

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212725Orig1s000**

**212726Orig1s000**

**RISK ASSESSMENT AND RISK MITIGATION  
REVIEW(S)**

Division of Risk Management (DRISK)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Application Type	NDA
Application Number	212725-6
PDUFA Goal Date	August 18, 2019
OSE RCM #	2018-2755, 2757, 2758, 2759
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	August 6, 2019
Subject	Addendum to June 4, 2019 DRISK review
Established Name	Entrectinib
Trade Name	Roslytrek
Name of Applicant	Genentech
Therapeutic Class	TRK inhibitor
Formulation(s)	Oral capsules
Dosing Regimen	600 mg orally once daily

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## 1 Introduction

The DRISK review dated June 4, 2019 found that the safety profile for entrectinib is acceptable based on the proposed indication and the likely patient population, and healthcare providers who will prescribe and administer entrectinib. We had determined that a risk evaluation and mitigation strategy (REMS) was not necessary to ensure the benefits outweighed the risks. The most important serious adverse events addressed in the prior review are congestive heart failure, central nervous system effects, QTc interval prolongation, vision disorders, and embryo-fetal toxicity.

Since that review, two additional safety issues, skeletal fractures and hyperuricemia, have been included in the *Warnings and Precautions* section of the draft Roslytrek labeling. This review addresses whether a REMS is needed to mitigate these risks.

## 2 Risk Assessment & Safe-Use Conditions

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The safety database comprised data from 355 patients who received entrectinib in clinical trials.

### 2.1 SKELETAL FRACTURES

Skeletal fractures occurred in 6% of adult patients and 23% of pediatric patients who received entrectinib in clinical testing. In adult patients, some fractures occurred in the setting of trauma, while fractures in pediatric patients occurred in the absence of trauma. The fractures were mostly lower extremity fractures, and some patients experienced bilateral lower extremity fractures. The median time to onset for adults was 3.8 months (range, 0.3 to 18.5 months), and the median time to onset for pediatric patients was 4 months (range, 1.8 to 7.4 months). The draft labeling advises prescribers to assess for fracture should patients experience pain, deformity, or impairment in mobility. No patients discontinued Rozlytrek due to fractures and there is no data on whether discontinuation of entrectinib is necessary for healing of the fractures.

### 2.2 HYPERURICEMIA

Hyperuricemia occurred in 9% of patients who received entrectinib in clinical testing. Grade 4 hyperuricemia occurred in 1.7% of patients. The draft labeling advises prescribers to assess serum uric acid levels prior to initiating therapy with entrectinib and periodically during treatment, and to monitor patients for signs and symptoms of hyperuricemia during therapy. Prescribers should initiate treatment with urate-lowering medications as indicated, and withhold entrectinib for signs and symptoms of hyperuricemia. Based on the severity of

hyperuricemia, entrectinib can be resumed at the same or reduced dose, or permanently discontinued upon following resolution of the episode.

### 3 Risk Management Activities Proposed by the Applicant

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The Applicant did not propose any risk management activities for entrectinib beyond professional labeling.

### 4 Discussion of Need for a REMS

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The Clinical Reviewers believe the data support a favorable benefit:risk assessment for entrectinib for the treatment of patients with metastatic NSCLC that is ROS1-positive and for the treatment of patients with NTRK fusion positive, (b) (4) metastatic solid tumors who have either progressed (b) (4) (b) (4). In ROS1 positive NSCLC, clinical testing showed a clinically meaningful treatment effect, with a response rate of 77%. Testing also showed durable efficacy. In NTRK fusion positive solid tumors, the overall response rate was 57%, with 50% having a partial response. Twenty-nine percent had a duration of response that exceeded 12 months.

The clinical reviewers believe the adverse events are appropriately handled with labeling alone.

This reviewer recommends that, should entrectinib be approved, a REMS is not needed to ensure its benefits outweigh its risks. Skeletal fractures and hyperuricemia will be communicated through warnings and precautions in labeling. These risks of entrectinib do not warrant a boxed warning. A REMS is not needed to address the risks of entrectinib.

