

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213411Orig1s000**

**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: March 25, 2020

To: Duyen Kelly Mach, PharmD  
Regulatory Project Manager  
**Division of Oncology I (DO1)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Susan Redwood, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Maritsa Serlemitsos-Day, PharmD, BCPS  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TUKYSA (tucatinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: 213411

Applicant: Seattle Genetics, Inc.

## 1 INTRODUCTION

On November 11, 2019, Seattle Genetics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 213411 for TUKYSA (tucatinib) tablets, for oral use. The proposed indication for TUKYSA (tucatinib) is in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 3 prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting.

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 1 (DO1) on December 6, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TUKYSA (tucatinib) tablets, for oral use.

## 2 MATERIAL REVIEWED

- Draft TUKYSA (tucatinib) tablets PPI received on November 11, 2019, and received by DMPP and OPDP on March 10, 2020.
- Draft TUKYSA (tucatinib) tablets Prescribing Information (PI) received on November 11, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 10, 2020.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> 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 we:

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

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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

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

## Memorandum

**Date:** March 23, 2020

**To:** Mirat Shah, MD, Clinical Reviewer  
Division of Oncologic Diseases I (DO-1)

Duyen Kelly Mach, Regulatory Project Manager, DO-1

William Pierce, PharmD, Associate Director for Labeling, DO-1

**From:** Maritsa Serleimitsos-Day, PharmD, BCPS, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kevin Wright, PharmD, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Tukysa™ (tucatinib) tablets, for oral use

**NDA:** 213411

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In response to DO-1's consult request dated December 6, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Tukysa™ (tucatinib) tablets, for oral use (Tukysa). Tukysa is a kinase inhibitor indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DO-1 (Rajesh Venugopal) on March 10, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI 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 March 16, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Maritsa Serleimitsos-Day at (301) 796-1760 or [maritsa.serleimitsos-day@fda.hhs.gov](mailto:maritsa.serleimitsos-day@fda.hhs.gov).

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MARITSA SERLEMITSOS-DAY  
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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)

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Date of This Memorandum: March 19, 2020  
Requesting Office or Division: Division of Oncology 1 (DO1)  
Application Type and Number: NDA 213411  
Product Name and Strength: Tukysa (tucatinib) Tablets, 50 mg and 150 mg  
Applicant/Sponsor Name: Seattle Genetics, Inc.  
OSE RCM #: 2019-2389-2  
DMEPA Safety Evaluator: Tingting Gao, PharmD  
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on March 16, 2020 for Tukysa. Division of Oncology 1 (DO1) requested that we review the revised container labels for Tukysa (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.<sup>a</sup>

## 2 CONCLUSION

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

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<sup>a</sup> Gao T. Label and Labeling Memo for Tukysa (NDA 213411). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 12. RCM No.: 2019-2389-1.

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION  
DIVISION OF HEPATOLOGY and NUTRITION (DHN)**

**Medical Officer Consult Reply and Responses to Questions**

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<b>de novo submission</b>	NDA 213411
<b>Sponsor</b>	Seattle Genetics, Inc.
<b>Drug</b>	Tucatinib
<b>Proposed Indication</b>	Pretreated, locally advanced, unresectable or metastatic HER2 + breast cancer
<b>Consulting Division</b>	DO1
<b>Consult Due Date</b>	March 17, 2020
<b>Date review Completed</b>	March 16, 2020
<b>Clinical Reviewer</b>	Mari Blackburn, DO
<b>Team Leader</b>	Frank Anania, MD
<b>Signatory</b>	Joe Toerner, MD
<b>Project Manager</b>	Cheronda Cherry-France

**Background**

**Reason for consultation**

The Division of Oncology 1 (DO1) is requesting consultation from DGIEP to seek concurrence of independent adjudication from an outside hepatologist for NDA 213411, an application submitted for a new molecular entity (NME) tucatinib. Tucatinib is a tyrosine kinase inhibitor that is being considered for the treatment of both advanced and metastatic human epidermal growth factor receptor 2 positive (HER2+) carcinoma of the breast. The NDA has been granted priority review with a PDUFA goal date of 20 August 2020. As a result of the hepatologist's consultation, the Sponsor amended its NDA application based on the consultant's findings that tucatinib was only associated only with mild and self-limited drug-induced liver injury (DILI), but not more serious DILI that would meet the criteria of hepatocellular jaundice, or *Hy's Law*. DO1 provided the report of [REDACTED] (b) (6)

[REDACTED] report outlines 11/404 subjects in HER2CLIMB (ONT-380-206) receiving a triple drug regimen including tucatinib, capecitabine and trastuzumab in a multinational, double-blind, randomized, placebo-controlled, phase 2 trial. The trial enrolled 612 participants and is now closed to accrual but still open for data collection. DO1 submitted the Hepatologist's findings to DGIEP to confirm that none of the identified subjects with DILI in the phase 2 trial met *Hy's Law* criteria.

**Materials reviewed for consultation:**

1. Hepatology Consultant's statement
2. NDA Clinical Safety Report for 11 subjects

## Pharmacology of Tucatinib

Tucatinib is an orally bioavailable, small molecule tyrosine kinase inhibitor (TKI) that is highly selective for HER2, a growth factor receptor that is over-expressed and involved in the pathogenesis and progression of multiple cancers, including breast cancer. Tucatinib is primarily metabolized by CYP2C8 and mainly eliminated through the hepatobiliary route. Renal clearance is minimal. Since tucatinib is eliminated by extensive hepatic metabolism the concern for potential liver toxicity is reasonable. However, the HER-2 gene is considered a poor prognostic factor in women with carcinoma of the breast and in this study tucatinib was indicated for patients with incurable locally advanced or metastatic disease. Additionally, tucatinib studies have enrolled significant numbers subjects with past or active brain metastases for which efficacious systemic treatment remains an unmet medical need. Therefore, the benefit-risk in women who could take tucatinib for its intended use as indicated in the phase 2 clinical trial is quite high.

## Protocol Review

### Phase 2 trial ONT-380-206 (HER2CLIMB)

ONT-380-206 (HER2CLIMB) is a phase 2 randomized, double-blinded, active comparator study of tucatinib vs. placebo in combination with capecitabine and trastuzumab in women with pretreated unresectable, locally advanced, or metastatic HER2+ breast carcinoma under NDA 213411. Eligible subjects received treatment administered in 21 day-cycles and either tucatinib or placebo was given orally (PO) twice daily (BID). The tucatinib dose was 300 mg. Capecitabine was also administered at 1000 mg/m<sup>2</sup> PO BID on Days 1–14 of each 21-day cycle. Trastuzumab was given as a loading dose of 8 mg/kg intravenous (IV) followed by 6 mg/kg once every 21 days (or as 600 mg of trastuzumab given subcutaneously once every 3 weeks). The later 2 agents were also administered to placebo-treatment patients and represent current standard-of-care for women with advanced breast CA.<sup>1</sup> The end of the study treatment was defined as the discontinuation of tucatinib/placebo even if subjects continue receiving trastuzumab and/or capecitabine alone. Treatment was continued until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.

Prior to the trial there was no report that any of the enrolled women had underlying non-metastatic liver disease. There was no evidence of hepatic steatosis, obesity, diabetes, anesthesia allergies or viral hepatitis in study subjects. No trial inclusion or exclusion criteria addressed liver disease as a concern and no screening for viral hepatitis was performed prior to study entry.

During the phase 2 trial 11/612 (1.8%) subjects in the trial developed elevations of liver enzyme levels which prompted concerns for drug induced liver injury (DILI). Of these 11 subjects, two subjects were in the placebo arm. In the tucatinib treatment arm of 404 patients, 86 (21%) had increased levels of aspartate aminotransferase (AST), 81(20%)

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<sup>1</sup> Murthy R, et al., (2018). Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomized, open-label, phase 1b study. *Lancet Oncol* 19(7): 880-8.

had increased levels of alanine aminotransferase (ALT), and 75 (19%) had increased levels of total bilirubin (TBL). In the placebo arm, 22/191 subjects (11%) had increased AST, 13 (7%) increased ALT, and 20 (10%) had increased TBL. Table 1(below) summarizes the subjects' liver biochemical excursions in the trial. As noted by the Hepatology consultant in DILI, 7/11 subjects had elevations in their alkaline phosphatase (ALP). And, elevations in ALP are not typical of patients who experience Hy's Law DILI.

### Hy's Law

Hy's Law<sup>2</sup> defines DILI as it arises nearly always from hepatocellular injury that results in concomitant hyperbilirubinemia (jaundice). It is a serious form of DILI and be an ominous indicator of acute liver failure and need for liver replacement therapy. It is characterized by any one of the following three findings.

1. A drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
2. Among trial subjects demonstrating aminotransferase (AT) elevations, AT much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP).
3. Another explanation cannot be found to explain the combination of increased aminotransferases and total bilirubin, such as acute (viral) preexisting liver disease, or a concomitant medication that also causes the same or similar pattern of liver injury (<https://www.fda.gov/media/116737/download>)

### Normal Values

**Table 1** contains the normal liver biochemistry values that generally are accepted by the Division that were used for the purpose of adjudication of identified cases.

**Table 1:** DHN ULN values

Lab test	ULN
Alanine aminotransferase (ALT)	≤ 30 U/L or IU/L
Aspartate aminotransferase (AST)	≤ 35 U/l or IU/L
Total bilirubin (TB) or (TBL)	≤ 1.3 mg/dL or IU/L
Direct bilirubin (DB)	≤ 0.3 mg/dL
Alkaline phosphatase (ALP)	≤ 125 IU/L
INR, PT	Proposed by sponsor

<sup>2</sup> Merz, M, et al, Methodology to Assess Clinical Liver Safety Data, 2014, [Drug Saf.](#); 37: 33–45.

Among 404 patients receiving the triple drug regimen including tucatinib, capecitabine and trastuzumab, 9/404 (2.2%) subjects had (AST/ALT  $\geq$  3XULN with total bilirubin  $\geq$ 2XULN).

The independent expert hepatologist adjudicated 11 cases, two of which were in the control (placebo) arm, and 9 in the tucatinib arm. In the expert hepatologist's opinion, only 3 of these met the additional threshold of having alkaline phosphatase (ALP)  $\leq$  1.5 x upper limit of normal (ULN).

### **Tucatinib + Capecitabine +Trastuzumab Subjects**

**Case** (b) (6) This was a 57-year-old white female with adenocarcinoma of the breast. The patient was admitted with metastases to lung, bone, and distant lymph nodes at study entry. Reported prior adjunctive therapy included radiation to the left breast nodal basin and radiosurgery to a liver mass. There is no past medical history or other known risk factors to consider for DILI adjudication. Entry liver biochemistry on day -15 included AST 73 U/L (1.6X ULN), ALT 57 U/L (1.0X ULN), ALP 287 U/L (2.3XULN), and bilirubin of 17.1  $\mu$ mol/L (1X ULN). (The normal range in system internationale (SI) for TBL is [0-17 $\mu$ mol/L])<sup>3</sup>.

On study day 32 liver biochemistries revealed AST 251 U/L (5.5X ULN), ALT 168 U/L (3.0X ULN), and TBL of 63.3  $\mu$ mol/L (2.8X ULN); ALP was not performed on this date. As a result, dosing with tucatinib and capecitabine was interrupted due to the elevation of AST. By study day 66 the patient's liver biochemistry included normal transaminases: AST 38 U/L (WNL), and ALT 28 U/L (WNL), ALP 172 U/L (1.4X ULN), and TBIL 2.1 mg/dL (1.6X ULN).

