozlytrek that were not effective. The identified reports support the need for formulations and techniques that allow administration to adult and pediatric patients who have difficulty or are unable to swallow whole capsules.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Rozlytrek PI, IFUs, container labels, and carton labeling can be improved to promote the safe and effective use of the product. We provide recommendations for DO2 in Section 4.1 and recommendations for Genentech, Inc. in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section
    a. See recommendations in tracked changes in Appendix E

2. Instructions For Use- Rozlytrek Oral Pellets
    a. See recommendations in tracked changes in Appendix E

3. Instructions For Use- Rozlytrek Oral Capsules
    a. (b) (4)

(b) (4)

b. See recommendations in tracked changes in Appendix E

4.2 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of NDA 218550:

A. Carton Labeling

1. Remove the (b) (4) from the "Giving Rozlytrek" section on the back panel. We recommend this revision to reduce the risk of users adding a full dose of Rozlytrek pellets to (b) (4) of soft food instead of adding the pellets to one or more spoonful of soft food. Then, enlarge the image of the spoon to show the spoon with soft food with increased prominence.

We recommend the following be implemented prior to approval of this NDA Supplement (NDA 212725/Supp 009):

A. General Comments (Container labels & Carton Labeling)

1. To inform healthcare providers, patients, and caregivers of for the new option to prepare an oral suspension using Rozlytrek capsules and to prompt the pharmacist to provide instructions, we recommend adding the following statements to the container labels and carton labeling:

> Capsules may be administered whole or may be used to prepare an oral suspension.
>
> PHARMACIST: Dispense with the included Instructions For Use

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rozlytrek received on April 28, 2023 from Genentech, Inc..

<table>
<tr><th colspan="3">Table 2. Relevant Product Information for Rozlytrek</th></tr>
<tr><td>Initial Approval Date</td><td>NDA 218550: N/A</td><td>NDA 212725: August 15, 2019</td></tr>
<tr><td>Active Ingredient</td><td colspan="2">entrectinib</td></tr>
<tr><td>Indication</td><td colspan="2">• For the treatment of adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test.
• For the treatment of adult [redacted] (b) (4) with solid tumors that:
- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.</td></tr>
<tr><td>Route of Administration</td><td colspan="2">Oral</td></tr>
<tr><td>Dosage Form</td><td>Oral Pellets (proposed)</td><td>Capsules</td></tr>
<tr><td>Strength</td><td>50 mg per stick pack</td><td>100 mg and 200 mg</td></tr>
<tr><td>Dose and Frequency</td><td colspan="2">Adults: 600 mg orally once daily with or without food until disease progression or unacceptable toxicity.
Pediatric (older than 6 months):
<table><tr><th>Body Surface Area (BSA)*</th><th>Recommended Dosage
Orally, once daily [redacted] (b) (4)</th></tr><tr><td>≥ 1.51 m^2</td><td>600 mg [redacted] (b) (4)</td></tr><tr><td>1.11 to 1.50 m^2</td><td>400 mg [redacted] (b) (4)</td></tr><tr><td>0.81 to 1.10 m^2</td><td>300 mg [redacted] (b) (4)</td></tr><tr><td>0.51 to 0.80 m^2</td><td>200 mg [redacted] (b) (4)</td></tr><tr><td colspan="2">[redacted] (b) (4)</td></tr></table></td></tr>
</table>

	Pediatric (*> 1 Month to ≤ 6 Months)*: 250 mg/m^2 orally once daily [redacted] (b) (4)	
How Supplied	42-count carton (each packet contains 50 mg entrectinib)	30-count 100 mg capsules 90-count 200 mg capsules
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]* . Store in the original container to protect from moisture.	Store [redacted] (b) (4) in the original container to protect from moisture.
Container Closure	60 mm x 25 mm Laminated foil stick packs in paper cartons	HDPE bottles

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 23, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Rozlytrek. Our search identified 2 previous reviews[a,b], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Little, C. Label and Labeling Review for Entrectinib (NDA 212725 and NDA 212726). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 12. RCM No.: 2018-2756-1 and 2018-2760-1..

[b] Little, C. Label and Labeling Review for Entrectinib (NDA 212725 and NDA 212726). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 04. RCM No.: 2018-2756 and 2018-2760.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

On August 28, 2023, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR
Search Strategy and Terms	Match Any of the Words: Rozlytrek entrectinib

C.2 Results

The search retrieved no relevant articles associated with label and labeling for (product name).