### 5 Conclusion & Recommendations

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Based on the available data, a REMS is not necessary to ensure the benefits of entrectinib outweigh its risks.

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I concur.

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Subject	Evaluation of Need for a REMS
Established Name	Entrectinib
Trade Name	Roslytrek
Name of Applicant	Genentech
Therapeutic Class	TRK inhibitor
Formulation(s)	Oral capsules
Dosing Regimen	600 mg orally once daily

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## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) entrectinib is necessary to ensure the benefits outweigh its risks. Genentech submitted New Drug Applications (NDAs 212725 and 212726) for entrectinib with the proposed indications for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive (NDA 212725) and for the treatment of adult and pediatric patients<sup>a</sup> with neurotrophic tyrosine receptor kinase (NTRK) fusion positive, (b) (4) metastatic solid tumors who have either progressed (b) (4) (NDA 212726). The risks associated with entrectinib include congestive heart failure, central nervous system effects, QTc interval prolongation, vision disorders, and embryo-fetal toxicity. The applicant did not submit a proposed REMS. The applicant submitted a risk management plan detailing the actions the applicant feels is appropriate to manage the risks associated with entrectinib.

Should entrectinib be approved, this reviewer's recommendation is that a REMS is not needed to ensure its benefits outweigh its risks. The most important adverse events occurring in clinical testing, congestive heart failure, central nervous system effects, QTc interval prolongation, vision disorders, and embryo-fetal toxicity, can be described and managed via labeling.

DRISK and the Division of Oncology Products 2 (DOP 2) agree that the safety profile for entrectinib is acceptable for the patient population, and healthcare providers who will prescribe and administer entrectinib are likely to be able to manage the entrectinib-emergent adverse events without additional risk mitigation measures beyond labeling.

## 1 Introduction

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This review evaluates whether a REMS for the NME entrectinib is necessary to ensure the benefits outweigh its risks. Genentech submitted NDA 210656 for entrectinib with the proposed indications for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive (NDA 212725) and for the treatment of adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion positive, (b) (4) metastatic solid tumors who have either progressed (b) (4) (NDA 212726).<sup>b</sup> This application is

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<sup>a</sup> (b) (4)

<sup>b</sup> The indication statement was changed to: Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. Adult and pediatric patients 12 years of age and older with solid tumors that are neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive without a known acquired mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no (b) (4)

under review in DOP 2. The applicant did not submit a proposed REMS with this application. The applicant submitted a risk management plan detailing the actions the applicant feels is appropriate to manage the risks associated with entrectinib.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Entrectinib, a new molecular entity<sup>c</sup>, is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC, proto-oncogene tyrosine-protein kinase ROS (ROS1), anaplastic lymphoma kinase (ALK), JAK2, and ACK1.

Entrectinib will be supplied as 100 mg and 200 mg capsules. Entrectinib will be administered 600 mg once daily orally, until disease progression or unacceptable toxicity.<sup>d</sup>

Entrectinib was granted breakthrough therapy designation May 12, 2017 for the treatment of adult and pediatric patients with NTRK fusion positive, locally advanced or metastatic solid tumors who have either progressed following prior therapies or as initial therapy where there are no acceptable standard therapies. Breakthrough therapy designation was requested for metastatic NSCLC that is ROS1-positive; this request for breakthrough therapy designation was subsequently withdrawn. Orphan status was granted July 1, 2017 for NTRK fusion positive, locally advanced or metastatic solid tumors that have either progressed following prior therapies or as initial therapy where there are no acceptable standard therapies.

Entrectinib is not approved in any jurisdiction.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761097 relevant to this review:

- 05/12/2017: Breakthrough therapy designation granted for NTRK fusion positive solid tumors
- 07/01/2017: Orphan status granted for NTRK fusion positive solid tumors
- 11/07/2018: Pre-NDA meeting; Agency stated REMS not required for NDA submission; need for REMS would be determined during review
- 02/13/2019: Priority review granted for both NDAs; PDUFA 08/18/19

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<sup>c</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

<sup>d</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 03/18/2019: A Post Mid-cycle meeting for both NDAs was held between the Agency and the Applicant via teleconference; the Division indicated that there were no major safety concerns identified and a REMS was likely not needed