*Reviewer comment: Prior to receiving the study drug the subject had been diagnosed with bone metastases which may account for the patient's elevated alkaline phosphatase at baseline (>1.5X ULN). It is not known whether the patient had liver metastases. While the expert hepatologist reported that the subject had been treated with hepatic stenting prior to starting the study, we were not provided these details nor was the Division provided fractionation of bilirubin. However, the consultant noted bilirubin fractionation at day 28 the indirect bilirubin declined. Also, of note the hepatology consultant had either converted bilirubin values into mg/dL or had the equivalents of these; the Division only had total bilirubin in this case (and most others) in SI units [ $\mu$ mol/L].*

*The Sponsor in this case as in most of the cases to be adjudicated, either discontinued (or withheld) both tucatinib and capecitabine. According to LiverTox,<sup>4</sup> capecitabine can*

<sup>3</sup> Source: NORMAL LABORATORY VALUES. aidsinfonet.org.2014. International Association of Providers of AIDS Care. ([http://www.aidsinfonet.org/fact\\_sheets/view/120](http://www.aidsinfonet.org/fact_sheets/view/120)).

<sup>4</sup> LiverTox, Clinical and Research Information on Drug-Induced Liver Injury Bethesda (MD): [National Institute of Diabetes and Digestive and Kidney Diseases](https://www.ncbi.nlm.nih.gov/books/NBK547852/); 2012-. (<https://www.ncbi.nlm.nih.gov/books/NBK547852/>).

be associated with both mild elevations in transaminases or mild elevation of serum bilirubin in up to 40% of patients on this drug. However, since hyperbilirubinemia is usually the indirect fraction, which in this case it was, this raises suspicion that capecitabine was a possible culprit. However, if the bilirubin was increased from the drug capecitabine it would not typically be associated with transaminitis. Within four weeks of discontinuation of both drugs, the subject's transaminase levels also decreased to normal ranges as did the ALP and TB.

The expert hepatologist summarized that this patient's findings were possibly consistent with DILI caused by either tucatinib or capecitabine. The Division agrees that either drug could be associated with DILI in this patient. However, the subject's elevated ALP level (2.3xULN) at study entry cannot be discounted. Since the patient had an elevated ALP, either due to bone metastases and/or possibly liver metastases, it is highly unlikely that this is a Hy's law case of hepatocellular jaundice as there are too many confounders.

**Case** (b) (6): This was a 38-year-old white female diagnosed with invasive carcinoma with liver metastases at study entry. Pertinent medical history included chronic nausea, insomnia, anorexia, generalized pruritis and elevated transaminases at baseline. The subject had been treated with systemic therapy for metastatic disease from (b) (6). Surgical history for breast cancer included a bilateral mastectomy in (b) (6).

The subject's liver biochemistries at baseline included AST 166 U/L (3.6X ULN), ALT 203 U/L (3.1X ULN), ALP 857 U/L (6.8X ULN), TBL of 22.23  $\mu\text{mol/L}$  (1X ULN). On study day 12, liver biochemistry showed decline in ALT 114 U/L (1.7X ULN), AST 138 U/L (3.0X ULN), ALP 626 U/L (5.0X ULN), with increased TBL 46.2  $\mu\text{mol/L}$  (2.1X ULN). The subject's tucatinib and capecitabine were interrupted due to the increase in bilirubin, while trastuzumab was maintained at the usual dose. On study day 23 the patient was hospitalized due to increasing bilirubin and hypokalemia. A CT scan of the abdomen detected hepatomegaly with scattered lesions consistent with progressive metastatic disease. The subject's last study drug was administered on study day 12, and further treatment for cancer was discontinued due to disease progression.

*Reviewer Comment: The patient entered the study with liver metastases and significant ALP elevation which indicates the presence of cholestasis. Upon discontinuation of all study drugs on study day 12, the subject had mild, transient improvement in her AST, ALP, AST and TBL levels. However, by study day 50 her TBL had increased to 208.6  $\mu\text{mol/L}$  (9.4x ULN). The progression of the subject's metastatic liver disease obscures a clear cause for the finding of Hy's Law criteria on study day 12. The independent reviewer concluded that DILI was possible but metastatic disease was the more likely cause of abnormal liver biochemistries levels. Given the short exposure to tucatinib, the Division would state that this is not a Hy's Law DILI and any association of tucatinib with*

*these mild transaminase elevations is at most possible but highly unlikely. We concur with the expert hepatologist's opinion that this is not DILI.*

(b) (6) This was a 55-year-old black/African American woman diagnosed with adenocarcinoma of breast. The subject had metastases in the liver, distant lymph nodes, and bone at study entry. The subject received prior systemic therapies for the treatment of breast cancer from (b) (6). Surgical history for breast cancer included a bilateral mastectomy. Pertinent medical history included ongoing fatigue. Past medical history included obesity and nausea.

Liver biochemistry results on study day-9 included AST 57 U/L (1.2X ULN), ALT 45 U/L (1.5X ULN), ALP 327 U/L (2.6X ULN) and TBL 15.4 µmol/L (0.9X ULN). The subject's liver biochemistry results on study day 63 were notable for AST 100 U/L (2.2X ULN), ALT 109 U/L (1.7X ULN), ALP 122 (WNL), and TBL 17.1 µmol/L (1X ULN). On study day 210 the subject's liver biochemistry results were as follows: ALT 44 U/L, ALP 224 U/L (1.8X ULN), AST 51 U/L (1.1X ULN) and TBL 13.7 µmol/L (0.8X ULN). Treatment with all 3 study drugs was discontinued due to progressive disease, tucatinib on study day 230, capecitabine on study day 223, and trastuzumab on study day 220. On study Day 232 the subject was hospitalized for progressively worsening nausea and vomiting and was diagnosed with pancreatitis. The results of the patient's computed tomography scan revealed probable metastatic disease to the liver and possibly to the pancreas. Concomitant medications included carvedilol, enalapril, spironolactone, lorazepam, denosumab, omeprazole, Vicodin, and ondansetron. The patient was discharged to home in stable condition on study day 237. On study day 259, the subject discontinued from the study due to withdrawal of consent. On the same day, the liver biochemistry studies included AST 158 U/L (3.4X ULN), ALP 403 U/L (3.2X ULN), ALT 49 (1.6X ULN) U/L, and bilirubin 230.9 µmol/L (10.4X ULN).

*Reviewer comment: In this subject's transaminases the actual criteria that met Hy's Law did not become manifest until after all drugs, including tucatinib were discontinued. The question that is raised in this case is whether tucatinib had a latency effect that would be associated with liver injury. Given the patient's overt tumor burden with extensive metastatic disease and elevated ALP at baseline, and rising bilirubin in the setting normal or near normal ALT (AST is not a liver specific transaminase), the totality of evidence does not suggest this is DILI either. The stability of ALT values throughout her course, the presence of bone and liver metastases, and the sharp rise in bilirubin in the presence of a stable ALT all suggest that tucatinib was not responsible for the increases in liver biochemistries observed in this patient. Furthermore, this case underscores to DGIEP the benefit-risk of use for tucatinib in women afflicted with severely advanced carcinoma of the breast.*

(b) (6) This was a 67-year-old white female diagnosed with invasive ductal carcinoma with metastases to the liver, local/regional lymph nodes, and to the intra-abdominal viscera at study entry. Pertinent medical history included chronic ALP

elevation. The subject had received prior systemic therapy for metastatic disease from (b) (6). Concomitant medications of interest included: prednisone, duloxetine, estradiol, gabapentin.

The subject's liver biochemistries at baseline included ALT 33 U/L (1.0X ULN), AST 40 U/L (1.1X ULN), ALP 443 U/L (4.1X ULN), and TBL 18.8 µmol/L (1.1X ULN). On study day 11, the subject's liver biochemistry results included AST 52 U/L (1.3X ULN), ALT 49 U/L (1.5X ULN), ALP 341 U/L (3.2X ULN), and TBL 23.9 µmol/L (1.2X ULN). On study day 49 the subject's liver biochemistry demonstrated the following increases: AST 220 U/L (5.5X ULN), ALT 248 U/L (7.5X ULN), ALP 230 U/L (2.1X ULN), and TBL 51.3 µmol/L (2.5X ULN.) Treatment with all 3 study drugs was discontinued. The subject's last dose of tucatinib, capecitabine, and trastuzumab was administered on study day 48, study day 35, and study day 42, respectively. A CT scan and PET scan of the abdomen and pelvis were performed on study day 58 and detected peritoneal thickening, ascites, and mesenteric haziness consistent with peritoneal carcinomatosis. No information on the patient's clinical course was available. By study day 79 transaminase levels were normal, and ALP 254 U/L (2.4X ULN) was below baseline level and TBL had decreased to 23.9 µmol/L (1.2X ULN).

*Reviewer comment: The subject was admitted into the study with an elevated ALP level, a finding consistent with liver metastases, and nearly normal transaminase and TBL levels. After receiving her third treatment cycle, the subject developed elevations of transaminase levels which were much greater than 3X ULN and TBL greater than 2-fold ULN which are consistent with Hy's Law. Further concerning for DILI was the reduction in ALP by almost 50% as transaminase levels and TBL increased significantly. This injury pattern suggests a reduction in cholestasis through reduced tumor burden while demonstrating hepatocellular injury though an ALT level which was normal initially, rose to 7.5xULN after drug exposure, and returned to normal 30 days after withdrawal of the treatment regimen. The independent hepatologist concluded that this case probably was DILI due to tucatinib and capecitabine. The Division concurs.*

(b) (6) This was a 44-year-old white female diagnosed with ductal carcinoma *in situ*, with metastases to the lung, liver, bone, and local/regional lymph nodes at study entry. The subject received prior systemic therapy for the treatment of breast cancer in (b) (6). Baseline liver biochemistry studies from study day -7 included ALT 17 U/L (0.5X ULN) AST 55 U/L (1.6X ULN) ALP 403 U/L (3.1X ULN), and TBL 10.3 µmol/L (0.6X ULN). On study day 36 the results from routine liver biochemistry screening were: ALT 39 U/L (1.1X ULN), ALP 360 U/L (2.8X ULN), AST 93 U/L (2.7X ULN) and TBL 27.4 µmol/L (1.3X ULN). On study day 41 computerized tomogram revealed progression of metastatic disease, specifically in the lung, liver and bones with significant tumor burden in the liver and possible malignant ascites. Treatment with all 3 study drugs was discontinued due to disease progression. The subject's last dose of tucatinib, capecitabine, and trastuzumab was administered on study day 42, study day 35, and

study day 22, respectively. On study day 82 the subject died due to disease progression.

*Reviewer Comment: The Division concurs with the outside hepatologist, there is no evidence presented that DILI is a concern in this case history. The patient had extensive hepatic tumor burden with what appears to be malignant ascites. This case should be removed from the rank of DILI subjects in the NDA review.*

(b) (6) This was a 28-year-old with invasive ductal carcinoma with metastases in the liver, brain, bone, local/regional lymph nodes, and pleural effusion at study entry. The subject underwent systemic therapy for the treatment of breast cancer from (b) (6). Surgical history for breast cancer included right mastectomy. The patient was treated with radiation therapy to multiple bone, brain, and lymph node metastases. Pertinent medical history included fatigue, constipation, and elevated alkaline phosphatase. At the screening visit on study day-14, the subject's liver biochemistry results included AST 25 U/L (WNL), ALT 20 U/L (WNL), alkaline ALP 173 U/L (1.4X ULN), and TBL 3.4 µmol/L (WNL). On study day 22 the patient presented to the emergency department with severe abdominal pain. The patient's liver biochemistry studies then revealed an AST 104 U/L (2.9x ULN), ALT 243 U/L (4.7x ULN), ALP 428 U/L (3.4xULN), and TBL 46.2 µmol/L (2.1xULN). The subject's last dose of tucatinib, capecitabine, and trastuzumab was administered on study day 21, study day 14, and study day 1, respectively. During the hospitalization the patient required stenting of the common bile duct.

