CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213411Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities. While the application review is completed by the FDA, the application is still under review at the other regulatory agencies.

Application Type	NDA
Application Number(s)	213411
Priority or Standard	Priority
Submit Date(s)	December 20, 2019
Received Date(s)	December 20, 2019
PDUFA Goal Date	August 20, 2020
Division/Office	DO1/OOD/OND/CDER
FDA's Review Completion Date	*Electronic Stamp Date*
Established Name	Tucatinib
(Proposed) Trade Name	TUKYSA
Pharmacologic Class	Kinase inhibitor
Code name	ARRY-380
Applicant	Seattle Genetics
Formulation(s)	50mg or 150mg tablets
Dosing Regimen	300 mg orally twice daily, with or without food, in combination with trastuzumab, and capecitabine 1000 mg/m^2 orally twice daily (b) (4)
Applicant Proposed Indication(s)/Population(s)	Tucatinib (TUKYSA) is indicated 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.
Recommendation on Regulatory Action	*Regular Approval*
FDA's Recommended Indication(s)/Population(s) (if applicable)	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.

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OPQ=Office of Pharmaceutical Quality, OPDP=Office of Prescription Drug Promotion, OSI=Office of Scientific Investigations, OSE= Office of Surveillance and Epidemiology, DEPI= Division of Epidemiology, DMEPA=Division of Medication Error Prevention and Analysis, DRISK=Division of Risk Management

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Glossary

ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BC	breast cancer
BICR	blinded independent central review
BID	twice daily
BUN	blood urea nitrogen
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum serum concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
%CV	percent coefficient of variation
CYP	cytochrome p
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOP	end of phase
EOT	end of treatment
EQ-5D	European Quality of Life 5-Dimensional
EQ-5D-5L	European Quality of Life 5-Dimensional-5L
eTMF	electronic trial master file
GCP	good clinical practice

GLP	good laboratory practice
GSHv	group sequential Holm variable
HER2/3/4	human epidermal growth factor receptor-2/3/4
HR	hazard ratio
HRQoL	health-related quality of life
HRU	Health resource utilization
hERG	human ether-a-go-go-related gene
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IPD	important protocol deviation
iPSP	initial pediatric study plan
IRB	Institutional Review Board
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	intent-to-treat; intention-to-treat
IV	Intravenous(ly)
LFT	liver function test
MATE	multidrug and toxin extrusion protein
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition scan
NA	Not applicable
NDA	New Drug Application
NOEL	no-observed-effect level
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
OSI	Office of Scientific Investigations
Pbo	placebo
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFSBrainMets	PFS in subjects with brain metastases at baseline
P-gp	P-glycoprotein
PIC	powder-in-capsule

PK	pharmacokinetic
PO	oral dose
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PRO	patient-reported outcome
PS	performance status
PSS	physiological salt solution
QT	QT interval
QTc	corrected QT interval
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategies
RP2D	recommended phase 2 dose
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	stable disease
STD	standard deviation
SSQ	special search query
$T_{1/2}$	terminal half-life
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
TK	toxicokinetic
TKI	tyrosine kinase inhibitor
US	United States
USD	United States dollar
VAS	visual analogue scale
WHODRUG	World Health Organization Drug Dictionary

Section 1 was completed by the FDA

1 Executive Summary

1.1. Product Introduction

Tucatinib is an oral tyrosine kinase inhibitor of HER2. It does not have approval for any indication worldwide.

The applicant proposed the following indication for NDA 213411:

TUKYSA is indicated 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.

The recommended indication for regular approval is:

TUKYSA is 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.

The recommended dose for tucatinib is 300 mg taken orally twice daily, with or without food. In combination with tucatinib, trastuzumab can be administered at standard intravenous or subcutaneous doses. The recommended dose for capecitabine is 1000 mg/m^2 orally twice daily (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for the regular approval of tucatinib, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is based on efficacy and safety data from a single randomized (2:1), double-blind, placebo-controlled clinical trial (HER2CLIMB) in 612 patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior trastuzumab, pertuzumab, and T-DM1. Patients were randomized to either tucatinib or placebo, with trastuzumab and capecitabine. The trial demonstrated statistically significant and clinically meaningful improvements in the primary efficacy outcome of progression-free survival (PFS) assessed by blinded independent central review (BICR) and the key secondary outcome of overall survival (OS). Estimated median PFS assessed by BICR in the first 480 randomized patients was 7.8 months (95% CI: 7.5, 9.6) in the tucatinib arm compared to 5.6 months (95% CI: 4.2, 7.1) in the control arm (HR: 0.54, 95% CI:

0.42, 0.71, p<0.00001). Median OS, assessed in all 612 randomized patients, was 21.9 months (95% CI: 18.3, 31.0) in the tucatinib arm compared to 17.4 months (95% CI: 13.6, 19.9) in the control arm (HR: 0.66, 95% CI 0.50, 0.87, p=0.00480).

Patients with active brain metastases have been historically excluded from breast cancer clinical trials; however, HER2CLIMB permitted enrollment of patients with treated and progressing brain lesions and untreated brain lesions, as well as patients with treated and stable brain lesions. This is consistent with FDA's recommendations to broaden cancer clinical trial eligibility for patients with brain metastases as outlined in the Draft FDA Cancer Clinical Trial Eligibility Criteria: Brain Metastases Guidance for Industry. Patients with brain metastases made up 48% of the overall study population in HER2CLIMB. The key secondary outcome of $PFS_{brainmets}$ examined PFS specifically in this subgroup and also showed a statistically significant and clinically meaningful improvement in favor of the tucatinib arm. The remaining key secondary outcome was ORR by BICR, which was also statistically significant and clinically meaningful in favor of the treatment arm.

Tucatinib demonstrated acceptable tolerability for the indicated population which has a serious and life-threatening disease. Adverse reactions were common on the tucatinib arm, but generally managed with standard medical care, supportive therapy, treatment interruption, and/or dose reduction. Discontinuation of tucatinib was infrequent, and occurred in 6% of patients. The most common adverse reactions (≥30%) on the tucatinib arm were diarrhea, palmar-plantar erythrodysaesthesia (PPE) syndrome, nausea, fatigue, hepatotoxicity, vomiting, and stomatitis. The most common Grade≥3 adverse reactions (≥5%) were PPE syndrome, diarrhea, hepatotoxicity, increased ALT, and fatigue. Important safety signals with tucatinib include diarrhea which led to two deaths and hepatoxicity; both are labeled as Warnings and Precautions.

This NDA represents a new treatment option for patients with advanced unresectable or metastatic HER2-positive breast cancer, including those with brain metastases who have received one or more prior anti-HER2-based regimens in the metastatic setting. Tucatinib in combination with trastuzumab and capecitabine demonstrated statistically significant and clinically meaningful improvements in PFS, OS, $PFS_{brainmets}$, and ORR in a heavily pretreated HER2-positive metastatic breast cancer population. Patients had received at least 1 prior line of systemic therapy in the metastatic setting (median: 3 lines, range: 1 to 14). Progression-free survival and overall response rate endpoints are standard efficacy endpoints for oncology clinical trials and have been used in other FDA approvals. The use of a single randomized trial to support approval is acceptable due to the disease setting, consistent demonstration of superiority across multiple efficacy endpoints, and robust efficacy results on statistical evaluation. Therefore, the FDA review team recommends granting regular approval to TUKYSA (tucatinib).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer affecting women after skin cancer, with more than 270,000 new diagnoses and more than 40,000 deaths in the United States each year. Rarely, male patients develop breast cancer, and often present at a higher stage than female patients. Different histopathological subtypes of breast cancer are defined by expression of the estrogen receptor (ER), progesterone receptor (PR), and/or human epidermal growth factor receptor 2 (HER2). Approximately 20% of patients with breast cancer will have HER2-positive disease, which is associated with younger age at diagnosis and a more aggressive phenotype. Between 20-50% of patients with HER2-positive metastatic breast cancer (MBC) will develop brain metastases.

The preferred first-line treatment for patients with HER2-positive MBC in the U.S. is trastuzumab, pertuzumab, and a taxane, followed by T-DM1 as second-line treatment at disease progression. Patients with HER2-positive MBC who develop disease recurrence during or within six months of adjuvant therapy with trastuzumab and a taxane may receive T-DM1 as first-line treatment in the metastatic setting. After T-DM1, treatment options include trastuzumab with chemotherapy, the FDA-approved combinations of lapatinib and capecitabine or neratinib and capecitabine, and fam-trastuzumab deruxtecan which is under an accelerated approval. No therapy has shown an overall survival benefit in the post-T-DM1 setting. HER2-positive MBC remains incurable, and there are no approved systemic therapies specifically for patients with brain metastases. There is an unmet medical need for treatment options to improve clinical outcomes in all patients with HER2-positive MBC, including those with brain metastases.

The safety and efficacy assessment of tucatinib is primarily based on data from HER2CLIMB, a phase 2, randomized (2:1), double-blind, placebo-controlled clinical trial in 612 patients with advanced unresectable or metastatic HER2-positive breast cancer, including those with brain metastases, who had received prior trastuzumab, pertuzumab, and T-DM1. Patients received either tucatinib 300 mg or placebo orally twice daily, with trastuzumab intravenously or subcutaneously at standard doses, and capecitabine 1000 mg/m^2 orally twice daily on days 1 to 14 of each 21-day cycle. Patients continued treatment until disease progression or unacceptable toxicity. Tumor assessments, including brain-MRI in patients with history or presence of brain metastases at baseline, occurred every 6 weeks for the first 24 weeks and every 9 weeks thereafter. The primary efficacy outcome was PFS assessed by BICR in the first 480 randomized patients. The estimated median PFS assessed by BICR for patients on the tucatinib arm was 7.8 months (95% CI: 7.5, 9.6) versus 5.6 months (95% CI: 4.2, 7.1) for patients on the control arm, with a hazard ratio of 0.54 (95% CI: 0.42, 0.71; p<0.00001). Key secondary outcomes with alpha allocation included OS, $PFS_{brainmets}$, and confirmed

ORR. Median OS, assessed in all 612 randomized patients, was 21.9 months (95% CI: 18.3, 31.0) in the tucatinib arm compared to 17.4 months (95% CI: 13.6, 19.9) in the control arm (HR: 0.66, 95% CI 0.50, 0.87, p=0.00480). HER2CLIMB also met its $PFS_{brainmets}$ and ORR endpoints.