### 3 Therapeutic Context and Treatment Options

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#### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

According to the Centers for Disease Control and Prevention, an estimated 228,150 adults (116,440 men and 111,710 women) in the United States will be diagnosed with lung cancer in 2019. Lung cancer represents about 13% of all new cancer diagnoses. NCLC is the most common type of lung cancer, accounting for 84% of all lung cancer diagnoses.<sup>1</sup>

ROS1 rearrangements occur rarely in NSCLC, occurring in up to 1.8% of patients with NSCLC.<sup>2,3</sup> ROS1 rearrangements are more commonly found in patients with a history of never smoking or only mild smoking with adenocarcinoma histology. The 5-year survival rate for NSCLC is 23%.<sup>4,e,f</sup>

The frequency of NTRK fusion positive solid tumors is not established. In some cancers, NTRK fusions appear to be rare events, for example, occurring less than 2% of the time in colorectal cancer. In some rare cancers, for example, mammary analogue secretory carcinoma, NTRK fusion occurs more commonly. Overall, a prevalence of 0.32% was found in one study of 10,000 tumor samples.<sup>5</sup>

#### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The approval for crizotinib, initially approved August 2011, was expanded March 2016 to include ROS1 positive NSCLC. ROS1 positive NSCLC is not typically fully responsive to chemotherapy and there is a need for additional treatments that target ROS1 positive NSCLC.<sup>6</sup>

Larotrectinib was approved November 2018 for the treatment of patients with NTRK fusion positive solid tumors.

### 4 Benefit Assessment<sup>7,9</sup>

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The efficacy of entrectinib in ROS1-positive NSCLC was examined in pooled data from 3 multi-center, single-arm, open-label trials in patients with histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC.<sup>8</sup> Efficacy was assessed in 53 patients. Patients received 600

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<sup>e</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug.*

<sup>f</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

<sup>9</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

mg entrectinib daily. Treatment continued until disease progression or unacceptable toxicity. Patients had a median age of 53 years (range, 27 to 73 years). Sixty-four percent of the patients were female, 59% were white, and 59% never smoked. The overall response rate was 77%, with 72% having a partial response. Fifty-six percent had a duration of response that exceeded 12 months, and 29% had a duration of response that exceeded 18 months.

The efficacy of entrectinib in NTRK fusion positive solid tumors was examined in pooled data from 54 patients in 3 multi-center, single-arm, open-label trials in patients with unresectable or metastatic solid tumors with NTRK gene fusion positive tumors.<sup>9</sup> Patients received 600 mg entrectinib daily. Treatment continued until disease progression or unacceptable toxicity. Patients had a median age of 57 years (range, 21 to 83 years). Fifty-nine percent of the patients were female, and 80% were white. The most common cancers were sarcoma (24%), lung cancer (19%), salivary gland tumors (13%), breast cancer (11%), thyroid cancer (9%), and colorectal cancer (7%). The overall response rate was 57%, with 50% having a partial response. Twenty-nine percent had a duration of response that exceeded 12 months.

## 5 Risk Assessment & Safe-Use Conditions<sup>10, h</sup>

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The safety database comprised data from 355 patients who received entrectinib in clinical trials.

The most important serious adverse reactions are congestive heart failure (CHF), central nervous system (CNS) effects, QTc interval prolongation, vision disorders, and embryo-fetal toxicity. These events are described in the *Warnings and Precautions* section of the draft labeling. A boxed warning has not been proposed by the applicant or the Agency for any of these events.

### 5.1 CONGESTIVE HEART FAILURE

Congestive heart failure occurred in 12 of 355 patients (3.4%), including Grade 3-4 (1.4%) and Grade 5 (0.6%). Entrectinib was interrupted in 5 patients and discontinued in 4 patients because of CHF. The draft labeling advises prescribers to assess baseline left ventricular ejection fraction (LVEF), monitor patients clinically for possible signs and symptoms of CHF. Should signs and symptoms warrant, LVEF should be reassessed, and entrectinib held, resumed at a lower dose, or discontinued.