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

D.1 Methods

On August 23, 2023, we searched FAERS using the criteria in the table below and identified 10 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[c] We excluded 7 cases because they described off-label use (n=1), off-label use & wrong schedule (n=1), off-label use & dose omission (n=1), wrong storage (n=2), dose omission (n=1), and product quality issue (n=1).

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	August 23, 2019 to August 23, 2023
Product Name:	Rozlytrek
Product Active Ingredient (PAI):	entrectinib
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

D.2 Results

Our search identified 10 cases, of which 3 described wrong technique errors relevant for this review. In one case (FAERS #18889039), a patient developed difficulty swallowing capsules. The patient opened Rozlytrek capsules and mixed the contents in applesauce, but was unable to swallow the mixture. The patient inquired about other preparation options such as mixing the capsule contents with water. No harm was reported. In another case (FAERS #22679136) a patient reported difficulty swallowing so they tried chewing the capsule. No harm was reported. The last case (FAERS #22021526) described an adverse event of burning in throat when a patient reported swallowing capsules after "dividing them up a little" and the capsule "came back up into throat" and caused a burning sensation.

D.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of

[c] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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Clinical Inspection Summary

Date	September 12, 2023
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Marjilla Seddi1, MD, Medical Officer Amy Barone, MD, Team Leader (CDTL) Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	NDA 218550
Applicant	Genentech, Inc.
Drug	Entrectinib (Rozlytrek)
NME (Yes/No)	No
Therapeutic Classification	Kinase inhibitor
Proposed Indication(s)	Treatment of adults (b) (4) with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have a progressed following treatment or have no satisfactory alternative therapy
Consultation Request Date	January 27, 2023
Summary Goal Date	September 29, 2023
Action Goal Date	October 18, 2023
PDUFA Date	October 28, 2023

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study CO40778 (STARTRK-NG) and Study BO41932 (TAPISTRY) were submitted to the Agency in support of New Drug Application (NDA 218550) for entrectinib for the treatment of adults and (b) (4) with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have a progressed following treatment or have no satisfactory alternative therapy. One clinical investigator, Dr. Amar Gajjar (site # 19045), and the imaging Contract Research Organization (CRO) (b) (4) were inspected.

Inspections of Dr. Gajjar and (b) (4) revealed no discrepancies, regulatory violations or GCP non-compliance. Based on these inspections, Study CO40778 (STARTRK-NG) appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO for both Studies CO40778 and BO41932 appear acceptable in support of the proposed indication.

2. BACKGROUND

Genentech, Inc. submitted NDA 218550 seeking approval for entrectinib to extend their existing indication in solid tumors, specifically for adult and (b) (4) that have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have progressed following treatment or have no satisfactory alternative therapy, (b) (4)

The efficacy population to support the proposed indication consists of 33 subjects with NTRK fusion-positive tumors, 31 subjects enrolled in Cohort B and D of the pivotal Study STARTRK-NG and 2 patients enrolled in the supportive TAPISTRY study. The safety population consists of 76 pediatric subjects enrolled across studies STARTRK-NG, TAPISTRY, an STARTRK-02.

STARTRK-NG is an ongoing Phase I/II multicenter, open-label, dose escalation study in pediatric patients with relapsed or refractory extracranial solid tumors (Phase I, Cohort A), with additional expansion cohorts (Phase II, Cohorts B-E). Cohort B enrolled patients with primary brain tumors that have *NTRK1/2/3* or *ROS1* gene fusions, and Cohort D enrolled subjects with extracranial solid tumors that have *NTRK1/2/3* or *ROS1* gene fusions.

The primary efficacy endpoint was overall response rate (ORR) as assessed by Blinded Independent Committee Review (BICR) according to RECIST v1.1 for extracranial tumors, and according to RANO criteria for primary CNS tumors. The secondary efficacy endpoints included duration of response (DOR) as evaluated by BICR, and time to first objective response (CR or PR).

Subjects were to sign the informed consent form before any study-specific procedures were to be performed. Imaging assessments were to be performed at screening, after every even-numbered cycle, starting with Cycle 2, and after every 3 cycles starting with Cycle 18 until documented progression of disease regardless of treatment delays resulting from toxicity. Tumor assessments are also performed at the end of treatment if more than 4 weeks passed since the last imaging assessment.