*Reviewer Comment: The patient developed biliary obstruction from metastatic intrahepatic and extrahepatic tumor burden which required stenting. The Division concurs with the hepatologist's conclusion. This is also not a case of DILI.*

(b) (6) This was a 57-year-old white female with adenocarcinoma of the breast with metastases to the lung at study entry. The subject received systemic therapy for metastatic disease from (b) (6); and, prior radiation therapy was administered to the left breast and left subclavicular lymph node. All baseline liver biochemistry values on study day 1 were normal including ALT 16 U/L (WNL), AST 17 U/L (WNL), TBL 7 µmol/L (WNL), and ALP 108 U/L (WNL). On study day 35 her transaminases increased to ALT 94 U/L (2.7X ULN) and, AST 126 U/L (3.6X ULN), but TBL 17.1 µmol/L (1.0xULN), and ALP 132 U/L (1.1X ULN) remained normal. No action was taken with any study drugs. On study day 64 the patient's transaminases had increased further with ALT 118 (3.6X ULN), AST 97 (3X ULN) with ALP 135 (1.3X ULN) and TBL 19 µmol (1.1X ULN).

However, by study day 73 the subject's liver biochemistries had all increased with ALT 206 U/L (5.9X ULN), AST 166 U/L (4.7X ULN), total bilirubin 34.2 µmol/L (2.0X ULN), but ALP 156 U/L (1.3x ULN) remained normal. Laboratory studies were repeated on study day 76 and demonstrated that transaminase levels had not improved and that TBL had further increased: ALT 205 U/L (5.9X ULN), AST 161 (4.6X ULN), and TBL

39.3 µmol/L (2.3X ULN). Consequently, dosing with tucatinib was interrupted on study day 80; but capecitabine and trastuzumab were maintained at the initiating dose. On study day 83, the patient's transaminases and TBL remained elevated but were declining.

On day 85, during cycle 6, tucatinib was restarted at the original dose of 300 mg B.I.D., while capecitabine was reduced from 2000mg/m<sup>2</sup>/day to 1500mg/m<sup>2</sup>/day due to recently elevated, but now normalized TBL 15µmol/L. By study day 93 the subject's transaminases and TBL again were increasing with ALT 152U/L (2.9X ULN), AST 128 (3.5X ULN), TBL 26 µmol/L (2.1X ULN). Tucatinib was interrupted from day 93-94 and by day 106 the hepatocellular injury appeared to have resolved as all liver biochemistries normalized: ALT 22 U/L (WNL), ALP 126 (1.2X ULN), AST 22 U/L (WNL) and TBL 13µmol/L (WNL). On day 106 Tucatinib was restarted at a lower dose (250 mg B.I.D.)

Seven days later, on day 113, the patient's liver biochemistries again increased, with results including: ALT 60 U/L (1.7X ULN), AST 62 U/L (1.8X ULN), and total bilirubin of 35.9 µmol/L (2.1X ULN). On study day 116, tucatinib was again interrupted due to increased bilirubin (value not reported) while no change was made to capecitabine or trastuzumab. On study day 127 tucatinib was restarted at a reduced dose (200 mg BID). No further action was taken with any of the 3 study drugs. On study day 251 the subject had completed 12 cycles of study treatment. Treatment with all 3 study drugs was discontinued due to progressive disease.

*Reviewer comment: On study day 73 the subject's laboratory findings barely reached the level of Hy's Law DILI, with TBL 2X ULN and transaminase levels above the threshold of >3x ULN. The interruption in tucatinib and dose reduction of capecitabine did correspond with improved liver biochemistry tests. The Division notes that the patient had restarted tucatinib again with elevations in liver biochemistry that clearly did not meet Hy's Law criteria. The Division suspects that the patient began to accommodate the effect of tucatinib and subsequently the parameters for any significant transaminase or bilirubin increases were mitigated. This hypothesis may be supported by the fact that the patient was able to tolerate the reduced dose of tucatinib and the TBL did not increase to levels >2.0X ULN, and transaminase levels remained below 3X ULN.*

*Capecitabine has a known side effect of causing increased serum aminotransferase levels, usually under 5X ULN and mild to moderate TBL elevation in up to 40% of patients.<sup>5</sup> While Hy's Law criteria were met only briefly and transiently, recurrent episodes of TBL increasing above >2x normal occurred at three separate timepoints days, 73, 83, and 113 and did improve after the tucatinib was either interrupted, resumed, or a decreased dose was administered. The expert hepatic reviewer felt this patient had mild DILI due to tucatinib and/or capecitabine is probable. The Division*

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<sup>5</sup> LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. [National Institute of Diabetes and Digestive and Kidney Diseases](https://www.ncbi.nlm.nih.gov/books/NBK547986/); 2012: (<https://www.ncbi.nlm.nih.gov/books/NBK547986/>)

agrees. However, we'd like to point out this patient was distinct from all the others adjudicated, since she had the most likely example of liver biochemistry that met the definition of a true Hy's Law case of DILI following day 93 resumption of tucatinib. Interestingly, we suspect this patient was likely to accommodate DILI from tucatinib as evidenced by reduced increases in transaminases following successive rechallenges with lower dosing of tucatinib.

(b) (6) This was a 52-year-old white female diagnosed with adenocarcinoma *in situ* of the breast with liver metastases at study entry. The patient had systemic chemotherapy from (b) (6). Surgical history for breast cancer included a right mastectomy. No relevant medical history was reported. No history of alcohol use was noted. Concomitant medications of interest include amoxicillin/clavulanate and methimazole. At study day -9, hepatitis B, hepatitis C and other viral tests were negative. Liver biochemistry studies on study day -9 were normal and included AST 30 U/L, ALT 20 U/L, ALP 123 U/L, and TBL 13.7 µmol/L. On study day 34 the subject's liver biochemistry studies included AST 142 U/L (4.2X ULN), ALT 269 U/L (4.9X ULN), ALP 135 U/L (1.0X ULN), and TBL 27.4 µmol/L (2.3X ULN). Dosing with tucatinib was interrupted from study day 38 to study day 42 due to transaminase elevations, but capecitabine and trastuzumab were not interrupted nor dose-reduced. On study day 43, serum ALT returned to normal ALT 74 U/L (1.3X ULN) but AST was not reported, and TBL had fallen to 30.8 µmol/L (1.5X ULN); as a result, the tucatinib was restarted. On study day 61, liver biochemistry results of AST 35 U/L (1.0X ULN), ALT 42 U/L WNL, ALP 151 U/L (1.0X ULN), TBL 25.7 µmol/L (1.3X ULN), direct bilirubin (DBR) 0.7 mg/dL (0.5X ULN), were reported. Treatment with all 3 study drugs was eventually discontinued due to progressive disease

*Reviewer Comment: The subject developed transaminase and TBL elevations which met the threshold of Hy's Law on day 37, in the second treatment cycle. Tucatinib was withheld for five days and restarted at a reduced dose, consistent with the study protocol. The subject's liver biochemistry studies remained stable and at levels below concern for DILI for the remainder of the time she received the study regimen. This case is consistent for DILI caused by tucatinib which resolved with dose reduction. It should be noted that the Sponsor reported that the subject was taking amoxicillin/clavulanate and methimazole, both of which are well-established causes of liver injury, at the time of "the event", the timepoint of which was not specified. It is the expert hepatologist's opinion is that DILI caused by tucatinib is probable and capecitabine is probable. The Division agrees with the assessment that DILI caused by tucatinib is probable. The Division does not fully agree with the outside hepatologist's opinion that capecitabine contributed to DILI since liver biochemistry results returned to normal without any adjustment of capecitabine.*

(b) (6) This was a 38-year-old white female with invasive ductal carcinoma. The subject had renal, brain, lung, liver, and bone metastases at study entry. The subject received prior systemic therapy for the treatment of breast cancer from (b) (6)

Surgical history for breast cancer included a right mastectomy. Additional adjuvant treatment included radiation therapy for cerebral and cerebellar metastases. Screening liver biochemistry studies on study day -19 included ALP 217 U/L (2.0xULN), AST 36 U/L (1.2XULN), ALT 32 U/L (WNL), TBL 13 µmol/L (1.0 X ULN).

On study day 64, during cycle 4, the patient's TBL increased to 44 µmol/L (2X ULN) while transaminases remained normal, ALP 147 U/L (1.3X ULN), AST 44 U/L (1.4x ULN), ALT 30 (WNL). No changes to the drug regimen were reported. On study day 106 the subject's TBL, AST, and ALT increased, laboratory values included: TBL 55 µmol/L (2.6X ULN), ALT 50 U/L (1.4X ULN), AST 100 U/L (3.2X ULN), and ALP 207 U/L (1.9X ULN). Dosing with tucatinib and capecitabine was interrupted on study day 106. Laboratory values peaked on day 108 with the following results: ALT 142 (4.7X ULN), AST 199 (6.6X ULN), TBL 44 (2.2X ULN) and ALP 386 U/L (3.9X ULN). By study day 111 the subject's reported liver biochemistry levels improved: TBL 25 µmol/L (1.3X ULN), AST 54 U/L (1.8X ULN) and ALT 58 (1.9X ULN), and ALP 292 U/L (2.9X ULN). Tucatinib and capecitabine were restarted on day 114.

Treatment with all 3 study drugs was discontinued due to the progressive disease. The subject's last dose of tucatinib, capecitabine, and trastuzumab was administered on study day 231, 224 and 211 respectively. The subject's final liver biochemistry studies were recorded on study day 232 with the following values: ALP 135 U/L (1.2xULN), AST 34 U/L (1.1xULN), ALT 23 (1.2xULN) and TB 25 µmol/L (1.2xULN).

*Reviewer Comment: The subject developed transaminase elevations of AST 3.2X ULN, and TBL 2.6X UL on day 108. Values then peaked and rose to the level of Hy's Law on study day 108 with TBL 2.2X ULN, AST 4.7X ULN, and AST 6.6X ULN during cycle 6 of the study regimen. The levels improved when tucatinib and capecitabine were withheld and did not increase when they were resumed. In the outside hepatologist's opinion, this case represents possible DILI due to tucatinib and capecitabine. The patient's initial liver biochemistry vs. the biochemistry recorded at day 64 are not substantially different. While we don't have bilirubin fractionation a total bilirubin of 2.0 would not likely merit reduction or discontinuation of the study drug. It was not until day 106 that the total bilirubin rose to > 2.6 X ULN with a single AST elevation. With these data and a follow-up ALP that was elevated, coupled with the fact that the Sponsor discontinued medications for progressive disease, the Division does not agree this case is likely representative of DILI, or there was not enough information for us to confidently make that assessment.*

## Placebo Cases

(b) (6) This was a 57-year-old white woman with invasive ductal carcinoma and was admitted to the study with liver metastases. The subject received systemic therapy for the treatment of breast cancer from (b) (6). Pertinent surgical history included a lumpectomy and biliary stent insertion. On study day 1, the patient received standard of control (placebo+cap+tra) and the subject's reported liver biochemistry values were: TBL 21 µmol/L (1.2X ULN) AST 106 U/L (3.0X ULN); ALT 136 U/L (3.9X ULN); ALP

1069 U/L (8.9X ULN); and gamma-glutamyl transferase (GGT) 899 U/L (25.4X ULN). On study day 6 the subject developed nausea and hyperbilirubinemia and her reported liver biochemistry levels became markedly abnormal: TBL 69 µmol/L (4.0X ULN), AST 89 U/L (2.5X ULN), ALT 110 U/L (3.1X ULN), ALP 790 U/L (6.6X ULN) and GGT 773 U/L (22X ULN). Dosing with placebo and capecitabine was interrupted from study day 6 and study day 7 respectively, due to TBL increase. Trastuzumab was continued. On study day 9, endoscopic retrograde cholangiopancreatography (ERCP) was performed and the patient was found to have a biliary occlusion in hilar region of the liver. A new stent was placed in both the left and right ducts through existing stents. Following biliary decompression, study day 22, the patient's liver biochemistries were markedly improved with a total bilirubin of 28 µmol/L (1.6X ULN), AST 98 U/L (2.8X ULN), ALT 73 U/L (2.1X ULN), ALP 702 U/L (5.9X ULN) and GGT 457 U/L (22X ULN). On study day 23, dosing with capecitabine was resumed at the pre-discontinuation dosage. On study day 29 laboratory results showed total bilirubin of 24 µmol/L (1.4xULN), AST of 88 U/L (2.5xULN), ALT of 72 U/L (2.1xULN), and GGT of 553 U/L (27X ULN). On study day 29 treatment with placebo was resumed with a reduced dose of 250 mg. Ultimately, treatment with all the placebo and the 2 SOC treatments were discontinued due to progressive disease. On study day 236 the subject died due to disease progression.