In HER2CLIMB, 48% of patients had a presence or history of brain metastases at baseline; of these patients, 40% had treated and stable brain metastases, 37% had treated but radiographically progressing brain metastases, and 23% had untreated brain metastases. All patients received prior trastuzumab and T-DM1, and all but two patients had prior pertuzumab. Patients had received at least 1 prior line of systemic therapy in the metastatic setting (median: 3 lines, range: 1 to 14). Men were eligible and five men enrolled onto HER2CLIMB.

Tucatinib demonstrated acceptable tolerability for the indicated population which has a serious and life-threatening disease. Adverse reactions were common in the tucatinib arm, but generally managed with standard medical care, supportive therapy, treatment interruption, and/or dose reduction. The most common adverse reactions (≥30%) on the tucatinib arm were diarrhea, PPE syndrome, nausea, fatigue, hepatotoxicity, vomiting, and stomatitis. The most common Grade≥3 adverse reactions (≥5%) were PPE syndrome, diarrhea, hepatotoxicity, increased ALT, and fatigue. Serious adverse reactions and deaths were balanced between the two arms. The most common serious adverse reactions (≥2%) on the tucatinib arm were diarrhea, vomiting, nausea, abdominal pain, and seizure.

Drug interruptions, dose reductions, and discontinuations were more common on the tucatinib arm compared to the control arm. However, tucatinib discontinuation was infrequent and occurred in only 6% of patients. Important safety signals for tucatinib include diarrhea and hepatotoxicity. All grade diarrhea was markedly higher, and grade ≥3 diarrhea was higher on the tucatinib arm compared to the control arm. Two patients experienced Grade 4 diarrhea on HER2CLIMB which led to death. All grade and grade ≥3 hepatotoxicity were both higher on the tucatinib arm than on the control arm. There were no cases of hepatotoxicity leading to liver failure or death. Diarrhea and Hepatotoxicity, as well as Embryo-Fetal Toxicity are labeled as Warnings and Precautions.

Overall, the benefit-risk profile of tucatinib based on the results of HER2CLIMB is favorable and this New Drug Application (NDA) represents a new treatment option for patients with advanced unresectable or metastatic HER2-positive breast cancer, including those with brain metastases. Tucatinib in combination with trastuzumab and capecitabine demonstrated statistically significant and clinically meaningful improvements in PFS, OS, $PFS_{brainmets}$, and ORR in a heavily pretreated HER2-positive metastatic breast cancer population. Tucatinib is the first drug to show an improvement in median OS in the post-T-DM1 treatment setting. Patients with active brain metastases are typically excluded from breast cancer clinical trials but were included as part of the baseline brain metastases subgroup in HER2CLIMB. This will be the first drug approval specifically for patients with breast cancer and brain metastases.

TUKYSA (tucatinib) is recommended for regular approval for the following indication:

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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Breast cancer is the most common cancer in women after skin cancer, with over 276,000 new cases and estimated 42,170 deaths in the United States in 2020 • Approximately 20% of patients with breast cancer have HER2-positive disease. • Advanced or metastatic breast cancer (MBC) is incurable. • Between 20-50% of patients of HER2-positive MBC will develop brain metastases.	**HER2-positive advanced or metastatic breast cancer is a serious and life-threatening condition.**
Current Treatment Options	• HER2-positive MBC is not curable. Treatment is palliative, with the goals of reducing cancer-related symptoms, delaying disease progression, and prolonging survival. • FDA-approved treatments for HER2-positive MBC include trastuzumab, pertuzumab, and docetaxel for patients who are treatment-naïve in the metastatic setting, and T-DM1 for patients who have previously received trastuzumab and a taxane. • Other treatment options include trastuzumab with chemotherapy, the FDA-approved combinations of lapatinib and capecitabine or neratinib and capecitabine, and fam-trastuzumab deruxtecan which is under an accelerated approval.	**There is an unmet medical need to improve the outcomes in patients with HER-positive MBC, including in those with brain metastases.** **No therapy has shown an overall survival benefit in the post-T-DM1 setting.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There are no systemic treatment options specifically for patients with HER2-positive MBC and brain metastases.	
Benefit	• HER2CLIMB enrolled 612 patients with HER2-positive advanced unresectable or MBC, including those with brain metastases, who had received prior trastuzumab, pertuzumab, and T-DM1. • Median PFS by BICR was 7.8 months (95% CI: 7.5, 9.6) in the tucatinib arm compared to 5.6 months (95% CI: 4.2, 7.1) in the control arm (HR 0.54, 95% CI: 0.42, 0.71, p<0.00001). • Median OS was 21.9 months (95% CI: 18.3, 31.0) in the tucatinib arm compared to 17.4 months (95% CI: 13.6, 19.9) in the control arm (HR: 0.66, 95% CI 0.50, 0.87, p=0.00480). • The median PFS in those with brain metastases at baseline ($PFS_{brainmets}$) was 7.6 months (95% CI: 6.2, 9.5) compared to 5.4 months (95% CI: 4.1, 5.7) in the control arm (HR: 0.48, 95% CI: 0.34, 0.69, p<0.00001). • In patients with measurable disease, ORR was 40.6% (95% CI: 35.3, 46.0) in the tucatinib arm compared to 22.8% (95% CI: 16.7, 29.8) in the control arm (p=0.00008).	**HER2CLIMB met its primary and all key secondary endpoints in a heavily pretreated HER2-positive MBC population.** **Tucatinib is the first drug to show an improvement in median OS in the post-T-DM1 treatment setting.** **This will be the first drug approval specifically for patients with breast cancer and brain metastases.** **Patients with active brain metastases are typically excluded from breast cancer clinical trials, but were included as part of the baseline brain metastases subgroup in HER2CLIMB.**
Risk and Risk Management	• The most common adverse reactions (≥30%) on the tucatinib arm were diarrhea, palmar-plantar erythrodysaesthesia syndrome, nausea, fatigue, hepatotoxicity, vomiting, and stomatitis. The most common Grade≥3 adverse reactions (≥5%) were PPE syndrome, diarrhea, hepatotoxicity, increased ALT, and fatigue. • Drug interruptions, dose reductions, and discontinuations were more common on the tucatinib arm compared to the control arm. Tucatinib discontinuation was infrequent, occurring in only 6% of patients.	**The safety profile of tucatinib in combination with trastuzumab, and capecitabine is acceptable for the intended population, and is manageable with current labeling.** **Diarrhea, hepatotoxicity, and embryo-fetal toxicity are included under Warnings and Precautions. There is no indication for REMS.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	Section 8.1.2
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Cross-Disciplinary Team Leader

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Breast cancer (BC) is the most common form of cancer in women worldwide (Ferlay 2018), with approximately 2 million patients diagnosed with BC in 2018 and more than 600,000 deaths. Approximately 1% of BC cases occur in men (Siegel 2019).

Human epidermal growth factor receptor-2 (HER2) is a member of the HER family of receptor tyrosine kinases that also includes epidermal growth factor receptor (EGFR or HER1), HER3, and HER4. HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. In healthy human adults, HER2 is expressed in epithelial cells in the gastrointestinal, respiratory, urinary, and female reproductive tract, as well as in tissues including breast, skin, cardiomyocytes, and Schwann cells. In non-malignant cells, amplification of the HER2 gene is not observed, and HER2 protein levels are low in comparison to tumors with HER2 gene amplification (De Potter 2001; Goodearl 2001; Hsu 2018; Poon 2013; Press 1990; Sliwkowski 1999; Uhlen 2015). In cancer cells, HER2 protein levels can be increased 10 to 100-fold above levels found in normal cells (Kraus 1987; Sliwkowski 1999).

Between 15% and 30% of breast cancers overexpress the HER2 receptor and are classified as HER2+ BC (Cronin 2010; Loibl 2017; Owens 2004; Slamon 1987; Wolff 2014). Historically, HER2+ BC tends to be more aggressive and more likely to recur than HER2-negative BC (American Cancer Society 2018; Loibl 2017; Slamon 1987). HER2+ BC also disproportionately affects younger BC patients, where the proportion of HER2 positivity is higher compared to older patients (Murphy 2019).

Once HER2+ BC has metastasized, the estimated 5 year overall survival (OS) rate ranges from 15% to 26% (American Cancer Society 2018; National Cancer Institute 2018; National Cancer Institute (NCI)).

The introduction of HER2-targeted therapies has led to significant and ongoing improvements in disease-free survival (DFS), progression free survival (PFS), and OS in both the adjuvant and metastatic settings (Baselga 2012; Geyer 2006; Slamon 2001; Verma 2012). However, as patients live longer due to this improvement in systemic disease control, more patients develop brain metastases. Data from retrospective studies suggest that the incidence of brain metastases in HER2+ patients ranges from 21% to 50% (Clayton 2004; Goldhirsch 2013; Lin 2013b; Pestalozzi 2013). Both the biologic tropism of HER2+ disease for the brain and better control of systemic disease likely contribute to the high incidence of brain metastases in this setting, as well as the fact that current therapies (which are largely antibody-based) may not effectively treat micrometastases in the brain.

BC patients with brain metastases have a worse prognosis relative to those without brain metastases. In one registry of 1,012 patients with HER2+ MBC, evidence of brain metastases was associated with markedly shortened survival relative to patients without brain metastases (Brufsky 2011). After first diagnosis of brain metastases, the median OS for these patients was only 13.0 months (range, 0.1 to 55.5 months). Patients with brain metastases survived only about half as long from initial metastatic diagnosis compared to patients without brain metastases; among patients with brain metastases, median OS was 26.3 months compared to 44.6 months in patients without CNS metastases.

Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's assessment of HER2+ breast cancer.

2.2. Analysis of Current Treatment Options

The Applicant's Position:
Current treatment options for patients with HER2+ metastatic breast include a range of HER2-targeted therapy based on inhibition of HER2 using either antibodies (trastuzumab and pertuzumab), antibody-drug conjugates (ado trastuzumab emtansine [T-DM1]), or small molecule tyrosine kinase inhibitors (TKIs; lapatinib and neratinib) in both the adjuvant and metastatic settings (Baselga 2012; Geyer 2006; Slamon 2001; Verma 2012).

First-line treatment for most patients with HER2+ MBC is a combination of trastuzumab plus pertuzumab and chemotherapy. However, within 2 years, the majority of patients treated with this combination will progress (Baselga 2012; Swain 2013). After progression on trastuzumab, pertuzumab, and chemotherapy, standard of care treatment for patients with HER2+ MBC is T-DM1. T-DM1 is often a second line metastatic treatment, but may be given as a first-line metastatic treatment in patients who relapse rapidly after receiving a pertuzumab-based regimen in the adjuvant or neoadjuvant setting (Cardoso 2018; Giordano 2018).

Treatment of patients after progression on T-DM1 remains a clinical challenge, and the prognosis of these patients remains poor. There is no single established standard of care (Dieras 2017; Verma 2012) and no approved therapies have demonstrated clinically meaningful improvements in PFS or OS (Blackwell 2012; Geyer 2006; Verma 2012). Preferred regimens based on American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN) guidelines for these patients include continuation of HER2 targeted therapy with trastuzumab or lapatinib in combination with cytotoxic chemotherapy, such as capecitabine (Cardoso 2018; Giordano 2018; Gradishar 2016). However, the efficacy of these regimens in this setting remains modest, with reported median PFS of 3.3 to 4.9 months (Krop 2014; Rugo 2019) and median OS of 15.8 to 17.2 months (Krop 2017; Rugo 2019). There remains significant unmet medical need for HER2+ MBC patients who have progressed despite receiving current standard of care, including 3 prior anti-HER2 agents, and better treatment options for these patients are urgently needed to improve efficacy and tolerability.

Treatment for brain metastases usually includes either surgical resection, radiosurgery, and/or whole brain radiotherapy in addition to continuation of systemic anti-HER2 therapy. Unfortunately, these treatments often result in significant neurologic toxicities, which may impair quality of life. Stereotactic radiosurgery has been increasingly used to avoid the neurologic toxicities of whole brain radiotherapy, but the trade-off for this decrease in toxicity has been inferior control of distant brain relapse outside of the radiation fields (Brown 2016; Chang 2009; Kaidar-Person 2016).

Despite recent improvements in the treatment of HER2+ MBC overall, systemic therapies have not yet demonstrated a clinically meaningful impact on the treatment of patients with brain metastases. Recent data suggests that the incidence of first relapse occurring in the CNS is increasing in patients who have received trastuzumab-based adjuvant therapy, and up to half of HER2+ patients with metastatic disease will develop CNS metastases (Duchnowska 2018; Lin 2013a; Mounsey 2018; Pestalozzi 2013; Witzel 2016). No systemic agents are specifically approved for treatment of patients with HER2+ MBC with brain metastases, and outside of clinical trials, these patients are generally treated with therapies not labeled for this indication (Lin 2015). A recent meta-analysis showed that lapatinib, either alone or in combination with capecitabine, was associated with a median PFS of 4.1 months and median OS of 11.2 months in this setting (Petrelli 2017). Historically, patients with active brain metastases, defined as untreated or progressing brain metastases at the time of study entry, have been excluded from clinical trials because of their poor prognosis (Lin 2017). Thus, there is a high unmet need for effective and well-tolerated systemic treatment options for patients with brain metastases.

Development of systemic treatments for patients with brain metastases will require including these patients in clinical trials in order to provide a robust demonstration of a therapy's safety and efficacy across the broader patient population likely to use the treatments in clinical practice, which has been strongly advocated for in recent years by various groups such as the ASCO-Friends of Cancer Research Eligibility Criteria Working Group (Kim 2017; Lin 2017) (FDA Draft Guidance for Industry, “Cancer Clinical Trial Eligibility Criteria: Brain Metastases.” March 2019).

Regulatory Authorities Assessment:

The regulatory authorities generally agree with the applicant’s assessment of current treatment options for patients with HER2+ MBC in the U.S. with the following comments and clarifications.

The preferred first-line treatment for patients with HER2-positive MBC in the U.S. is trastuzumab, pertuzumab, and a taxane based on data from the CLEOPATRA clinical trial (n=808 patients). Patients receiving pertuzumab, trastuzumab, and docetaxel had a median overall survival of 56.5 months compared to 40.8 months in patients receiving placebo, trastuzumab, and docetaxel (HR 0.68, 95% CI 0.56, 0.84, p<0.001). The standard-of-care

second-line treatment is T-DM1 based on results from the EMILIA clinical trial (n=991 patients). Patients receiving T-DM1 had a median overall survival of 30.9 months compared to 25.1 months in patients receiving lapatinib and capecitabine (HR 0.68, 95% CI 0.55, 0.85, p<0.001). Patients with HER2-positive breast cancer who developed disease recurrence during or within six months of adjuvant therapy with trastuzumab and a taxane were also eligible for EMILIA and may receive T-DM1 as first-line treatment in the metastatic setting. Following disease progression on T-DM1, therapeutic options include trastuzumab with chemotherapy, the FDA-approved combinations of lapatinib and capecitabine or neratinib and capecitabine, or trastuzumab deruxtecan which is under an accelerated approval.

On December 20, 2019, the FDA granted accelerated approval to fam-trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive breast cancer who received two or more prior anti-HER2-based regimens in the metastatic setting. DESTINY-Breast01, a multicenter single arm trial enrolling 184 patients, formed the basis for approval. All patients were exposed to T-DM1 prior to enrollment. The confirmed objective response rate (ORR) was 60.3% (95% CI: 52.9, 67.4) and the median duration of response was 14.8 months (95% CI: 13.8, 16.9).

On February 25, 2020, the FDA granted regular approval to neratinib in combination with capecitabine for patients with advanced or metastatic HER2-positive breast cancer who received two or more prior anti-HER2-based regimens in the metastatic setting. NALA, a multicenter, randomized (1:1), open label clinical trial enrolling 621 patients, formed the basis of approval. Patients were not required to receive prior T-DM1 and 54.3% were exposed to T-DM1 prior to enrollment. Patients receiving neratinib and capecitabine had a median PFS of 5.6 months compared to 5.5 months on the lapatinib and capecitabine arm (HR 0.76, 95% CI 0.63, 0.93) and a median OS of 21.0 months compared to 18.7 months (HR 0.88, 95% CI 0.72, 1.07).

Despite these treatment options, no treatment has shown a clinically meaningful and statistically significant OS benefit in the post-T-DM1 setting.

The FDA agrees that brain metastases are relatively common in patients with HER2+ MBC, affecting 20-50% of patients. However, the FDA disagrees that patients who received adjuvant trastuzumab have an increased incidence of CNS as first site of relapse as there is conflicting data to support this.

Patients with HER2+ MBC and brain metastases have relatively few systemic therapy options, and there are no therapies with specific labeled indications for patients with brain metastases. The regulatory authorities agree with the applicant that patients with HER2-positive MBC and brain metastases represent a population with high unmet medical need.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Tucatinib is not currently registered or approved in the United States (US) or any other part of the world. A summary of relevant regulatory history is included in Section 3.2.

Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
The development of tucatinib in subjects with advanced cancer was initiated by Array BioPharma, Inc. under investigational new drug (IND) 78304 in 2007. In 2013, tucatinib was licensed to Cascadian Therapeutics, Inc. (Cascadian; formerly Oncothyreon, Inc.) and clinical development in HER2+ BC continued under IND 119421. After Seattle Genetics' acquisition of Cascadian, sponsorship of both INDs was transferred on 28 Sep 2018. A summary of important regulatory events, milestones, and communication are in Table 1.

Table 1: Summary of Regulatory History

Date	Description	Reference
24-Jul-2007	Study May Proceed (IND 078304) Protocol ARRAY-380-101- First in human study to assess safety, PK and preliminary activity of tucatinib in subjects with advanced cancer	Reference ID 4063834
18-Oct-2013	Study May Proceed (IND 119421); Protocol ONT-380-004 - A Phase 1b study to assess the safety and tolerability of tucatinib combined with ado-trastuzumab emtansine (T-DM1) in HER2+ MBC subjects	Reference ID 3392509
04-Nov-2013	New Protocol ONT-380-005 - A Phase 1b study to assess the safety and tolerability of tucatinib combined with capecitabine and/or trastuzumab in HER2+ MBC subjects	IND 119421 SN0003
13-Aug-2015	New Protocol ONT-380-206 (HER2CLIMB) – A 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	IND 119421 SN0032
21-Jun-2016	IRB waiver granted for non-US sites conducting clinical trials (foreign clinical studies) under IND 119421	Reference ID 3969985
24-Jun-2016	Fast Track designation granted for the treatment of advanced HER2+ MBC	Reference ID 3950721
11-Oct-2016	Type B EOP1 meeting to discuss clinical, nonclinical, and CMC topics, including modification of the HER2CLIMB protocol to increase the sample size from 180 to approximately 480 and powering the study to enable	Reference ID 3998811

Date	Description	Reference
	demonstration of both improvement in PFS (primary endpoint) and PFS in subjects with brain metastases (secondary endpoint) to support an NDA. The Agency considered the nonclinical and clinical pharmacology plans to be generally acceptable, and recommended to include a strong CYP2C8 inhibitor in the planned drug-drug interaction trial and to specify administration of tucatinib with regard to food intake in the HER2CLIMB protocol. The Agency also confirmed carcinogenicity testing is not warranted to support the NDA, as recommended in ICH S9.	
03-Mar-2017	Agreed with the initial pediatric study plan (iPSP)	Reference ID 4063834
05-Jun-2017	Orphan drug designation granted for the treatment of BC patients with brain metastases	File No. 16-5707
24-Oct-2018	Type B EOP meeting to discuss modifications to the HER2CLIMB protocol to increase the sample size from 480 to 600 and to change the statistical testing from a hierarchical to parallel structure for the key secondary endpoints of $PFS_{BrainMets}$ and OS. The Agency's acceptance of the modifications was provided in the preliminary comments and the meeting was canceled.	Reference ID 4339701
25-Feb-2019	Type B pre-NDA meeting to discuss content and format of planned NDA primarily based on data from the pivotal trial HER2CLIMB. Agreements obtained for the presentation of information in the NDA including analysis of primary and key secondary endpoints in HER2CLIMB, ISE, ISS, narratives, case report forms, and BIMO data.	Reference ID 4398497
18-Oct-2019	Breakthrough therapy designation request submitted	IND 119421 SN0245

BIMO=Bioresearch Monitoring Program; EOP=end of phase; IRB=institutional review board; ISE=integrated summary of efficacy; ISS=integrated summary of safety; RTOR=Real Time Oncology Review

Regulatory Authorities Assessment:

The FDA generally agrees with the applicant's summary of pre-submission regulatory milestones with the following addition.