### 5.2 CENTRAL NERVOUS SYSTEM EFFECTS

Patients receiving entrectinib in clinical testing experienced a range of CNS effects, including cognitive impairment, mood changes, dizziness, and somnolence. In clinical testing, 93 of 355 (26%)

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<sup>h</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

patients experienced cognitive effects, including cognitive disorders (8%), confusion (7%), attention disturbance (4.8%), and impairment of memory (3.7%). Grade 3 events occurred in 4.5% of patients.

Mood effects included anxiety (4.8%), depression (2.8%), and agitation (2%). Grade 3 events occurred in 1.1% of patients. One Grade 5 event occurred; a patient receiving entrectinib committed suicide.

Dizziness occurred in 35% of patients. Insomnia occurred in 7% of patients, and somnolence occurred in 7% of patients. Grade 3 sleep disorders occurred in 0.6% of patients.

The draft labeling advises that patients should be told not to drive or use machinery if CNS effects occur. If warranted, entrectinib should be withheld and resumed at a lower dose, or permanently discontinued.

### **5.3 QTc INTERVAL PROLONGATION<sup>11</sup>**

QTc interval prolongation was reviewed by the Interdisciplinary Review Team for QT studies. The review concluded that no large QTc prolongation effect (i.e., >20 ms) of entrectinib was observed in the QT assessment of the ECG sub-study of patients (n=113) in an open-label, global Phase 2 study at the proposed therapeutic dose, 600 mg once daily. Analysis of the data did not suggest that entrectinib is associated with large mean increases in the QTc interval. Two patients had QTcF > 500 ms and 11 patients had an increase of QTcF over baseline that exceeded 60 ms. Regarding whether QT interval prolongation should be included in the Warnings and Precautions section of the labeling, the QT-IRT reviewer stated, "We defer to the Division regarding whether Warnings and Precautions for QT interval prolongation is necessary for the intended dose of 600 mg/day. The reviewer did not have specific edits to section 5.2 but stated that not all data presented by the sponsor in section 5.2 could be independently verified. The reviewer recommended the following for section 12.2, Cardiac Electrophysiology, "An ECG sub-study was conducted in 113 patients who received [Entrectinib] 600 mg once daily. Available data does not suggest a large mean increase (i.e., 20 ms) from baseline in QTcF."

The draft labeling describes the risk of QTc interval prolongation in section 5.3. The draft labeling advises healthcare providers to monitor patients at increased risk (e.g., patients with long QT syndrome, CHF, or significant bradyarrhythmias) for QTc prolongation. Should QTc prolongation occur, underlying causes should be addressed. Entrectinib should be discontinued if the patient experiences Torsades de pointes, polymorphic ventricular tachycardia, or signs or symptoms of a serious arrhythmia.

#### **5.4 VISION DISORDERS**

Vision changes occurred in 21% of patients receiving entrectinib in clinical testing. The visual effects most frequently reported included vision blurred (8.7%), photophobia (5.1%), diplopia (3.1%), visual impairment (2%), cataract (1.3%), photopsia (1.3%), and vitreous floaters (1.1%).

The draft labeling advises prescribers to withhold entrectinib and perform appropriate ophthalmological evaluations in patients experiencing severe vision loss. The decision to resume entrectinib at the same or reduced dose should be based on the potential benefit to the patient.

#### **5.5 EMBRYO-FETAL TOXICITY**

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies (pregnant rats exposed to approximately 2.7 times the recommended human dose), and its mechanism of action, it is believed that entrectinib can cause fetal harm when administered to a pregnant woman.

The draft labeling advises prescribers that female patients of reproductive potential should use effective contraception during treatment with entrectinib and for (b) (4) after discontinuing entrectinib.

### **6 Expected Postmarket Use**

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Entrectinib is likely to be used in both inpatient and outpatient healthcare setting. Because entrectinib will be taken orally, patients will be able to take entrectinib at home.