*Reviewer comment: This case underscores that tucatinib is not likely to be a significant cause of DILI, whether it meets Hy's Law criteria or not. This patient having received the placebo and the two SOC agents had a significant tumor burden that required repeated biliary decompression as well as the possibility almost certainly of hepatic or hilar metastases. There are no associated DILI-related events per Liver Tox with trastuzumab.<sup>6</sup> There is no association with DILI here, but it proves that the benefit-risk of the study drug is not likely changed by the level of cholestasis in these subjects, nor even baseline transaminase. The subject had a dramatic increase in TBL on study day 6 due to a hepatic stent occlusion. For the remainder of the study, despite disease progression, her TBL remained below 2xULN even with the resumption of cap which is associated with mild to moderate increases in TBL. The subject entered the trial with advanced disease and liver metastases; her ALP was greater than 2.9xULN throughout the trial. Her ALT level rarely rose above 2xULN after the stent occlusion was corrected. It is the Agency's opinion that this is not DILI.*

(b) (6) This was a 66-year-old white female diagnosed with adenocarcinoma of the breast and was admitted with metastases to the liver and distal lymph nodes at study entry. The subject received systemic therapy for the treatment of breast cancer from (b) (6). Surgical history for breast cancer included a tumorectomy. On study day -8, the laboratory results were as follows: AST 125 U/L (3.0X ULN), ALT 53 U/L (1.1X

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<sup>6</sup> LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. [National Institute of Diabetes and Digestive and Kidney Diseases](https://www.ncbi.nlm.nih.gov/books/NBK548559/); 2012: (<https://www.ncbi.nlm.nih.gov/books/NBK548559/>)

ULN), ALP 314 U/L (2.1 ULN), and bilirubin 13 µmol/L (1.0 X ULN). On study day 14 the subject's laboratory test results revealed: AST 258 U/L (6.3X ULN), ALT 84 U/L (1.7X ULN), ALP 265 U/L (2.1X ULN), and bilirubin 12.3 µmol/L (NL). Dosing with placebo was interrupted on study day 15 due to increased GGT. No action was taken with capecitabine and trastuzumab. Dosing with placebo was resumed on study day 31 at a reduced dose of 250 mg BID. On study day 65 liver biochemistry studies improved: AST 98 U/L (2.8XULN), ALT of 29 U/L, ALP 147 U/L (1.2 XULN) and TBL 24.8 µmol/L (1.0xULN). On study day 89 liver biochemistry studies worsened: AST 153 U/L (4.4X ULN), ALT 39 U/L (WNL), ALP 186 U/L (1.5 X ULN), and TBL 63.8 µmol/L (2.7X ULN). Ultimately all three agents were discontinued around day 88 due to disease progression.

*Reviewer Comment: The subject participated in the study for 81 days. Her ALT level remained < 1.7 x ULN throughout her enrollment and her TBL level remained within a normal range until her physician discontinued her participation due to disease progression on day 88. The more nonspecific liver biomarkers AST, ALP, and GGT were more significantly elevated and more labile. The investigator did interrupt the placebo and resumed it at a decreased dose while continuing the SOC agents which did not have a significant effect. The Division does not consider this to be DILI.*

Score	Causality	Likelihood (%)	Textual Definition
1	Definite	≥95%	Causality is “beyond a reasonable doubt”
2	Highly likely	75-94%	Causality supported by “clear and convincing evidence”
3	Probable	50-74%	Causality supported by the “preponderance of the evidence”
4	Possible	25-49%	Less than the preponderance of evidence but still possible
5	Unlikely	<25%	Causality unlikely or excluded

**Table 2: Assessing the likelihood for causality**

### Summary and Conclusion:

The Division was asked to evaluate an independent reviewer's adjudication of 11 Sponsor-reported cases of possible Hy's Law DILI related to tucatinib which is indicated for advanced HER 2+ breast cancer and is now under consideration as a new drug application under priority review. The Division of Oncology Products also provided brief case reports for DGIEP(DHN) to facilitate our review and to comment on the independent expert Hepatologist who conducted adjudication of the potential DILI cases in the treatment, not placebo, arm. Of the 11 cases reviewed, 9 were randomized to the tucatinib arm, and 2 were randomized to the placebo arm.

The patients' case histories reviewed from the placebo arm did not have evidence of DILI. Of the 9 patients treated with triple therapy, 4/9 had significant disease burden in the liver (metastatic disease) that made definitive assessment of DILI difficult to establish. Overall, the Division agreed with the independent expert's conclusion in all but 2/9 cases in which we did not consider liver biochemistry excursions likely to be DILI. This may have been due to information that was presented to the DILI expert that DHN did not have in the dataset given us. Most hepatologists label a drug potentially associated with DILI as cited in **Table 2, above**. DHN agrees with the conclusion that tucatinib-related DILI is a possibility.

#### *Tucatinib as a possible cause of DILI and not 'probable' or a 'definite' cause of DILI*

We should note that the external adjudicator appeared to have more data including fractionation of bilirubin. This would be of relevance for potential DILI related to capecitabine since, based on published reports, the drug is typically associated with a mild, indirect hyperbilirubinemia. In nearly all cases reviewed, the Sponsor was quick to discontinue or dose-reduce capecitabine. Hence, in our opinion since capecitabine can also result in an increase in total bilirubin (or may result in increased transaminases), the prompt discontinuation is confounding when trying to address the question whether tucatinib has a liver signal; and, moreover, whether the potential liver signal met Hy's Law criteria. Additional confounders in most of the cases we adjudicated included presence of significant tumor burden in the liver, the hepatobiliary tree, and bone. Each of these was likely to result in biomarkers suggestive of cholestasis, with elevations of alkaline phosphatase.

Since the benefit-risk of tucatinib, given the severity of the woman's illness, is high, we cite one case (b) (6) that we found most illustrative of tucatinib-associated DILI. The case demonstrates that the patient was able to accommodate tucatinib use, and with each successive rechallenged her transaminase elevations declined, albeit at lower dose administration. Since tucatinib administration occurred in this case along with a stable dose of capecitabine, the patient's transaminases and total bilirubin eventually remained normal despite the third dosing rechallenged of tucatinib.

The Division concludes there is possible liver signal associated with tucatinib, accompanied by a mild to modest transaminitis that will decline following drug withdrawal. Further, the drug may be restarted at a lower dose and patients are likely to

accommodate a reduced dose. The caveat being that any rechallenged patient should be carefully monitored with more frequent liver biochemical testing until the patient's liver biochemistry is normal.

As the expert independent adjudicator implied in his review, we concur that there is no evidence that tucatinib is associated with a *Hy's Law* signal associated with its use. We suspect, however, other concomitant medications, as well as significant metastatic disease most likely contributed to the hyperbilirubinemia (as well as alkaline phosphatase) in the cases identified in the phase 2 trial.

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/s/  
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JOSEPH G TOERNER  
03/17/2020 08:11:08 AM

## Clinical Inspection Summary

<b>Date</b>	March 12, 2020
<b>From</b>	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
<b>To</b>	Mirat Shah, M.D., Clinical Reviewer Sanjeeve Balasubramaniam, Clinical Team Leader Duyen Kelly Mach, Pharm.D., Regulatory Project Manager Division of Oncology 1
<b>NDA #</b>	213411
<b>Applicant</b>	Seattle Genetics, Inc.
<b>Drug</b>	Tucatinib
<b>NME (Yes/No)</b>	Yes
<b>Review Priority</b>	High
<b>Proposed Indication</b>	Treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer, including patients with brain metastases
<b>Consultation Request Date</b>	November 26, 2019
<b>Summary Goal Date</b>	March 20, 2020
<b>Action Goal Date</b>	April 20, 2020
<b>PDUFA Date</b>	June 20, 2020

### I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing, phase 2 study (ONT-380-206) were submitted to the Agency in support of this New Drug Application (NDA) for Tucatinib for the proposed indication. Four clinical investigators (CIs), Dr. Rashimi Murthy (Site 0003), Dr. Vandana Gupta Abramson (Site 0048), Dr. Erika Hamilton (Site 0055) and Dr. Elisavet Paplomata (Site 0070) were selected for clinical inspections.

The inspections verified the sponsor Seattle Genetics, Inc. submitted clinical data with source records at the CI sites. Based on the results of these CI inspections, Study ONT-380-206 appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

### II. BACKGROUND

Seattle Genetics, Inc. submitted NDA 213411 to seek accelerated approval for Tucatinib, a reversible and selective inhibitor of human epidermal growth factor receptor 2 (HER2), for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast

cancer, including patients with brain metastases. To support the application, the sponsor submitted clinical data from Study ONT-380-206, titled “Phase 2, Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma”.

The primary study objective was to assess the effect of Tucatinib vs. placebo in combination with capecitabine and trastuzumab on progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) based on blinded independent central review (BICR).

Study subjects were randomized in a 2:1 ratio to receive Tucatinib or placebo treatment on a 21-day cycle. Tucatinib 300 mg or placebo was given orally (PO) twice daily (BID). Capecitabine was given at 1000 mg/m<sup>2</sup> PO BID on Days 1-14 of a 21-day cycle. Trastuzumab was given at a loading dose of 8 mg/kg intravenously followed by 6 mg/kg (or 600 mg subcutaneously) on Day 1 of a 21-day cycle.

The primary efficacy endpoint was PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST 1.1), or death from any cause, whichever occurred first.

The study enrolled a total of 612 subjects in 155 study centers in the U.S., Canada, Europe, Israel and Australia. The first subject was randomized on February 23, 2016 and the last subject was randomized on May 3, 2019. Study ONT-380-206 is ongoing. The data cutoff date for primary analysis was September 4, 2019.

Four CIs, Dr. Rashimi Murthy (Site 0003), Dr. Vandana Abramson (Site 0048), Dr. Erika Hamilton (Site 0055) and Dr. Elisavet Paplomata (Site 0070) were requested for clinical inspection in support of the application. These sites were selected because of their relatively high subject enrollments and lack of recent inspections.

### III. RESULTS

#### 1. Dr. Rashimi Murthy, Site 0003

Department of Breast Medical Oncology  
University of Texas MD Anderson Cancer Center  
1155 Pressler Street  
Houston, TX 77030  
Date of Inspection: December 16-20, 2019

This clinical investigator was inspected on December 16-20, 2019 as a data audit for Study ONT-380-206. This was the initial inspection for Dr. Murthy. The study site screened a total of 35 subjects with 26 subjects signed the informed consent forms (ICF) and randomized 17 subjects. Thirteen (13) subjects completed the study and five (5) of them are in the long-term follow-up. The first subject was consented on [REDACTED] (b) (6). Eighteen (18) of the 26 consented subjects' records for protocol-required procedures were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, ICFs, documentation of eligibility criteria, medical records, adverse events (AEs) and serious adverse

events (SAEs), the investigational product (IP) accountability records, visit data, laboratory results, electronic case report forms (eCRFs), and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, staff training, financial disclosures and delegation of authority].

The inspection found adequate source documentation for all enrolled study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs.

The inspection identified two SAEs of pleural effusion (Subject (b) (6) and Subject (b) (6)) were not reported within the 24-hour timeframe. However, the SAEs were related to disease progression and were included in the study report. The inspection also identified some minor issues as instances that data were not entered in the eCRF in a timely manner and several subjects with missed assessments, e.g., EKG, radiology, and laboratory results. These were discussed at the end of the inspection. However, these observations appear unlikely to have significant impacts on the overall efficacy and safety results.