On October 21, 2019, the applicant agreed to participate in the Real-Time Oncology Review (RTOR) pilot. On the same day, the applicant agreed to participate in Project Orbis involving collaborative NDA review by FDA, the Australian Therapeutic Goods Administration, Singapore Health Sciences Authority, Health Canada, and Swissmedic.

On December 16, 2019, the FDA granted Breakthrough Therapy Designation to tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with locally

advanced unresectable or metastatic breast cancer, including patients with brain metastases, who have received two or more prior anti-HER2-based regimens in the metastatic setting.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 1 consulted OSI to perform an audit of the Sponsor and the overall trial conduct. The FDA selected four sites (0003, 0048, 0055, and 0070) for clinical inspection based on a relatively high numbers of patient enrollment and lack of recent inspections. Based on these clinical inspections all sites were generally in compliance with Good Clinical Practice (GCP) and all sites submitted acceptable data in support of the indication.

Clinical inspection summaries are included here:

Site 0003: Dr. Rashimi Murthy

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 long-term follow-up. The first subject was consented on (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) (4) 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.

OSI classification: No action indicated.

Site 0048: Dr. Vandana Abramson

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) (6) and the last subject was consented on (b) (6). 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, case report forms (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.

OSI classification: No action indicated.

<u>Site 0055: Dr. Erika Hamilton</u>

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 (b) (6) and the last subject was randomized on (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 (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 (b) (6) following an SAE of elevated bilirubin between the source document (09/09/2016) 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.

OSI classification: No action indicated.

Site 0070: Dr. Elisavet Palomata:

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 (b) (6). The first subject was consented on (b) (6) and the last subject was consented on (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 (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.
OSI classification: No action indicated.

4.2. Product Quality

FDA's Assessment:
The Product Quality review team examined assay stability, physical stability, content uniformity, impurities, and microbial limits. There was a higher level of the impurity (b) (4) when the applicant scaled up drug substance manufacturing. The applicant did

subsequent toxicology studies to qualify the impurity up to (b) (4)% and the Product Quality review team found this acceptable.

(b) (4) The applicant proposed releasing registration batches and also concurrently releasing process performance qualification (PPQ) batches for initial commercial distribution. The Product Quality review team found this approach acceptable because the clinical benefit of having this drug available earlier outweighed the limited risk.

Overall, the Product Quality review team recommends approval. For details, please refer to the full review, authored by Dr. Xiao Hong Chen.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

The applicant did not propose the use of a companion diagnostic or an FDA-approved test to select patients with HER2+ breast cancer.

In the HER2CLIMB study, HER2 positivity was confirmed centrally with an FDA-approved test, using fresh or archival tissue, and was based on ASCO-CAP guidelines requiring either ISH or FISH positivity or 3+ staining by IHC.

The Center for Devices and Radiologic Health (CDRH) provided consultation and agreed that no companion diagnostic device was needed. For full details, refer to the CDRH consult provided by Drs. Abukhdeir Abdelrahmman, Soma Ghosh, and Reena Philip.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Regulatory Authorities Assessment:

Tucatinib (ARRY-380 or ONT-380) is an orally administered small molecule tyrosine kinase inhibitor (TKI) targeting Human Epidermal Receptor 2 (HER-2 [ErbB2]). In this NDA, the Applicant submitted study reports of nonclinical pharmacology, pharmacokinetics, and toxicology studies to support the approval of tucatinib 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.

In pharmacology studies, tucatinib demonstrated higher inhibitory activity against HER2 compared to other protein serine/threonine or tyrosine kinases including the related tyrosine kinases EGFR and HER4. The tucatinib IC_{50} values for HER2 were in the nanomolar range in in vitro biochemical kinase assays and cell-based assays. Tucatinib inhibited HER2 autophosphorylation and downstream signaling through the MAP kinase (ERK1/2 and MEK1) and PI3 kinase (AKT) signal transduction pathways in HER2 expressing cell line BT-474. Cell viability assays showed that the HER2 expressing breast cancer cell line BT-474 was more sensitive to tucatinib treatment than the EGFR amplified tumor cell line A431. In vitro, the inhibitory effect of tucatinib on cell proliferation correlated with HER2 expression in different breast cancer derived cell lines. In vivo, single agent tucatinib showed anti-tumor activity and inhibition of HER2 phosphorylation in mouse xenograft models of HER2 expressing tumor cells. The combination of tucatinib with trastuzumab increased tucatinib-induced apoptosis of BT-474 cells. The combination of tucatinib with trastuzumab demonstrated greater anti-tumor activity compared to either single agent alone in the BT-474 in vivo mouse model. The approved Established Pharmacologic Class (EPC) of "kinase inhibitor" is applicable to tucatinib based on its pharmacologic activity.

Following oral administration, tucatinib exposure in rats and monkeys increased with increasing dose and was greater than dose proportional across the dose range tested. Tmax occurred at 1 to 2 hours in rats and 1 to 4 hours in monkeys. Following oral administration of [^{14}C]-tucatinib and whole-body autoradiography, the highest distribution of tucatinib in rats was in the uveal tract, eyes, pigmented skin, liver, testes, epididymis (male), and thymus (female); tucatinib was not detected in CNS tissues. In an intracranial mouse tumor model of BT-474 breast cancer cells, autoradiography did not detect tucatinib in brain slices following oral administration of [^{14}C]-tucatinib. After extracting and directly measuring [^{14}C]-radioactivity using a scintillation counter, the Applicant demonstrated that radioactivity was higher in the right side of the brain implanted with tumor compared to the left side of the brain without tumor. Tucatinib is metabolized by multiple enzymes and primarily eliminated by

metabolism through the hepatobiliary route in rats and monkeys. There are no human disproportionate metabolites requiring additional nonclinical studies.

Twice daily oral administration of tucatinib was assessed in repeat-dose toxicity studies for up to 3 months in rats and monkeys, consistent with the clinical route of administration and intended dosing schedule. The pivotal repeat-dose toxicology studies were conducted in compliance with Good Laboratory Practice regulations (21 CFR part 58). Administration of tucatinib to rats and monkeys resulted in body weight loss, reduced food consumption, and adverse effects in the gastrointestinal (GI) system (rat and monkey), liver (rat and monkey), hemolymphoid system (rat), skeletal muscle (rat), and reproductive system (rat). The adverse effects in the GI system, including macroscopic findings of intestinal red discolorations and microscopic findings of intestinal erosion/ulceration, were observed in the 28-day rat study and are considered the cause of death in rats at doses ≥120 mg/kg/day (approximately 16 times the human exposure at the recommended dose of 300 mg twice daily). Tucatinib increased gastric secretion volume and acidity and induced superficial mucosal lesion and hemorrhagic ulcers in the stomach of rats after a single dose of 100 mg/kg tucatinib. GI toxicity in monkeys included bloody stool and mucoid feces with no abnormal findings in pathological examinations at 40 mg/kg/day (approximately 3 times the human exposure at the recommended dose of 300 mg twice daily). In rats and monkeys, treatment-related liver toxicities included changes in clinical pathology, increases in liver weight and hepatocyte hypertrophy. In the 13-week studies, liver toxicities were observed in female rats at doses ≥ 20 mg/kg/day (similar to the human exposure at the recommended dose of 300 mg twice daily based on AUC) and in monkeys at 40 mg/kg/day (approximately 3 times the exposure in humans at the recommended dose of 300 mg twice daily based on AUC). Toxicities in the GI system and liver were observed in both rats and monkeys and are considered the major toxicities associated with tucatinib treatment. Toxicities in the GI tract and liver were also observed in patients treated with tucatinib.

Additional target organs in rats included the hemolymphoid system (lymphoid depletion), male and female reproductive organs, and skeletal muscle (myofiber degeneration/regeneration and hemorrhage) in male rats in the 28-day study. No changes in skeletal muscle were observed in the 13-week rat study at similar or higher doses. The changes in the female reproductive system and associated tissues occurred at doses ≥ 6 mg/kg/day and included uterine atrophy, vaginal atrophy, changes in corpora lutea, and decreased uterus/cervix weights. Tucatinib-related effects on male reproductive organs were decreased prostate weights, atrophy and edema in the testes and oligospermia/germ cell debris in the epididymides at doses ≥ 120 mg/kg/day. Lobular atrophy of the mammary gland was observed in male rats at doses ≥ 6 mg/kg/day.

In repeat-dose toxicology studies with tucatinib, toxicities were generally dose-dependent and were reversible or showed tendency of reversibility after a 4-week treatment-free recovery period. The treatment-related toxicities were associated with the pharmacologic activity of tucatinib.