The patient population likely to receive entrectinib will be patients of varying age (the median age of patients in clinical testing was 53 (ROS1 NSCLC) and 57 (NTRK fusion positive solid tumors) years of age, and the range of ages in adult patients was 21 to 83 years of age. Five patients were younger than 17 years of age and were ultimately excluded from the efficacy analysis because so few pediatric patients were included in the study. Patients would be expected to be able to report their treatment-emergent signs and symptoms to their health care providers, and to undergo appropriate laboratory testing.

### **7 Risk Management Activities Proposed by the Applicant**

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The Applicant did not propose any risk management activities for entrectinib beyond professional labeling.

## 8 Discussion of Need for a REMS

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The Clinical Reviewers believe the data support a favorable benefit:risk assessment for entrectinib for the treatment of patients with metastatic NSCLC that is ROS1-positive and for the treatment of patients with NTRK fusion positive, (b) (4) metastatic solid tumors who have either progressed (b) (4). In ROS1 positive NSCLC, clinical testing showed a clinically meaningful treatment effect, with a response rate of 77%. Testing also showed durable efficacy. In NTRK fusion positive solid tumors, the overall response rate was 57%, with 50% having a partial response. Twenty-nine percent had a duration of response that exceeded 12 months.

The review division has advised that the data do not support the need for a REMS. The Clinical Reviewers' preliminary findings were that the applications were appropriate for accelerated approval, with warnings (not boxed) for congestive heart failure, central nervous system effects, QTc interval prolongation, vision disorders, and embryo-fetal toxicity.<sup>1</sup> The clinical reviewers believe the adverse events are manageable with dose reduction, interruption, or discontinuance, and the events are appropriately handled with labeling alone.

This reviewer recommends that, should entrectinib be approved, a REMS is not needed to ensure its benefits outweigh its risks. Congestive heart failure, central nervous system effects, QTc interval prolongation, vision disorders, and embryo-fetal toxicity can be adequately described in the labeling. None of the risks of entrectinib warrants a boxed warning. The most important of the adverse events, CHF, is known to occur with other drugs used to treat cancer, and oncologists are familiar with monitoring for this adverse event. A REMS is not needed to address the risks of entrectinib.

## 9 Conclusion & Recommendations

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Based on the available data, a REMS is not necessary to ensure the benefits of entrectinib outweigh its risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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<sup>1</sup> The clinical review was ongoing at the time of this review.

## 10 Appendices

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### 10.1 REFERENCES

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<sup>1</sup> Centers for Disease Control and Prevention. <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics>. Accessed April 30, 2019.

<sup>2</sup> Warth A, Muley T, Dienemann H, et al. ROS1 expression and translocations in non-small-cell lung cancer: clinicopathological analysis of 1478 cases. *Histopathology*. 2014;65:187–94.

<sup>3</sup> Go H, Kim DW, Kim D, et al. Clinicopathologic analysis of ROS1-rearranged non-small-cell lung cancer and proposal of a diagnostic algorithm. *J Thorac Oncol*. 2013;8:1445–50.

<sup>4</sup> Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. *Oncologist*. 2013;18:865–75.

<sup>5</sup> Zehir A, Benayed R, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med*. 2017;23:703-713.

<sup>6</sup> Park S. Characteristics and Outcome of ROS1-Positive Non-Small Cell Lung Cancer Patients in Routine Clinical Practice. *J Thorac Oncol*. 2018 Sep;13(9):1373-1382.

<sup>7</sup> Marcus L, Donoghue M, Mushti S, Jiang X. Efficacy data summarized from Clinical Reviewers' and Statistical Reviewers' presentations at the Mid-cycle Team Review Meeting, March 7, 2019 and from the FDA-edited labeling as of May 17, 2019.

<sup>8</sup> ClinicalTrials.gov Identifiers: NCT02097810, NCT02568267

<sup>9</sup> ClinicalTrials.gov Identifiers: NCT02097810, NCT02568267

<sup>10</sup> Marcus L, Donoghue M. Safety data summarized from Clinical Reviewers' presentations at the Mid-cycle Team Review Meeting, March 7, 2019 and from the FDA-edited labeling as of May 17, 2019.

<sup>11</sup> Zheng, N. Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review. April 8, 2019

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ELIZABETH E EVERHART  
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I concur.

CYNTHIA L LACIVITA  
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Concur