In general, this clinical site appeared to be in compliance with Good Clinical Practices (GCP) except the observations noted above. Data submitted by this clinical site appear acceptable in support of this specific indication. At the end of the inspection, no Form 483 (Inspectional Observations) was issued.

## **2. Dr. Vandana Gupta Abramson, Site 0048**

719 Thompson Lane, Suite 25000

Nashville, TN 37204

Date of Inspection: January 13-16, 2020

This clinical investigator was inspected on January 13-16, 2020 as a data audit for Study ONT-380-206. This was the initial inspection for Dr. Abramson. The study site screened a total of 14 subjects and enrolled 10 subjects. Five (5) subjects have expired and three (3) subjects remain in the long term follow-up. The first subject was consented on (b) (4) and the last subject was consented on (b) (4). All of the 10 enrolled subjects' records for protocol-required procedures were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, ICFs for all 14 screened subjects, documentation of eligibility criteria, electronic medical records (EMR), AEs and SAEs, the IP accountability records, visit data, laboratory results, CRFs, and related regulatory documents (e.g., IRB approvals and communications, staff training, financial disclosures and delegation of authority).

The inspection found adequate source documentation for all study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified for all subjects. There was no evidence of underreporting of AEs or SAEs. In general, this clinical site appeared to be in compliance with GCP. Data submitted by this clinical site appear acceptable in support of the indication. At the end of the

inspection, no Form 483 was issued.

**3. Dr. Erika Hamilton, Site 0055**  
250 25th Avenue North, Suite 307  
Nashville, TN 37203  
Dates of Inspection: January 13-24, 2020

This clinical investigator was inspected on January 13-24, 2020 as a data audit for Study ONT-380-206. Dr. Hamilton was previously inspected on 05/08-12/2017 with VAI and a Form 483 was issued for subjects receiving incorrect dosing diaries for 7 of 42 cycles. For Study ONT-380-206, the study site screened a total of 22 subjects and enrolled 14 subjects. Five (5) subjects completed the study and 9 subjects discontinued (2 subjects withdrew consent, 6 subjects expired and 1 subject lost-to-follow up). The first subject was consented on [REDACTED] (b)(6) and the last subject was randomized on [REDACTED] (b)(6). At the time of the inspection, the site was actively treating subjects but closed to enrollment. Seven (7; 50%) of the 14 enrolled subjects' records for protocol-required procedures were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, ICF procedures and documentation, documentation of eligibility criteria, EMR, AEs and SAEs, the IP accountability records, visit data, laboratory results, CRFs, and related regulatory documents (e.g., IRB approvals and communications, financial disclosures and delegation of authority).

The inspection found adequate source documentation for all of the inspected subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs or SAEs.

Verbal observations discussed with the CI were: 1) Subject [REDACTED] (b)(6)'s cycle 11 capecitabine dose was documented as "not administered" which was unclear whether the subject took the dose at home or whether the dose was missed; and 2) a discrepancy on the date of IP discontinuation for Subject [REDACTED] (b)(6) following an SAE of elevated bilirubin between the source document ([REDACTED] (b)(6)) and the SAE form (09/19/2016). However, these are isolated findings that may not change the safety or efficacy profile of the study drug.

In general, this clinical site appeared to be in compliance with GCP except the observations noted above. Data submitted by this clinical site appear acceptable in support of the indication. At the end of the inspection, no Form 483 was issued.

**4. Dr. Elisavet Paplomata, Site 0070**  
1364 Clifton Road NE  
Atlanta, GA 30322  
Dates of Inspection: January 30 to February 7, 2020

This clinical investigator was inspected on January 30 to February 7, 2020 as a data audit for Study ONT-380-206. This was the initial inspection for Dr. Paplomata. During the inspection, it was found out that Dr. Paplomata left the study site on 01/15/2020 and Dr. Suchita Pakkala, a sub-

investigator, has become the CI for the study site since 12/27/2019. The study site screened a total of 27 subjects and enrolled 16 subjects. Thirteen (13) subjects completed the study and three (3) subjects withdrew consents. Six (6) subjects were in the long-term follow-up and one (1) subject remains in the study with the last follow-up visit on [REDACTED] (b) (6). The first subject was consented on [REDACTED] (b) (6) and the last subject was consented on [REDACTED] (b) (6). All of the 16 randomized subjects' records for protocol-required procedures were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, ICF procedures and documentation, documentation of eligibility criteria, EMR, AEs and SAEs, the IP accountability records, visit data, laboratory results, and related regulatory documents (e.g., IRB approvals and communications, financial disclosures, staff training and delegation of authority).

The inspection found adequate source documentation for all study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. The investigator found that there was one AE of right hip pain (grade 1) for Subject [REDACTED] (b) (6) that was not documented in the electronic data capture system. Although this non-serious AE was not included in the study report, this is an isolated finding that may not change the safety profile of the study drug.

In general, this clinical site appeared to be in compliance with GCP except the observations noted above. Data submitted by this clinical site appear acceptable in support of the indication. At the end of the inspection, no Form 483 was issued.

PRIMARY REVIEW: { See appended electronic signature page }

Ling Yang, M.D., Ph.D., FAAFP  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Min Lu, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA 213411  
Review Division /Division Director/J. Beaver  
Review Division /Medical Team Leader/S. Balasubramaniam  
Review Division /Project Manager/K. Mach  
Review Division/Medical Officer/M. Shah  
OSI/Office Director/D. Burrow  
OSI/DCCE/ Division Director/N. Khin  
OSI/DCCE/Branch Chief/K. Ayalew  
OSI/DCCE/Team Leader/M. Lu  
OSI/DCCE/GCP Reviewer/L. Yang  
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague  
OSI/Database PM/Dana Walters

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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)

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Date of This Memorandum: March 12, 2020  
Requesting Office or Division: Division of Oncology 1 (DO1)  
Application Type and Number: NDA 213411  
Product Name and Strength: Tukysa (tucatinib) Tablets, 50 mg and 150 mg  
Applicant/Sponsor Name: Seattle Genetics, Inc.  
OSE RCM #: 2019-2389-1  
DMEPA Safety Evaluator: Tingting Gao, PharmD  
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

---

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on February 28, 2020 for Tukysa. Division of Oncology 1 (DO1) requested that we review the revised container labels for Tukysa (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.<sup>a</sup>

## 2 CONCLUSION

The revised container labels are unacceptable from a medication error perspective. The revised container labels may be further improved for readability.

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<sup>a</sup> Gao, T. Label and Labeling Review for Tukysa (NDA 213411). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Feb 18. RCM No.: 2019-2389.

### 3 RECOMMENDATIONS FOR SEATTLE GENETICS, INC.

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

#### A. Container labels

1. We acknowledge that we recommended to include space for patient to write the "Date of first opening \_\_\_/\_\_\_/\_\_\_" followed by "Discard unused tablets 3 months after opening." to the side panel. We also acknowledge that we recommended to revise the side panel to read "Store in original container to protect from moisture. Once opened, the product must be used within 3 months." In reviewing the revised container labels (being able to visually see the mock up container labels), however, we find the principal display panel (PDP) and the side panel to be overcrowded as currently presented. Because the "Store in original container to protect from moisture" is already communicated on the PDP with the "Attention: ... store Tukysa in original container..." statement, revise the statements "Store in original container... within 3 months." on the side panel to read "Discard unused tablets 3 months after opening." In addition, consider changing the font color of this statement to draw attention to this important information. After presenting the statement "Discard unused tablets 3 months after opening." with adequate prominence on the side panel, remove the following statements from the PDP because this information will already be captured on the side panel.

Date of first opening \_\_\_/\_\_\_/\_\_\_

Discard unused tablets 3 months after opening.

Alternatively, you may propose other ways to improve the readability of the container labels.

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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\*\*\*

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Date of This Review:	February 18, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 213411
Product Name, Dosage Form, and Strength:	Tukysa (tucatinib) Tablets, 50 mg and 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Seattle Genetics, Inc.
FDA Received Date:	November 12, 2019 and December 13, 2019
OSE RCM #:	2019-2389
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

---

## 1 REASON FOR REVIEW

As part of the review process for Tukysa (tucatinib) Tablets, the Division of Oncology 1 (DO1) requested that we review the proposed Tukysa prescribing information (PI) and container labels for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this 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 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 Tukysa PI and container labels and determined that they may be improved to ensure safe product use. Furthermore, we noted that Section 16 How Supplied/Storage and Handling of the PI and the container labels states "Dispense in original container only", and that Section 16 also states "Discard any unused tablets 3 months after opening the bottle." In email (b) (4)

a silica gel desiccant is included in the HDPE bottle to protect the proposed product from moisture, and that the product should be discarded after 90 days once the bottle is opened. (b) (4)

## 4 CONCLUSION & RECOMMENDATIONS

The proposed Tukysa PI and container labels may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

### 4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

#### A. Prescribing Information

##### 1. Dosage and Administration Section, 2.1 Recommended Dosage

- a. Consider using assertive language to improve readability. For example, "Swallow TUKYSA tablets whole."

##### 2. Dosage and Administration Section, 2.2 Dose Modifications

To minimize the risk of wrong dose errors, indicate the number of tablets required for each dose (b) (4)

##### 3. How Supplied/Storage and Handling Section

- a. Revise the statement (b) (4) to "Dispense to patient in original container only. Store in the original container to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant." to aid users in understanding why the product must be stored in original container.
- b. Consider adding this statement "Once opened, the product must be used within 3 months." before the statement "Discard any unused tablets 3 months after opening the bottle." to state the desired action for the first 3 months (use within 3 months), followed by the recommended action after 3 months (discard after 3 months).

#### B. Patient Prescribing Information

##### 1. "How should I take [TRADE NAME]?" Section

- a. Consider revising the instructions to use assertive language to improve readability. For example, "Swallow [TRADE NAME] tablets whole. Do not chew, crush, or split [TRADE NAME] before swallowing".

##### 2. How should I store [TRADE NAME]? Section

- a. Consider revising (b) (4) to (b) (4)

Providing the rationale “protect from moisture” will aid the patients in understanding why the product must be stored in original container.

## 4.2 RECOMMENDATIONS FOR SEATTLE GENETICS, INC.

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

### A. Container Labels

1. Add the statement “Attention: Dispense and store Tukysa in original container to protect from moisture.” to the principal display panel to alert pharmacist/dispensers to dispense Tukysa in its original container.
2. Revise the statements [REDACTED] (b) (4) on the side panel to read “Store in original container to protect from moisture. Once opened, the product must be used within 3 months.” This will provide the correct storage instructions to the users and minimize the risk of deteriorated drug medication errors.
3. To minimize the risk of administration of deteriorated product, we recommend including space for patients to write the “Date of first opening”, followed by instructions to discard the remainder contents 3 months after opening on the side panel. For example:  
Date of first opening \_\_\_/\_\_\_/\_\_\_  
Discard unused tablets 3 months after opening.
4. Revise the usual dosage statement from [REDACTED] (b) (4) to “Recommended Dosage: See prescribing information” to be consistent with the terminology in the PI.
5. Consider revising the expiration date to the format YYYY-MMM. FDA’s current thinking has been published in the *Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers*. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tukysa received on November 12, 2019 from Seattle Genetics, Inc..