Tucatinib had no adverse effect on ECG, respiration, or neurological behavior in safety pharmacology studies. In the 13-week monkey study with twice daily administration, tucatinib treatment elevated heart rates on Day 2 and with reduced severity on Day 92 of the dosing phase in males at doses ≥ 5 mg/kg/day. Elevated heart rates resolved during the recovery phase. Elevated heart rates were not noted during ECG assessment.

Tucatinib did not induce mutations in the bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro chromosome aberration test or the in vivo mouse bone marrow micronucleus assay at doses up to the high dose of 2000 mg/kg.

No fertility and early embryonic development studies have been conducted or are warranted to support this NDA submission. In the 13-week study in rats, tucatinib induced reproductive toxicities including uterine atrophy, vaginal atrophy, changes in corpora lutea at doses ≥6 mg/kg (approximately 0.1 times the human exposure at the recommended dose of 300 mg twice daily based on AUC). Tucatinib treatment resulted in atrophy and edema in the testes and oligospermia/germ cell debris in the epididymides in male rats at doses ≥ 120 mg/kg/day (approximately 13 times the human exposure at the recommended dose of 300 mg twice daily based on AUC). Based on findings in animals, tucatinib may impair male and female fertility.

The Applicant conducted pilot embryo-fetal development studies in rats and rabbits. Tucatinib was administered to animals at oral doses up to 150 mg/kg/day during the period of organogenesis. In rats, oral administration of tucatinib resulted in maternal toxicity (body weight loss, reduced body weight gain, low food consumption) and embryofetal toxicities including a reduced number of live fetuses, decreased fetal weights and fetal abnormalities (increase in skeletal variations, incomplete ossification) at doses ≥ 90 mg/kg/day (approximately 3.5 times the human exposure at the recommended dose based on AUC). In rabbits, oral administration of tucatinib resulted in maternal toxicity (minimal body weight loss and low food consumption) at doses ≥ 120 mg/kg and embryofetal toxicities including increased resorptions, decreased percentages of live fetuses, and skeletal, visceral, and external malformations in fetuses at doses ≥ 90 mg/kg/day (1.3 times the human exposure at the recommended dose based on AUC). Fetal abnormalities in rabbits included domed head, brain dilation, incomplete ossification of frontal and parietal bones, and a hole in the parietal bone. Exposure multiples were calculated using the mean $AUC_{0\text{-}12h}$ of 16400 ng.hr/mL in rats and 6370 ng.hr/mL in rabbits and the mean human $AUC_{\text{-last}}$ of 4724 ng.h/mL at a recommended human dose of 300 mg twice daily.

Based on findings in animals and mechanism of action, tucatinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential and male patients with female partners of reproductive potential should use effective contraception during treatment with tucatinib and for 1 week after the last dose, which covers a period of at least 5 half-lives for tucatinib ($T_{1/2}$ = 8.7 h). Because of the potential for serious adverse reactions in a breastfed child, women should not breastfeed during treatment with tucatinib and for 1 week after the last dose. Tukysa is indicated in combination with trastuzumab and capecitabine. Therefore, the Tukysa prescribing information includes a reference to the trastuzumab and capecitabine prescribing information for pregnancy, contraception, infertility, and lactation information.

No carcinogenicity studies were conducted or warranted to support this NDA, as the proposed indication was for advanced cancer.

Recommendation
The regulatory authorities agree that the nonclinical data submitted in this NDA are adequate to support approval of Tukysa for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer.

The TGA nonclinical team is in general agreement with the assessment but has not completed their review.

Of note, the FDA clinical pharmacology team recommended using human exposure data from Study ONT-380-005, which included patients with metastatic breast cancer receiving tucatinib, trastuzumab, and capecitabine with the same proposed dosing regimen. Therefore, animal to human exposure multiples were calculated using AUC_{last} of 4724 ng*hr/mL from the intensive PK data in Study ONT-380-005. The other regulatory authorities calculated exposure multiples using AUC_{tau} of 5234 ng*hr/mL predicted from population PK analysis. Given only about 10% difference between 4724 and 5234 ng*hr/mL, either value can be chosen without significant influence on the calculation of animal to human exposure multiples. The FDA clinical pharmacology team preferred the value of 4724 ng*hr/mL, as it is derived from the observed data in patients who were treated with the proposed dosing regimen.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
NA

Regulatory Authorities Assessment:
The applicant did not reference any NDAs or BLAs.

5.3. Pharmacology

Regulatory Authorities Assessment:

Primary pharmacology

The effect on HER2 and other kinase activities

The Applicant conducted enzyme linked immunosorbent assays (ELISA) to determine the kinase activity of tucatinib and its active metabolite (AR00440993) on ErbB2 (HER2), ErbB1 (EGFR) and ErbB4 (HER4) along with a full kinase panel from Millipore, Inc. [Study Report TRN-5457]. The study results were summarized by the Applicant and presented in the data section of Secondary Pharmacology. The results indicate tucatinib is a kinase inhibitor mainly against ErbB kinase family members. Tucatinib has higher inhibitory activity against HER2 compared to EGFR and HER4. The tucatinib IC_{50} values for HER2 from two tested batches were 22 nM and 6.9 nM respectively.

The effect on HER2 mediated signaling

Tucatinib inhibited HER2 phosphorylation with an IC_{50} value of 9.88 nM in HER2 expressing cell line BT-474 cells (Study Report TRN-5480) while the tucatinib IC_{50} for blocking EGFR phosphorylation in the EGFR amplified cell line A431 was 13.18 µM (Study Report TRN-5477). The ability of tucatinib to block downstream cell signaling was further evaluated in BT-474 cells by measuring phosphorylation of HER3, AKT, ERK1/2, and MEK1, yielding IC_{50} values between 0.24 and 4.9 nM. Tucatinib also inhibited cell proliferation of BT474 and A431 cells with IC_{50}s of 15 nM and 2981 nM, respectively (Study Report TRN-5456). The study results indicated that HER2 expressing cell line BT-474 was more sensitive to tucatinib than EGFR expressing cell line A431. These study results suggested that tucatinib-induced inhibition of HER2 phosphorylation and its downstream signaling resulted in inhibition of BT-474 cell proliferation.

In Vitro Antitumor activity

The Applicant evaluated tucatinib-mediated cytotoxic activity using Promega's Cell Titer-Glo (CTG) Luminescent Cell Viability assay in 22 breast cancer cell lines with various ranges of HER2 expression levels. Tucatinib showed cytotoxic activity with EC_{50} values of 18 - 431 nM in all evaluated HER2-high (>300,000 HER2 receptors/cell) breast cancer cell lines. In contrast, cytotoxic activity of tucatinib was low in HER2-low and HER2-negative breast cancer cell lines, with EC_{50} values ranging from 4938 - >25,000 nM (Study Report TRN-5430). These data suggested that the antitumor activity of tucatinib is dependent upon HER2 amplification in breast cancer cells.

In vivo anti-tumor activity

Mice received intracranial injections of BT474 cells and started daily treatment with tucatinib (ONT-380) at 75 mg/kg for up to 8 weeks starting two days after the implantation. By Day 56, tucatinib treated mice showed increased survival (69%) compared to the dose group receiving vehicle (23%). The median day of death was 41 for mice treated with vehicle and 54 for mice

receiving tucatinib. The treatment with tucatinib also resulted in reduced levels of phosphorylated ErbB2 in brain homogenates compared with the vehicle treated group (Study Report TRN-5455). No systemic exposure data were submitted with this study.

Anti-tumor activity of combination therapies in vitro and in vivo
BT-474 cells treated with tucatinib and trastuzumab (pre-treated or in concurrent use) showed significantly decreased levels of HER3 phosphorylation and subsequent decrease in Akt signaling compared to the cells treated with tucatinib alone. Tucatinib also inhibited phosphorylation of HER2, ERK1/2 and MEK1 induced by trastuzumab. Furthermore, the combination of tucatinib and trastuzumab increased caspase 3/7 activity, a measurement for apoptosis, up to 2-fold compared with the treatment of tucatinib alone (Study Report TRN-5517).

Secondary Pharmacology

Data:

Biochemical assays using purified recombinant protein kinases were conducted to evaluate the ability of tucatinib to inhibit the intended target, HER2, and related protein tyrosine kinases EGFR and HER4. HER3 was not evaluated because it has minimal kinase activity. Tucatinib was also evaluated in a panel of 223 protein kinases to determine its capacity to inhibit the activity of diverse serine/threonine and tyrosine kinases.

Based on Ki calculations, tucatinib has a 28- to 88-fold increase in potency for HER2 relative to EGFR and a 92 to 105-fold increase in potency for HER2 relative to HER4. Therefore, tucatinib is a (b) (4) inhibitor of HER2 and has reduced potency for related kinases.

A kinome screen showed that the only kinases potently inhibited by tucatinib when tested at concentrations ~500 or 5000-fold above the calculated Ki value for HER2 were members of the ErbB family, including EGFR, HER4, and mutant versions of EGFR (L858R, L861Q, T790M/L858R).

The Applicant's Position:

Tucatinib is a (b) (4) inhibitor of the HER2 tyrosine kinase.

Regulatory Authorities Assessment:

The Applicant uses terminologies such as (b) (4) "and (b) (4) to describe the study results; such terms should be avoided as they are vague, subjective, and promotional.

The regulatory authorities agree with the assay results summarized by the applicant. The study results indicated that tucatinib has an inhibitory effect mainly against ErbB family members and has higher activity against HER2 compared to EGFR and HER4.

Safety Pharmacology

Data:

Gastrointestinal effects: Potential effects of single doses of oral tucatinib at 0, 10, 30, and 100 mg/kg on gastric secretion volume, pH, acidity, intestinal transit time, and local gastric irritation were evaluated in rat studies. Positive controls were pentagastrin at 32 µg/kg by subcutaneous injection (gastric secretion volume, pH, and acidity); morphine at 20 mg/kg (intestinal transit); or aspirin at 250 mg/kg (gastric irritation). Each study had 10 male Sprague/Dawley rats per group.