Study STARTRK-NG enrolled the first subject on May 3, 2016. At the time of the data cut-off date (August 2, 2022), the study had enrolled 68 subjects across 25 centers in 9 countries: United States (14), China (2), Spain (1), United Kingdom (2), France (2), Italy (1), Germany (1), Canada (1), Hong Kong (1).

Clinical Investigator Dr. Amar Gajjar (Site # 19045) and the imaging CRO, (b) (4) were inspected.

3. RESULTS (by site):

1. **Dr. Amar Gajjar (Site # 19045)**
   St. Jude Children's Research Hospital
   262 Danny Thomas Pl
   Memphis, TN 38105

   Inspection dates: July 17 – July 21, 2023

   Dr. Gajjar was inspected as a routine PDUFA inspection for Study STARTRK-NG. This was the first FDA inspection of Dr. Gajjar.

   At the time of the inspection, the site had screened and enrolled 9 subjects in the study. Of the 9 subjects enrolled, one was still receiving the investigational product, one withdrew from study, one switched to another clinical site, 2 were in long-term follow-up, and 4 had died.

   Source records for all 9 subjects were reviewed. Records reviewed included but were not limited to informed consent forms, medical histories, inclusion and exclusion criteria, investigational drug administration, adverse events reporting, concomitant medications, protocol deviations, and subject dispositions. Source records were compared with data listing tables submitted to the NDA. The inspection did not identify discrepancies with informed consents, under-reporting of adverse events or concomitant medications.

   The following radiographic scans performed at the site were not submitted for central review:

   Subject (b) (6): According to the medical notes, the subject had clinical deterioration and an outside CT scan on (b) (6) that showed progressive disease, but the scan was not submitted for central review.

   This subject had primary CNS tumor and was enrolled into (b) (4) of the study on (b) (6) and received 10 cycles of entrectinib 400 mg/m^2. The last dose of study drug was on (b) (6). The subject experienced an SAE of pancreatitis on (b) (6) and was taken off the study per protocol on (b) (6) due to drug interruption lasting more than (b) (6) days due to the SAE, deteriorating condition with inability to travel to the clinical site.

   Reviewer's comment: Although submission of the unscheduled imaging conducted at the outside facility for central review may have contributed to tumor response assessment, this was not mandatory per Imaging Charter. Per BICR, subject (b) (6) achieved a partial remission (PR) of the CNS tumor per RANO criteria following 2 cycles (b) (6) of entrectinib and remained stable at the last assessment at cycle 9 (b) (6) The Sponsor did not report disease progression based on outside assessment on (b) (6). The subject died on (b) (6) due to disease progression. The review division may consider the impact of Subject (b) (6) date of

progression for the supportive efficacy data (exploratory cohort), and censor as appropriate.

Additional records reviewed include, but were not limited to, site's overall adherence to the study protocols, IRB approval letters and correspondence, delegation of authority logs, monitoring reports, financial disclosure reports, electronic case report forms, drug accountability records, site staff training records and responsibility logs.

Based on the results of the inspection, data generated at Dr. Gajjar's site appear acceptable in support of the proposed indication in the NDA.

(b) (4)

(b) (4) was inspected as a routine PDUFA inspection for Study STARTRK-NG and TAPISTRY. The firm was previously inspected in (b) (4)

This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for studies STARTRK-NG and TAPISTRY. The inspection reviewed the procedures for receipt, evaluation, and transfer of data from the site and to reviewers, including blinding procedures for image receipt. Reader assessments were reviewed including the adjudication process.

Tumor response data from all 33 subjects included in the efficacy population (31 enrolled in the STARTRK-NG and 2 subjects enrolled in the TAPISTRY trials) were reviewed and compared with the line listings. The inspection reviewed all imaging time points for all subjects per protocol as related to the efficiency endpoint of ORR conducted using either RECIST v1.1 or RANO. All CR and PR tumor responses were confirmed by imaging at least 4 weeks after initial documentation. There were not discrepancies between the reads reported at the site with the line listings.

Additional records and procedures reviewed included imaging charter, organizational chart, software features such as access permissions, software data, reader reports and audit trails, site personnel training, standard operating procedures (SOPs), electronic case report for (eCRF) extractions, and communication plans.

(b) (4) assessment, procedures in performing image analysis, compliance with the Imaging Review Charter, clinical protocol, and appropriate regulations appeared to be adequate. The imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

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/s/

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