Table 2. Relevant Product Information for Tukysa									
Initial Approval Date	N/A								
Active Ingredient	tucatinib								
Indication	in combination with trastuzumab and capecitabine for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 3 prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting.								
Route of Administration	Oral								
Dosage Form	Tablets								
Strength	50 mg and 150 mg								
Dose and Frequency	<p>300 mg twice daily</p> <table border="1"> <thead> <tr> <th>Dose Level</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>First dose reduction</td> <td>250 mg twice daily</td> </tr> <tr> <td>Second dose reduction</td> <td>200 mg twice daily</td> </tr> <tr> <td>Third dose reduction</td> <td>150 mg twice daily</td> </tr> </tbody> </table>	Dose Level	Dose	First dose reduction	250 mg twice daily	Second dose reduction	200 mg twice daily	Third dose reduction	150 mg twice daily
Dose Level	Dose								
First dose reduction	250 mg twice daily								
Second dose reduction	200 mg twice daily								
Third dose reduction	150 mg twice daily								
How Supplied	<p>50 mg: bottle of 60 tablets</p> <p>150 mg: bottle of 60 tablets and bottle of 120 tablets</p>								
Storage	<p>Store at controlled room temperature, 20°C to 25°C (68°F to 77°F). Dispense only in original container. Do not discard desiccant. Replace cap securely each time after opening.</p> <p>Discard any unused tablets 3 months after opening the bottle.</p>								
Container Closure	<p>The tucatinib drug product is packaged in round, white, pharmaceutical grade HDPE bottles with a silica gel desiccant. The closure is an induction-sealed, white, <span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span> screw cap.</p> <p>The 150 mg strength tablets are packaged in 75 cc or 150 cc bottles containing 60 or 120 tablets, respectively. The 50 mg strength tablets are packaged in 75 cc bottles containing 60 tablets.</p>								

## 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,<sup>a</sup> along with postmarket medication error data, we reviewed the following Tukysa labels and labeling submitted by Seattle Genetics, Inc.

- Container labels received on December 13, 2019
- Patient Information (Image not shown) received on November 12, 2019, available from <\\cdsesub1\evsprod\nda213411\0008\m1\us\114-labeling\draft\labeling\draft-tucatinib-ppi.docx>
- Prescribing Information (Image not shown) received on November 12, 2019, available from <\\cdsesub1\evsprod\nda213411\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx>

### G.2 Label and Labeling Images

#### Container labels



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<sup>a</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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## Consult Memorandum

**Date:** February 13, 2020  
**To:** Mirat Shah, Medical Officer, CDER/OND/OHOP/DOPI  
Duyen Mach, RPM, CDER/OND/OHOP/DOHRA/OHRAB1  
**From:** Abdelrahman Abukhdeir, Ph.D., CDRH/OHT7/DMGP/MPCB  
**Through:** Soma Ghosh, Ph.D., Chief, CDRH/OHT7/DMGP/MPCB  
Reena Philip, Ph.D., Director, CDRH/OHT7/DMGP  
**Subject:** CDER consult request for NDA213411  
**ICC Number:** ICC2000074

**Protocol:**

HER2CLIMB

Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma

**Drug Sponsor:** Seattle Genetics, Inc.

**Drug Name:** Tucatinib in Combination with Capecitabine and Trastuzumab

**Analyte Detected:** HER2

**Device Sponsor:** Not specified

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**I. PURPOSE**

Seattle Genetics has submitted data from a phase II pivotal trial in support of tucatinib in combination with capecitabine and trastuzumab in patients with pretreated unresectable locally advanced or metastatic HER2+ breast carcinoma.

**II. PROPOSED DRUG INDICATION**

Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma.

**III. DEVICE USE IN THE PHASE II STUDY**

Per the attached protocol (ONT-380-206), centrally confirmed HER2 results (either IHC, ISH, or FISH) prior to randomization from either submitted tissue blocks/slides or from a previous study (with approval from the sponsor). HER2 status will be verified by central laboratory analysis using ASCO/CAP guidelines.

Optional Pre-screening:

HER2+ by ISH or FISH (or centrally confirmed HER2+ by ISH, FISH or 3+ staining by IHC in a previous study as approved by the medical monitor).

The Sponsor is not proposing the use of a companion diagnostic or FDA-approved test to select HER2+ patients.

**IV. Response to CDER inquiry:**

**Tucatinib requires HER2+ testing, the team would like to have a CDRH reviewer at the labeling meeting.**

CDRH response to CDER:

The sponsor is proposing to treat HER2+ metastatic breast cancer patients with tucatinib (following at least three prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting) in combination with capecitabine and trastuzumab without the use of a companion diagnostic to screen for HER2 amplification. CDRH has no issue with this population of patients being selected for tucatinib treatment without a companion diagnostic device, since in the clinical setting patients will have been screened for HER2 amplification for previous HER2-directed therapies.

CDRH would like to replace [REDACTED] (b) (4)  
[REDACTED] from Section 14.1 of the drug label with the following sentence:

*“HER2 positivity was based on archival or fresh tissue tested with a FDA-approved test at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive.”*

This consult review is limited to the information provided in NDA213411. If there are any questions regarding this review, please contact Abdelrahmman Abukhdeir by phone at (240) 402-6482 or by email at [Abdelrahmman.Abukhdeir@fda.hhs.gov](mailto:Abdelrahmman.Abukhdeir@fda.hhs.gov)

**Interdisciplinary Review Team for Cardiac Safety Studies**  
**QT Consultation Review**

Submission	NDA 213411
Submission Number	001
Submission Date	11/11/2019
Date Consult Received	11/27/2019
Drug Name	tucatinib
Indication	Treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases.
Therapeutic dose	300 mg; twice daily
Clinical Division	DO1

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

This review responds to your consult dated 11/27/2019 regarding the sponsor’s QT evaluation. The QT-IRT reviewed the following materials:

- Sponsor’s clinical study protocol # ONT-380-011 (SN0001; [link](#))
- Sponsor’s clinical study report # ONT-380-011 (SN0001; [link](#))
- Sponsor’s propose product label (SN0001; [link](#))
- Highlights of clinical pharmacology and cardiac safety (SN0003; [link](#))

**1 SUMMARY**

No significant QTc prolongation effect of tucatinib was detected in this QT assessment.

The QT effect of tucatinib was evaluated in a randomized, partially double-blind, 3-period-6-arm cross-over, single dose, positive and placebo-controlled thorough QT study (Study # ONT-380-011). The highest dose that was evaluated was 300 mg, which achieved therapeutic plasma exposure of tucatinib and ONT-993. The data from study # ONT-380-011 was analyzed using by-time analysis as the primary analysis, which did not suggest that tucatinib is associated with significant QTc prolonging (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by exposure-response analysis (section 4.5) and categorical analysis (section 4.4).

**Table 1: The Point Estimates and the 90% CIs (FDA Analysis)**

ECG parameter	Treatment	Time	ΔΔ	90% CI
QTc	tucatinib	4 hours	0.6	(-1.8, 3.0)

*For further details on the FDA analysis please see section 4.*

Therapeutic plasma exposures of tucatinib and ONT-993 were targeted with oral administration of tucatinib 300 mg twice daily for 4 days and a single 300-mg dose on the

fifth day. Tucatinib is metabolized primarily by CYP2C8 and concomitant administration of tucatinib with a strong inhibitor of CYP2C8 result in increased exposures of tucatinib (C<sub>max</sub>: 1.6-fold & AUC: 3.1-fold). Considering that the concomitant administration of tucatinib with a strong inhibitor of CYP2C8 results in increased tucatinib exposures, the sponsor is proposing to avoid concomitant administration of tucatinib with a strong inhibitor of CYP2C8.

### 1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

### 1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

## 2 RECOMMENDATIONS

### 2.1 ADDITIONAL STUDIES

Not applicable.

### 2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0001 ([link](#)) from the QT-IRT. Our changes are highlighted ([addition](#), ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

#### 12.2 Pharmacodynamics

##### Cardiac Electrophysiology

[Redacted text] (b) (4)

[Redacted text] (b) (4)

*We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.*

## 3 SPONSOR’S SUBMISSION

### 3.1 OVERVIEW

#### 3.1.1 Clinical

Seattle Genetics Inc. is developing tucatinib combination with trastuzumab and capecitabine for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 3 prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting. Tucatinib (ARRY-380, ONT-380; MW: 480.52 g/mol) is a kinase inhibitor of human epidermal growth factor receptor-2 (HER2; ErbB2). The proposed dose is 300 mg (150 mg × 2 tablets; with or without food) twice daily with dose

reduction or interruptions based on individual safety and tolerability. The peak concentration of  $670 \pm 190$  ng/mL ( $T_{max}$ : 2 h) is expected at the steady-state with maximal proposed clinical dosing regimen (MTD: 600 mg twice daily). The product is formulated as immediate-release tablet formulation containing 50 mg and 150 mg tucatinib. The product is intended for oral administration with trastuzumab and capecitabine.

The sponsor conducted a randomized, partially double-blind, placebo- and positive-controlled, (3-period) fixed-sequence cross-over study evaluating a steady-state therapeutic dose of tucatinib on QTcF in healthy subjects (Study # ONT-380-011). The QT-IRT has not reviewed the QT assessment conducted by the sponsor and we refer the reader to Appendix 5.1 for a detailed review of the sponsors QT assessment.

The primary analysis was based on by-timepoint analysis ( $\Delta\Delta QTcF$ ) using the Intersection Union Test. Therapeutic plasma exposures of tucatinib and ONT-993 were targeted with oral administration of tucatinib 300 mg twice daily for 4 days and a single 300-mg dose on the fifth day. Subjects ( $n=60$ ;  $\sim 10$ /sequence) were randomized to 1 of the 6 treatment sequences to receive – 1) tucatinib twice daily for 4 days and single dose on Day 5 (TRT-A), 2) matching placebo twice daily for 4 days and single dose on Day 5 (TRT-B), 3) a single oral dose of 400 mg of moxifloxacin (open-label). The study incorporated a 2-Williams-squares design to maintain the study blind for tucatinib and placebo.

Continuous ECG recordings (Holter) were started approximately 1.5 hours pre-dose on Days 1, 11, and 21 (3 Periods). Replicate 12-lead ECGs were extracted at the following timepoints relative to administration of study treatment: 80, 55, and 30 minutes pre-dose (to establish baseline). Continuous ECG recording were started approximately 45 minutes pre-dose on Days 5, 15, and 25 (3 Periods). Replicate 12-lead ECGs were extracted at the following timepoints relative to administration of study treatment: approximately 30 minutes pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 36 hours post-dose. Blood samples for determination of plasma tucatinib and ONT-993 concentrations were collected at the following timepoints relative to dosing on Days 5, 15, and 25 (3 Periods): pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 36 hours post-dose. A single blood sample was collected within 30 minutes pre-dose on Days 1, 11, and 21 (3 Periods).

The sponsor selected proposed therapeutic dose of 300 mg twice daily on the basis of previous clinical studies cancer patients. This dosing regimen was expected to offer steady-state therapeutic plasma exposures of tucatinib and ONT-993. Tucatinib exhibits dose proportional pharmacokinetics between 50 and 300 mg doses with  $\sim 1.54$ -fold accumulation for  $C_{max}$  at therapeutic doses (300 mg twice daily for 14 days; time to steady-state  $\sim 4$  days). Tucatinib is metabolized primarily by CYP2C8 and concomitant administration of tucatinib with a strong inhibitor of CYP2C8 result in increased exposures of tucatinib ( $C_{max}$ : 1.6-fold & AUC: 3.1-fold). The predominant metabolite (ONT-993) accounted for 9.16% of total plasma radioactivity exposure in human.

### **3.1.2 Nonclinical Safety Pharmacology Assessments**

Refer to highlights of clinical pharmacology and cardiac safety.

## 3.2 SPONSOR'S RESULTS

### 3.2.1 By-Time Analysis

Tucatinib excluded the 10 msec threshold at the therapeutic dose level for  $\Delta\Delta\text{QTc}$ .

*Reviewer's comment: Reviewer's analysis has similar results.*

#### 3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

*Reviewer's comment: Reviewer's analysis has similar results.*

##### 3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

### 3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 bpm), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

*Reviewer's comment: Reviewer's analysis has similar results.*

### 3.2.3 Exposure-Response Analysis

A full model included  $\Delta\Delta\text{QTcF}$  as the dependent variable, time-matched plasma concentrations of tucatinib and ONT-993 as the covariates, centered baseline QTcF as an additional covariate, and random intercept and slopes per subject.