Gastric secretion volume, pH, and acidity: Tucatinib at 100 mg/kg increased gastric secretion volume and acidity, whereas gastric secretion pH was unchanged at all doses. The NOEL was 30 mg/kg.

Intestinal transit time: Tucatinib did not significantly affect intestinal transit of charcoal meal. The NOEL was 100 mg/kg.

Local GI tolerance assay: Gastric irritation was significantly higher at 100 mg/kg versus the vehicle control group. The NOEL was 30 mg/kg.

Assessment of *behavior and physiologic functions:* Rats were left naïve or administered tucatinib at single doses of 0, 10, 30, and 100 mg/kg by oral gavage to examine any possible effect of tucatinib on a battery of behavioral and physiological parameters (Irwin test). There were no relevant changes in sensorimotor, neurobehavioral, and autonomic functions. A trend toward decreased body weight gain after 24 hours was observed after treatment with 100 mg/kg. Rectal temperature was not significantly different from control animals. The NOEL was 30 mg/kg based on decreased body weight gain.

Respiratory Function: Rats were evaluated for respiration by plethysmography at baseline and after single dose tucatinib administration of 0, 10, 30, or 100 mg/kg by oral gavage, or sodium pentobarbital (positive control) by intraperitoneal injection. There were no test article-related changes in any respiratory parameter measured. The NOEL was 100 mg/kg.

Cardiovascular assessments: Cardiovascular assessments included an in vitro hERG channel inhibition test and two in vivo studies in cynomolgus monkeys (a safety pharmacology study and cardiovascular evaluations during a 90-day toxicity study).

In vitro hERG channel inhibition: Tucatinib and control articles were applied via superfusion [10, 3.0, 1.0, and 0.3 µM tucatinib in physiological salt solution (PSS); PSS containing 0.1% DMSO and cisapride (100 nM or 0.1 µM) as vehicle and positive control, respectively] to human embryonic kidney cells (HEK293) expressing cloned hERG channels. The top concentration was limited to 10 µM due to solubility. Tucatinib inhibited hERG channel-mediated potassium currents at 0.3 to 10 µM superfusate concentrations with a calculated IC_{50} of 13.51 µM (the IC_{50} exceeds 10 µM, the highest concentration of tucatinib).

Safety pharmacology study: Six male cynomolgus monkeycls were administered tucatinib twice a day, 12 hours apart, on Days 1, 2, 7, and 12 at 0, 10, 30, and 45 mg/kg/dose (0, 20, 60, and 90 mg/kg/day) and were evaluated for changes in clinical signs, food consumption, and body weight. Cardiovascular data were recorded via telemetry prior to and following dose administration. Blood samples for toxicokinetic analyses were collected at various time points prior to and following each dose.

Test article-related findings were limited to transient distended abdomens on Day 7 in 5 of 6 animals after the second dose of 30 mg/kg (60 mg/kg/day); this resolved within 24 hours without intervention. Tucatinib was detected in the plasma of all animals at each non-zero dose level, and concentrations increased with increasing dose. The mean tucatinib plasma concentration values (± SDV) at 45 mg/kg/dose were 3.10 ± 1.74 and 0.099 ± 0.126 µg/mL at 2- and 12-hour post-dose, respectively. The NOEL was 10 mg/kg/dose.

General toxicity study: In a 90-day cynomolgus monkey study, males and females (6/sex/group) were administered tucatinib at 0, 2.5, 10, or 20 mg/kg/dose twice daily (5, 20, or 40 mg/kg/day) via oral gavage. Electrocardiograms, blood pressure, and vital signs were evaluated on Day 2 and during the last week of dosing. Tucatinib-related findings were limited to elevated heart rates (non-adverse) on Days 2 and 92 of the dosing phase in males administered ≥5 mg/kg/day during vital sign assessment. The NOEL for cardiovascular effects was not determined, based on the observation of increased heart rate by vital signs (but not by ECG measurements) at ≥5 mg/kg/dose.

The Applicant's Position:
The safety pharmacology of tucatinib did not identify any potential hazards for the cardiovascular, neurobehavioral, gastrointestinal, and respiratory systems.

Regulatory Authorities Assessment:
The regulatory authorities agree that there were no adverse effects of tucatinib on ECG, respiration, or neurological behavior. However, the study results showed drug-related adverse effects on the gastrointestinal system and treatment-related increases in heart rates. Additional noteworthy results and study methods are listed below.

Gastrointestinal effects (male rats):

Gastric secretion volume, pH, and acidity: Male rats were used in the study. Four-hour gastric secretion was obtained at approximately 3 hours after test item/vehicle administration. Tucatinib at 100 mg/kg increased the total gastric secretion volume and the gastric secretion acidity by 48% (not statistically significant) and 90% (statistically significant), respectively, when compared to the vehicle group.

Local GI tolerance assay: The whole stomach was removed and examined approximately 4 hours after test item/vehicle administration. Adverse effects on the stomach were scored as follows: Score 1 superficial mucosal lesion, Score 2 hemorrhagic ulcer, and Score 3 perforated ulcer. Score 2 lesions were observed in 10, 70, 30, 80% of animals in the vehicle, 10, 30, 100 mg/kg tucatinib groups, respectively. Score 2 lesions in the 100 mg/kg tucatinib group were statistically significant compared to the vehicle group. The total lengths of score 1 lesions at 100 mg/kg were also statistically significant (3 times higher) compared to the vehicle group.

Cardiovascular assessments:

In the 13-week monkey study, twice daily administration of tucatinib increased heart rates on Day 2 of the dosing phase in males at all doses. Mean heart rates were 41, 44, or 40 beats/minute higher than controls in males at 5, 20, or 40 mg/kg/day, respectively. Mean heart rates were also elevated by 20 to 28 beats/minute compared to the controls on Day 92 of the dosing phase and resolved during the recovery phase. Elevated heart rates were not noted during ECG assessment.

5.4. ADME/PK

Data:

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>TRN-5562: Pharmacokinetics of Tucatinib in Mice, Rats, and Monkeys following a Single Intravenous or Oral Dose</td><td>Following a single IV dose of tucatinib at 0.5 or 1 mg/kg, the clearance was moderate in rats and high in cynomolgus monkeys. Following oral administration (various formulations), exposure increased greater than dose-proportionally in mice (20 to 100 mg/kg) and rats (10 to 100 mg/kg). In cynomolgus monkeys, the exposure increase was less than dose proportional (15 to 45 mg/kg).
<table>
<tr><th>Species</th><th>Route</th><th>Dose (mg/kg)</th><th>$t_{1/2}$ (h)</th><th>$AUC_{24}h$ (µg·h/mL)</th><th>C_{max} (µg/mL)</th><th>Bioavailability (%)</th></tr>
<tr><td>Rat</td><td>IV</td><td>0.5</td><td>0.725</td><td>0.286</td><td>0.399</td><td>NA</td></tr>
<tr><td></td><td>Oral</td><td>10[a]</td><td>2.51</td><td>1.35</td><td>0.236</td><td>23.8</td></tr>
<tr><td></td><td></td><td>10[b]</td><td>NR</td><td>1.23</td><td>0.358</td><td>21.9</td></tr>
<tr><td>Monkey</td><td>IV</td><td>1</td><td>0.456</td><td>0.171</td><td>0.224</td><td>NA</td></tr>
<tr><td></td><td>Oral</td><td>15</td><td>1.95</td><td>7.35</td><td>2.75</td><td>>100</td></tr>
<tr><td></td><td></td><td>30</td><td>2.78</td><td>9.95</td><td>3.09</td><td>>100</td></tr>
<tr><td></td><td></td><td>45</td><td>3.62</td><td>14.2</td><td>3.60</td><td>>100</td></tr>
</table>
a. 0.5% Tween 80, pH 2.6
b. 0.5% sodium carboxymethyl cellulose + 0.1% Tween 80</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Study DM06-046: Assessment of Reversible Protein Binding of ARRY-432380 in Human, Monkey, Rat, and Mouse Plasma as Determined by Equilibrium Dialysis</td><td>Plasma protein binding of tucatinib was not species- or concentration-dependent.
<table>
<tr><th></th><th colspan="4">% Bound</th></tr>
<tr><th>Species</th><th>0.1 µM tucatinib</th><th>1 µM tucatinib</th><th>10 µM tucatinib</th><th>50 µM tucatinib</th></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>CD-1 mouse</td><td>94.8</td><td>98.7</td><td>96.7</td><td>98.2</td></tr>
<tr><td>Sprague-Dawley rat</td><td>100</td><td>98.4</td><td>97.5</td><td>97.3</td></tr>
<tr><td>Cynomolgus monkey</td><td>93.5</td><td>96.5</td><td>95.2</td><td>95.9</td></tr>
<tr><td>Human</td><td>97.8</td><td>97.1</td><td>97.9</td><td>97.5</td></tr>
</table>
</td></tr>
<tr><td>Study 170229: Pharmacokinetics and Biodistribution Study of [^{14}C]-Tucatinib in Mice Bearing Intracerebral BT-474 Tumor Cells</td><td>Radioactivity crossed the blood-brain tumor barrier and distributed preferentially into the tumor located in the striatum of the right hemisphere. The ratio of radioactivity in tumor vs normal brain at 3-hours post last dosing ranged from 3.6 to 10.9.
<table>
<tr><th rowspan="2">Parameter</th><th colspan="3">DPM</th></tr>
<tr><th>Mouse 1</th><th>Mouse 5</th><th>Mouse 9</th></tr>
<tr><td>Left striatum (no tumor)</td><td>404</td><td>496</td><td>372</td></tr>
<tr><td>Right striatum (tumor)</td><td>1359</td><td>793</td><td>926</td></tr>
<tr><td>Total (left + right)</td><td>1763</td><td>1289</td><td>1298</td></tr>
<tr><td>Tumor/normal brain radioactivity ratio</td><td>10.85</td><td>3.6</td><td>7.63</td></tr>
</table>
</td></tr>
<tr><td>Study 8369173: Quantitative Whole-Body Autoradiography of Rats Following Oral Administration of [^{14}C]-Tucatinib</td><td>Following a 26.8 mg/kg (303 µCurie/kg) single oral dose in Long Evans rats, [^{14}C]-tucatinib-derived radioactivity distributed into most tissues by 1-hour post-dose. Elimination of radioactivity was virtually complete by 168-hours post-dose. Tissue distribution was extensive through 8-hours post-dose. There was an affinity for pigmented tissues.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td>Study 8393554: Absorption, Metabolism, and Excretion of ^{14}C-Tucatinib Following Oral Administration to Monkeys

Study ONT-380-008: A Phase 1, Open-label Study of the Absorption, Metabolism, and Excretion of [^{14}C]-Tucatinib Following a Single Oral Dose in Healthy Male and Female Subjects

Study 14663: Cross-Species Metabolites in Safety Testing (MIST) Exposure Assessment of Tucatinib in Rat, Monkey, and Human Plasma Samples</td><td>In monkeys, tucatinib was the most abundant plasma component (67.5% of total radioactivity exposure through 24 h) followed by ONT-993 (2.70%). Tucatinib accounted for 11.8% of dose in feces and for 0.189% of dose in urine. ONT-993 was the most abundant excreted component, accounting for an average 16.4% and 0.53% of dose in feces and urine, respectively.