The sponsor's PK/PD model with tucatinib concentrations indicated a slightly negative slope which is not statistically significant (-0.003 msec per ng/mL; 90% CI: -0.0090 to 0.0036). The model predicted  $\Delta\Delta\text{QTcF}$  (90% two-sided upper confidence interval) values of -1.80 (0.30) ms at the mean peak parent plasma levels for the therapeutic dose (geomean  $C_{\text{max}}$  ~510 ng/mL) following oral administration for ~4 days. This indicated that there is no positive association between the peak concentrations of tucatinib and  $\Delta\Delta\text{QTcF}$  interval.

*Reviewer's comment: The results of the reviewer's analysis were in agreement with the sponsor's results. Please see section 4.5 for additional details.*

### 3.2.4 Cardiac Safety Analysis

There were no deaths or SAEs and none of the subjects discontinued the study due to AEs. There were no cardiac-related AEs.

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

## **4 REVIEWERS' ASSESSMENT**

### **4.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e.  $|\text{mean}| < 10$  bpm) were observed (see Section 0).

### **4.2 ECG ASSESSMENTS**

#### **4.2.1 Overall**

Overall ECG acquisition and interpretation in this study appears acceptable.

#### **4.2.2 QT Bias Assessment**

Not applicable.

### **4.3 BY TIME ANALYSIS**

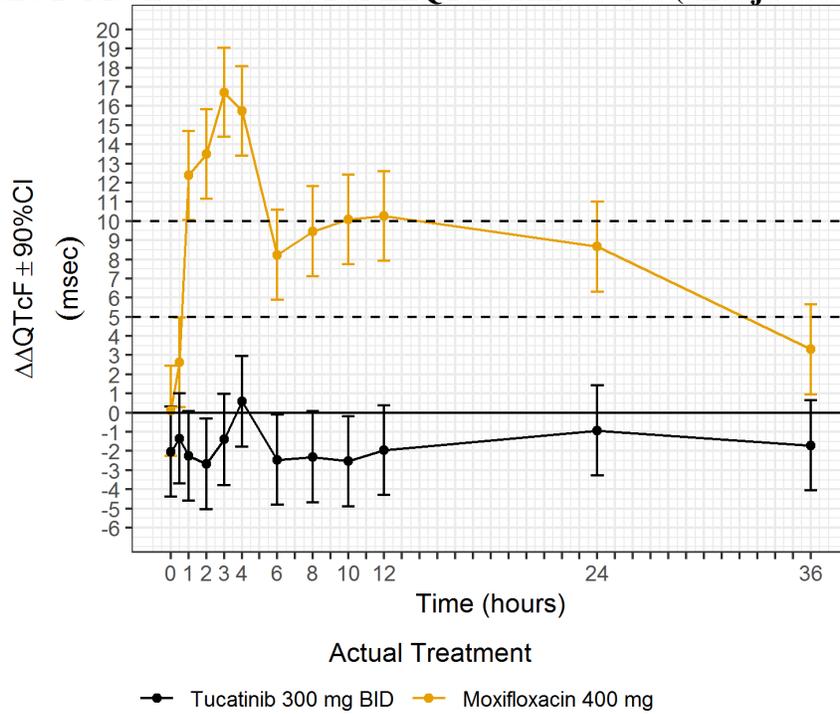
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g.,  $\Delta\text{QTcF}$ ,  $\Delta\text{HR}$ ) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and a compound symmetry covariance matrix for period within subject and variance component for subject to explain the association between repeated measures within period and subject.

#### **4.3.1 QTc**

Figure 1 displays the time profile of  $\Delta\Delta\text{QTc}$  for different treatment groups. The maximum  $\Delta\Delta\text{QTc}$  values by treatment are shown in Table 2. As shown in Figure 1 and Table 2, the upper 90% confidence limits between 0 to 36 hours are below 5.

**Figure 1: Mean and 90% CI of  $\Delta\Delta\text{QTcF}$  Timecourse (unadjusted CIs).**



**Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta\text{QTc}$**

Actual Treatment	N	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Tucatin b 300 mg BID	50	4	0.6	(-1.8 to 3.0)

#### 4.3.1.1 Assay sensitivity

The timecourse of changes in  $\Delta\Delta\text{QTcF}$  after Moxifloxacin 400mg, shown in Figure 1, demonstrates that the largest mean effect of Moxifloxacin 400mg is above 10 msec. The lower confidence limit of the largest mean effect, after Bonferroni adjustment for 4 time points, is above 5 msec, as listed in Table 3.

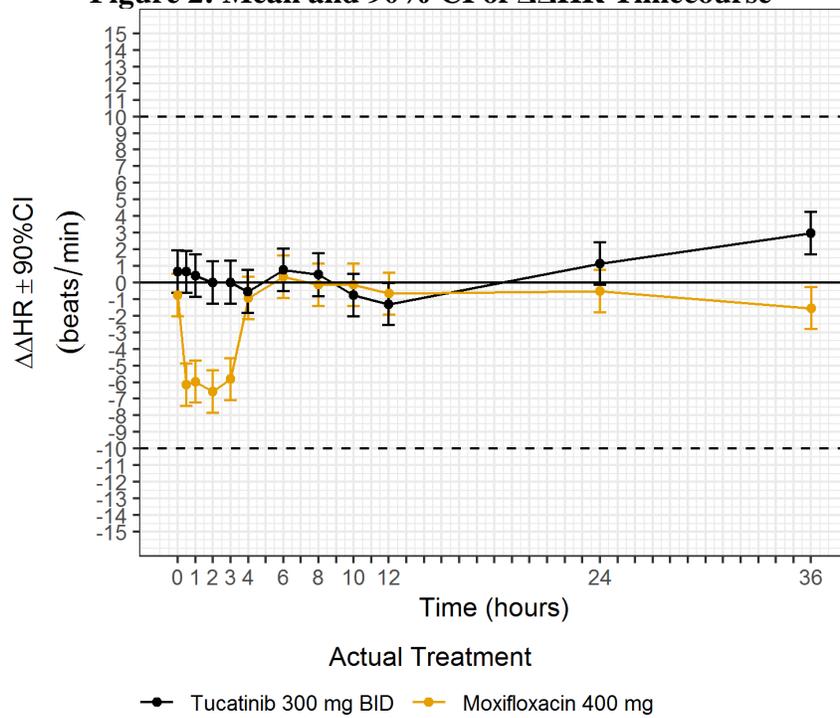
**Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for  $\Delta\Delta\text{QTc}$**

Actual Treatment	N	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	52	3	16.7	(13.5 to 19.9)

#### 4.3.2 HR

Figure 2 displays the time profile of  $\Delta\Delta\text{HR}$  for different treatment groups. The maximum  $\Delta\Delta\text{HR}$  values by treatment are shown in Table 4.

**Figure 2: Mean and 90% CI of  $\Delta\Delta$ HR Timecourse**



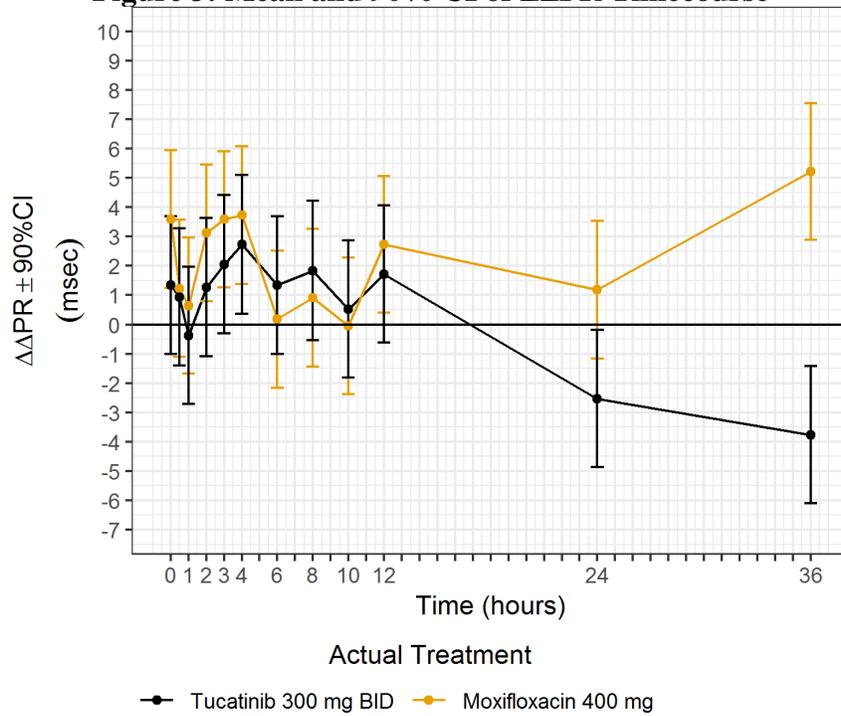
**Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta$ HR**

Actual Treatment	N	Time (hours)	$\Delta\Delta$ HR (beats/min)	90.0% CI (beats/min)
Tucatin b 300 mg BID	50	36	3.0	(1.7 to 4.2)

### 4.3.3 PR

Figure 3 displays the time profile of  $\Delta\Delta$ PR for different treatment groups. The maximum  $\Delta\Delta$ PR values by treatment are shown in Table 5.

**Figure 3: Mean and 90% CI of  $\Delta\Delta$ PR Timecourse**

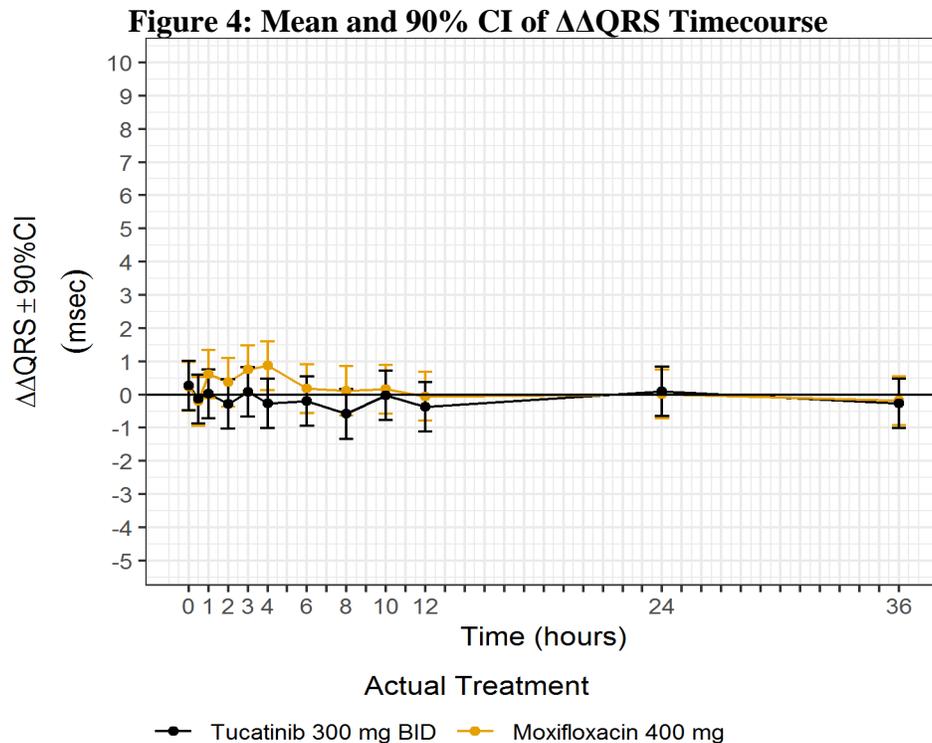


**Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta$ PR**

Actual Treatment	N	Time (hours)	$\Delta\Delta$ PR (msec)	90.0% CI (msec)
Tucatin b 300 mg BID	50	4	2.7	(0.4 to 5.1)

#### 4.3.4 QRS

Figure 4 displays the time profile of  $\Delta\Delta$ QRS for different treatment groups. The maximum  $\Delta\Delta$ QRS values by treatment are shown in Table 6.



**Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta$ QRS**

Actual Treatment	N	Time (hours)	$\Delta\Delta$ QRS (msec)	90.0% CI (msec)
Tucatin b 300 mg BID	51	0.01	0.3	(-0.5 to 1.0)

#### 4.4 CATEGORICAL ANALYSIS

Categorical analysis were performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. In this study, there wasn't unscheduled ECG.

##### 4.4.1 QTc

There are no subjects with QTcF value greater than 450 msec.

There are no subjects with  $\Delta$ QTcF value greater than 60 msec.

##### 4.4.2 HR

There are no subject with HR value greater than 100bpm.

##### 4.4.3 PR

There are no subjects with PR values greater than 220 msec.

#### 4.4.4 QRS

There are no subjects with QRS value above 120 msec and with 25% increase over baseline.

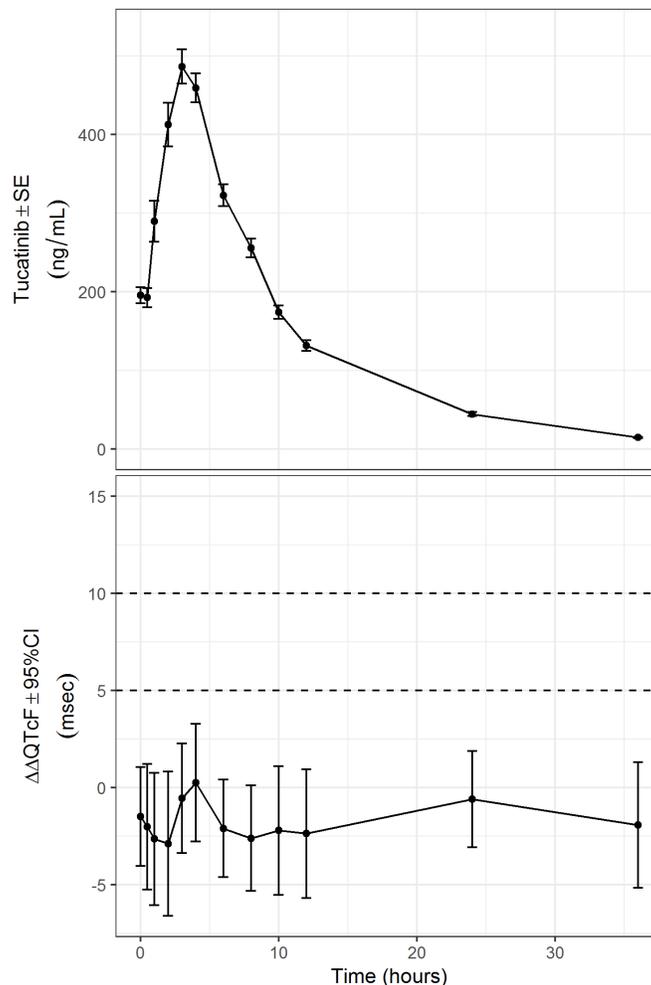
#### 4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between  $\Delta$ QTcF and concentration of tucatinib. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship using a linear 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  $\Delta$ QTcF; and 3) presence of non-linear relationship.

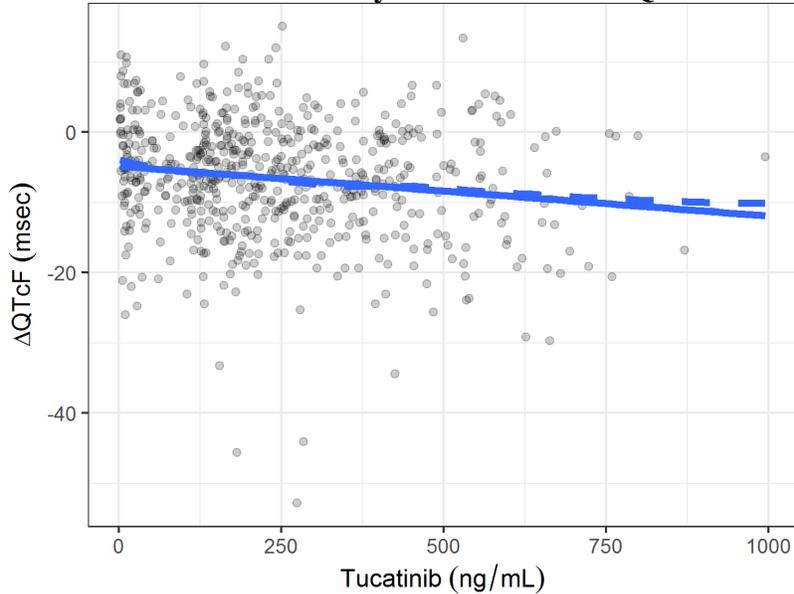
An evaluation of the time-course of drug concentration and changes in  $\Delta$ QTcF is shown in Figure 5. Considering the low magnitude of effect, there is no apparent correlation between the time at maximum effect on  $\Delta$ QTcF and peak concentrations of tucatinib indicating no significant hysteresis. Figure 2 shows the time-course of  $\Delta$ HR, which suggests an absence of significant  $\Delta$ HR changes (see Sections 4.3.2 and 4.4.2).

**Figure 5: Time course of tucatinib concentration (top) and QTc (bottom)**



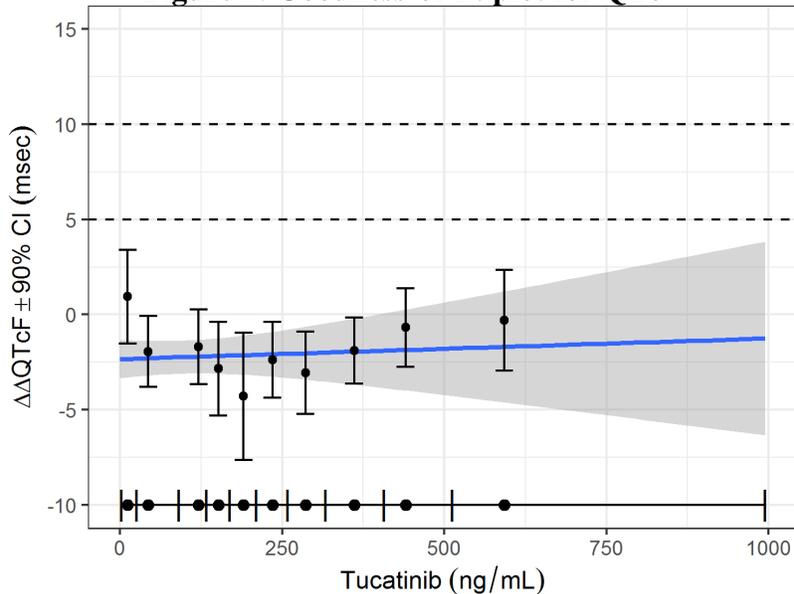
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between tucatinib concentration and  $\Delta$ QTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between tucatinib concentration and  $\Delta$ QTc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

**Figure 6: Assessment of linearity of concentration-QTc relationship**



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from tucatinib concentration-QTc model are provide in Table 7.

**Figure 7: Goodness-of-fit plot for QTc**



**Table 7: Predictions from concentration-QTc model**

<b>Actual Treatment</b>	<b>Tucatinib (ng/mL)</b>	<b><math>\Delta\Delta</math>QTcF (msec)</b>	<b>90.0% CI (msec)</b>
Tucatinib 300 mg BID	467.5	-1.8	(-4.1 to 0.4)

**4.5.1.1 Assay sensitivity**

Assay sensitivity was established using by time analysis. Please see section 4.3.1.1 for additional details.

## 5 APPENDIX

### 5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information								
Generic Name	Tucatinib			Brand Name	Not available			
Drug class	Inhibitor of the receptor tyrosine kinase human epidermal growth factor receptor 2 protein							
Combination product	No							
Indication	Treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases.							
Therapeutic Dose	300 mg; twice daily							
Maximum Tolerated Dose	600 mg twice daily (capsule formulation)							
Dosage Form	Tablet			Route of Administration	Oral			
2. Clinical Cardiac Safety								
Refer to highlights of clinical pharmacology and cardiac safety.								
3. QT Studies								
3.1 Primary Studies								
Protocol number / Population	ECG Quality		Arms		Sample size		ECG & PK assessments	
	Assessment	Ok?	Arms	High dose covers?	No subjects	Ok?	Timing	Ok?
Protocol number: ONT-380-011	Central read? Yes  Blinded? Yes	Yes	Highest dose: 300 mg twice daily for 4 days	Therapeutic	53 (8 to 9 for each of 6 arms. Two subjects in placebo-test-	Yes	Baseline: Pre-dose baseline  Timing: ECG: Approximately 30	Yes

Population: Healthy volunteers	Replicates? Yes		Placebo: Yes		moxi arm drop out.)		minutes pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 36 hours post-dose (on Days 5, 15, and 25); PK: Pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 36 hours post-dose (on Days 5, 15, and 25).	
Design: Crossover			Positive control: Yes					
<b>3.1 Secondary Studies</b>								
NA								
<b>3.3 Data pooling</b>								
Data pooling?						No		
Did sponsor propose an assessment for heterogeneity?						N/A		
Is the data pooling appropriate?						N/A		
<b>4. Analysis plan</b>								
<b>4.1 Study Objective related to QT</b>								
What QTc effect size is the analysis trying to exclude?						10 ms (E14)		
<b>4.2 Dose Justification</b>								
The sponsor selected 300 mg twice daily targeting steady-state therapeutic plasma exposures of tucatinib and ONT-993. Tucatinib is metabolized primarily by CYP2C8 and concomitant administration of tucatinib with a strong inhibitor of CYP2C8 result in increased exposures of tucatinib (Cmax: 1.6-fold & AUC: 3.1-fold). [See Section 3.1.1]								
<b>4.3 QT correction method</b>								
Is an HR increase or decrease greater than 10 bpm?						No		

Primary method for QT correction	QTcF
<b>4.4 Assay Sensitivity</b>	
Assay sensitivity methods proposed by sponsor	<input checked="" type="checkbox"/> Moxifloxacin <input type="checkbox"/> Exposure-margin <input type="checkbox"/> QT bias assessment <input type="checkbox"/> Not applicable (objective is large mean effects) <input type="checkbox"/> Other
<b>4.5 By Time Analysis</b>	
<b>4.5.1 Investigational drug</b>	
Primary analysis	Yes
Did the sponsor use IUT or descriptive statistics?	IUT
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	MMRM
For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc?	Yes
<i>linear mixed effects model with period, sequence, time, treatment, time-by-treatment, baseline as fixed effects. Covariance structure unknown</i>	
<b>4.5.2 Positive control</b>	
Primary analysis	Yes
Did the sponsor adjust for multiplicity?	Yes
<i>The same model as by-time analysis was used. 90% CI were calculated for all time points. Test for null hypothesis <math>\Delta\Delta QTcF \leq 5\text{msec}</math> were performed at postdose time 1, 2, 3 hours at 5% significant level. Multiplicity was adjusted by Hochberg procedure</i>	
<b>4.6 Concentration-QTc analysis</b>	
<b>4.6.1 Investigational drug</b>	

5.Primary analysis	No
What is the dependent variable in the sponsor's model?	Double delta
White paper model?	Yes
Which concentration covariate(s) are included in the model?	Multiple
Did the sponsor propose an assessment of delayed effects?	Yes
Did the sponsor propose an assessment of linearity?	Yes
Did the sponsor propose model selection criteria?	Yes
What methods did the sponsor use for predicting the QT effect?	<input checked="" type="checkbox"/> Model-based confidence intervals <input type="checkbox"/> Bootstrap-derived confidence intervals
See Section 3.1.1	
<b>4.6.2 Positive control</b>	
Primary analysis	No
Same model as investigational drug	N/A
<b>4.7 Categorical analysis</b>	
QTc?	Yes
$\Delta$ QTc?	Yes
PR?	Yes
QRS?	Yes
HR?	Yes
T-wave morphology?	Yes

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