In humans, tucatinib was the most abundant plasma component (75.6%) followed by ONT-993 (9.16%). Tucatinib accounted for 15.9% and 0.714% of dose in feces and urine, respectively. ONT-993 was the most abundant excreted component, accounting for an average 36.8% and 1.47% of dose in feces and urine, respectively.

All human plasma metabolites were also observed in rats and/or monkeys. Most identified metabolites were products of oxidative metabolism, such as hydroxylation, dehydrogenation, and dealkylation. Hydroxylation at the methyl group on the dimethyl dihydrooxazole of tucatinib appeared to be the predominant metabolic pathway. No human circulating metabolites exceeded 10% of total drug-related exposure.</td></tr>
<tr><td>Study DM09-027: Reaction Phenotyping for ARRY-432380 Metabolism in Human Liver Microsomes and Recombinant Human Cytochrome P450 Enzymes</td><td>CYP2C8 was the predominant contributor to tucatinib metabolism in vitro, followed by CYP3A4 and CYP3A5. ONT-993 was formed by CYP2C8.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Study DM08-075: Metabolism and Excretion of [^{14}C]-ARRY-432380 in Rats

Study 8393554: Absorption, Metabolism, and Excretion of ^{14}C-Tucatinib Following Oral Administration to Monkeys

Study ONT-380-008: A Phase 1, Open-label Study of the Absorption, Metabolism, and Excretion of [^{14}C]-Tucatinib Following a Single Oral Dose in Healthy Male and Female Subjects</td><td>Following a single oral dose of [^{14}C]-tucatinib to rats (30 mg/kg), cynomolgus monkeys (20 mg/kg), and humans (300 mg), the majority of the radioactivity was excreted into feces (and bile for BDC rats).
<table>
<tr><th>Matrix</th><th>BDC Rats</th><th>Intact Rats</th><th>Cynomolgus Monkeys</th><th>Humans</th></tr>
<tr><td>Bile</td><td>12.3</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Feces</td><td>80.2</td><td>90.9</td><td>76.6</td><td>85.8</td></tr>
<tr><td>Urine</td><td>1.1</td><td>0.5</td><td>1.78</td><td>4.09</td></tr>
<tr><td>Cage</td><td><0.01</td><td><0.01</td><td>4.43</td><td>-</td></tr>
<tr><td>Total</td><td>93.6</td><td>91.4</td><td>82.8</td><td>89.9</td></tr>
</table>
-No noteworthy findings.</td></tr>
<tr><td colspan="2">Drug Interactions</td></tr>
<tr><td>Study DM06-045: Evaluation of ARRY-432380 for Induction of CYP3A4 and CYP1A2 Activity in Primary Cultures of Human Hepatocytes

Study XT183058: Tucatinib: Cytochrome P450 Induction in Cultured Human Hepatocytes</td><td>At concentrations up to 30 µM of tucatinib, the extent of mRNA level increases were <20% of those with positive controls (rifampicin, 3-methylcholanthrene, and phenobarbital for CYP3A4, 1A2, and 2B6, respectively). Tucatinib did not induce CYP3A4 or CYP1A2 enzymatic activity</td></tr>
<tr><td>Study 8373547: Evaluation of Ki of Tucatinib for CYP2C8, CYP2C9, CYP3A4, and UGT1A1</td><td>Tucatinib was an inhibitor of CYP2C8, CYP2C9, CYP3A4/5, and UGT1A1, with Ki values of 0.170, 4.57, 0.805, and 1.81 µM, respectively.</td></tr>
<tr><td>Study XT195024: Tucatinib: Cytochrome P450 3A4/5 Inhibition in Human Liver Microsomes</td><td>Tucatinib inactivated CYP3A-mediated midazolam 1'-hydroxylation with a mean kinact value of 0.011 min-1 and a mean KI value of 0.54 µM.</td></tr>
<tr><td>Study OPT-2018-128: Assessment of Tucatinib as a Substrate of Human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP,

P-gp and BSEP Mediated Transport

Studies DM06-072-A2, OPT-2017-143, OPT-2018-167, OPT-2017-081, OPT-2018-241 2019-042: Assessment of Tucatinib as an Inhibitors of Various Human Transporters</td><td>Tucatinib was a substrate for BCRP and P-gp, but not for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, or BSEP.

IC_{50} values for transporter inhibition by tucatinib are presented below.
<table>
<tr><th>Transporter</th><th>Substrate</th><th>IC_{50}</th></tr>
<tr><td>P-gp[a]</td><td>Digoxin</td><td>3-10 µM</td></tr>
<tr><td>P-gp[b]</td><td>Digoxin</td><td>10-30 µM</td></tr>
<tr><td>OCT2</td><td>Metformin</td><td>14.7 µM</td></tr>
<tr><td>BCRP</td><td>prazosin</td><td>8.98 µM</td></tr>
<tr><td>BSEP</td><td>Taurocholate</td><td>8.48 µM</td></tr>
<tr><td>OATP1B1</td><td>Estradiol-17β-D-glucuronide</td><td>6.29 µM</td></tr>
<tr><td>OATP1B3</td><td>CCK-8</td><td>4.36 µM</td></tr>
<tr><td>MATE1</td><td>Metformin</td><td>0.340 µM</td></tr>
<tr><td>MATE2-K</td><td>Metformin</td><td>0.135 µM</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>OCT2</td><td>Creatinine</td><td>0.107 µM</td></tr>
<tr><td>MATE1</td><td>Creatinine</td><td>0.0855 µM</td></tr>
</table>
a. Caco-2 cells; b MDR1 LLC-PK1 cells.
</td></tr>
<tr><td colspan="2">TK data from general toxicology studies</td></tr>
<tr><td>Study 1140-028: 28-Day repeat-dose oral toxicity study of ARRY-432380 in rats followed by a 4-week recovery</td><td>
There were no significant differences in tucatinib exposure between male and female rats based on Day27 C_{max} and AUC_{12h} values (generally <2-fold). The mean C_{max} and AUC_{12h} values of tucatinib increased in a greater than dose proportionally manner on both days of analysis. Tucatinib mean AUC_{12h} values increased on average by 3.58-fold from Day 1 to Day 27 for doses of 10 and 30 mg/kg.
<table>
<tr><th>Dose (mg/kg/dose)</th><th>Day</th><th>C_{max} (µg/mL)</th><th>AUC_{12h} (µg·h/mL)</th></tr>
<tr><td>10</td><td>1</td><td>0.686</td><td>1.18</td></tr>
<tr><td></td><td>27</td><td>0.745</td><td>3.15</td></tr>
<tr><td>30</td><td>1</td><td>4.28</td><td>8.34</td></tr>
<tr><td></td><td>27</td><td>5.37</td><td>29.6</td></tr>
<tr><td>100/60a</td><td>1</td><td>16.5</td><td>90.7</td></tr>
<tr><td></td><td>27</td><td>9.27</td><td>72.5</td></tr>
</table>
a. In the 100 mg/kg dose group, doses were reduced to 60 mg/kg on Day 8 and thereafter.
</td></tr>
<tr><td>Study JAY00093: A 4-week toxicity study of ARRY-432380 administered twice-daily by nasal gavage to cynomolgus monkeys, with a 4-week recovery period</td><td>
There were no significant differences in tucatinib exposure between male and female cynomolgus monkeys based on individual plasma concentrations or AUC_{12h} values. The mean C_{max} and AUC_{12h} values of tucatinib increased in a linear and nearly dose proportional manner on both days of analysis. The mean C_{max} and AUC_{12h} values increased less than 2-fold from Day 1 to Day 28.
<table>
<tr><th>Dose (mg/kg/dose)</th><th>Day</th><th>C_{max} (µg/mL)</th><th>AUC_{12h} (µg·h/mL)</th></tr>
<tr><td>10</td><td>1</td><td>0.892</td><td>3.01</td></tr>
<tr><td></td><td>28</td><td>1.17</td><td>5.22</td></tr>
<tr><td>30</td><td>1</td><td>2.91</td><td>14</td></tr>
<tr><td></td><td>28</td><td>4.6</td><td>26.4</td></tr>
<tr><td>45</td><td>1</td><td>4.54</td><td>23.8</td></tr>
<tr><td></td><td>28</td><td>NS</td><td>NS</td></tr>
</table>
NS=no samples
</td></tr>
<tr><td colspan="2">TK data from reproductive toxicology studies</td></tr>
<tr><td>Study 20144956: An oral (gavage) dose range-finding embryo-fetal development study of tucatinib in rabbits</td><td>
Systemic exposure to tucatinib, as assessed by C_{max} and AUC_{12h}, increased in a greater than dose proportional manner between 60 and 150 mg/kg/day on GD 7 and GD 19. Systemic exposure to tucatinib increased on GD 19 compared to GD 7 and the accumulation ratios increased in a dose-dependent manner for AUC_{12h}.
<table>
<tr><th>Dose (mg/kg/day)</th><th>GD</th><th>C_{max} (µg/mL)</th><th>AUC_{12h} (µg·h/mL)</th></tr>
<tr><td>60</td><td>7</td><td>0.373</td><td>0.845</td></tr>
</table>
</td></tr>
</table>

Type of Study	Major Findings
	19 0.706 1.64 90 7 0.688 1.72 19 2.03 6.10 120 7 1.18 3.03 19 5.21 23.2 150 7 1.46 3.19 19 5.86 25.9
Study 20160869: An oral (gavage) dose range-finding embryo-fetal development study of tucatinib in rats	Systemic exposure to tucatinib, as assessed by C_{max} and AUC_{12h}, generally increased in a greater than dose proportional manner between 90 and 150 mg/kg/day but it was less marked on GD7. Dose (mg/kg/day) GD C_{max} (µg/mL) AUC_{12h} (µg·h/mL) 90 7 2.66 12.9 17 2.42 16.4 120 7 6.34 33.7 17 3.84 31.6 150 7 5.89 35.7 17 9.55 60.6

AUC=area under the plasma concentration-time curve; CYP=cytochrome P450; IV=intravenous

The Applicant's Position:

The nonclinical pharmacokinetic (PK) properties of tucatinib were characterized as moderate clearance in rats and high clearance in cynomolgus monkeys, exceeding hepatic blood flow. Following oral doses, tucatinib generally showed a greater than dose-proportional increase in exposure and accumulation. Plasma protein binding was 97.1% in human, independent of concentration, and consistent across species. Tucatinib was primarily metabolized by cytochrome P450 (CYP) 2C8 to form ONT-993, followed by CYP3A4. No circulating metabolites exceeded 10% of total drug-related exposure in human. The predominant circulating metabolite, ONT-993, has a potency corrected exposure of <10% of tucatinib. Therefore, tucatinib metabolites are not expected to meaningfully contribute to the safety or efficacy of tucatinib. Following a single oral administration of [^{14}C]-tucatinib, the majority of radioactivity was recovered in feces in rat, cynomolgus monkey, and human, primarily as metabolites, suggesting metabolism and hepatobiliary excretion as the major route of clearance. Renal elimination of tucatinib was minimal.

Regulatory Authorities Assessment:

The regulatory authorities generally agree with the applicant's summary of the study results. Additional noteworthy study results and comments on Applicant's summary are presented in table below.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2"><u>Absorption</u></td></tr>
<tr><td>TRN-5562: Pharmacokinetics of Tucatinib in Mice, Rats, and Monkeys following a Single Intravenous or Oral Dose (#TRN-5562)</td><td><u>Clearance:</u> Clearance following IV and oral administration are summarized below.
<table>
<tr><th>Species</th><th>Route</th><th>Dose (mg/kg)</th><th>CL or CL/F (mL/min/kg)</th></tr>
<tr><td rowspan="3">Rat</td><td rowspan="2">IV</td><td>0.5</td><td>29.6</td></tr>
<tr><td>1</td><td>46.9</td></tr>
<tr><td>Oral</td><td>10[a]</td><td>233</td></tr>
<tr><td rowspan="4">Monkey</td><td>IV</td><td>1</td><td>105</td></tr>
<tr><td rowspan="3">Oral</td><td>15[a]</td><td>42.6</td></tr>
<tr><td>30[a]</td><td>61.4</td></tr>
<tr><td>45[a]</td><td>58.1</td></tr>
</table>
a. Solution, 0.5% Tween 80, pH 2.6
CL or CL/F: Total body clearance without or with bioavailability adjusted
<u>Systemic exposure:</u>
It was noted that systemic exposure of tucatinib in animals was affected by the forms of active drug (free drug or salt), the drug formulation, and the animal gender used in the study.
<u>Bioavailability</u>
It appears that the Applicant calculated bioavailability in monkeys by comparing the AUCs from oral administration to the extrapolated AUCs using AUC of 1.0 mg/kg IV administration. The higher than 100% bioavailability is invalid and was likely due to non-linear pharmacokinetics.</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Study 170229: Pharmacokinetics and Biodistribution Study of [^{14}C] Tucatinib in Mice Bearing Intracerebral BT 474 Tumor Cells</td><td>Methods:
Route of administration: oral gavage
Treatment dose: 70 mg/kg
Treatment schedule: twice a day for 3 doses
Results: Autoradiography did not detect [^{14}C]-radioactivity in brain slices. As a result, the Applicant extracted and directly counted [^{14}C]-radioactivity using a scintillation counter. The study results shown in the table provided by the Applicant were [^{14}C]-radioactivity extracted from cutting pieces of brain slices. FDA agrees that radioactivity was higher in the right side of the brain implanted with tumor; however, there was insufficient data demonstrating that radioactivity crossed the</td></tr>
</table>

<table>
<tr><td></td><td>blood-brain tumor barrier and distributed preferentially into the tumor. It is possible that the high volume of circulating blood in tumors contributed to the observed high radioactivity in the brain with tumors.</td></tr>
<tr><td>Study 8369173: Quantitative Whole-Body Autoradiography of Rats Following Oral Administration of [^{14}C]-Tucatinib</td><td>• [^{14}C]-Tucatinib was not distributed to CNS tissues, indicating that it does not cross the blood: brain barrier.
• The tissues with the highest absorbed doses of radiation were uveal tract, eyes, pigmented skin, liver, testes, epididymis (male), and thymus (female).
• Radioactivity was only present in the uveal tract and eyes at 672 hours postdose (last time point).</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td colspan="2">Study ONT-380-008 is a pharmacokinetic/ADME study in healthy human subjects and not reviewed in the nonclinical section of the multi-disciplinary review. See the clinical pharmacology section 6 for information on human metabolism.</td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td colspan="2">The excretion table provided by the Applicant shows the percentage of radioactive dose in samples from rats, monkeys, and humans.</td></tr>
<tr><td colspan="2">Drug Interactions</td></tr>
<tr><td>Study XT195024: Tucatinib: Cytochrome P450 3A4/5 Inhibition in Human Liver Microsomes</td><td>IC_{50} on CYP3A-mediated midazolam 1’ hydroxylation: 3.3 µM.</td></tr>
<tr><td>TK data from general toxicology studies
Rat
A 28-Day toxicity study in rats (Study 1140-028)</td><td>• Both AUC and C_{max} were higher in female rats than in males.
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day</th><th>Sex</th><th>C_{max} (ng/mL)</th><th>$AUC1_{12h}$ (ng·h/mL)</th><th>AUC_{24h} (ng·h/mL)</th></tr>
<tr><td rowspan="4">20</td><td rowspan="2">1</td><td>M</td><td>394</td><td>846</td><td>1720</td></tr>
<tr><td>F</td><td>1190</td><td>1680</td><td>6540</td></tr>
<tr><td rowspan="2">27</td><td>M</td><td>508</td><td>2320</td><td>5810</td></tr>
<tr><td>F</td><td>1320</td><td>4350</td><td>7590</td></tr>
<tr><td rowspan="4">60</td><td rowspan="2">1</td><td>M</td><td>3340</td><td>3760</td><td>15100</td></tr>
<tr><td>F</td><td>5490</td><td>1890</td><td>55400</td></tr>
<tr><td rowspan="2">27</td><td>M</td><td>4780</td><td>27000</td><td>61500</td></tr>
<tr><td>F</td><td>7270</td><td>33600</td><td>78300</td></tr>
<tr><td rowspan="3">200/120[a]</td><td rowspan="2">1</td><td>M</td><td>14400</td><td>74900</td><td>174000</td></tr>
<tr><td>F</td><td>19900</td><td>117000</td><td>258000</td></tr>
<tr><td>27</td><td>M</td><td>9370</td><td>62800</td><td>NA</td></tr>
</table></td></tr>
</table>

		F	9410	92400	NA

[a]: In the 200 mg/kg/day dose group, doses were reduced to 120 mg/kg/day on Day 8 and thereafter.
NA: Not applicable. Samples were not available to determine the AUC value beyond the 12-hour time point.

A 13-week repeated dose study in rats (Study (8369684)
6, 20, 60 mg/kg/day twice daily

- C_{max} and AUC > dose proportional ↑
- Exposure in females > exposure in males except exposure in females = exposure in males at 60 mg/kg in Week 13
- $T_{1/2}$: not defined
- T_{max}: 1-2 hours
- Accumulation: 1.5-2.7, systemic exposure in week 13 compared to Day 1

Dose (mg/kg/day)	Time Point	Sex	C_{max} (ng/mL)	AUC_{12h} (ng·h/mL)	AUC_{24h} (ng·h/mL)
6	Day 1	M	23	61	173
		F	61	228	684
	Week 13	M	64	194	425
		F	173	536	1060
20	Day 1	M	227	1130	3740
		F	293	1650	5210
	Week 13	M	751	3290	6570
		F	1180	4320	11200
60	Day 1	M	2120	11100	35700
		F	4120	20500	52000
	Week 13	M	8250	44700	97700
		F	8010	40800	81200

Monkey
A 13-week repeated dose study in monkeys (study 8369685)
5, 20, 40 mg/kg twice daily

- Cmax and AUC > dose proportional ↑
- Exposures in males > exposures in females at ≤ 20 mg/kg/day; exposures in females > exposures in males at 40 mg/kg/day on Day 91
- No accumulation
- $T_{1/2}$: not defined
- T_{max}: 0.75-4 hours

Dose (mg/kg/day)	Day	Sex	C_{max} (ng/mL)	AUC_{12h} (ng·h/mL)	AUC_{24h} (ng·h/mL)
5	1	M	96	179	287

				F	45	111	199	
			91	M	99	264	522	
				F	36	128	292	
		20	1	M	851	2650	6100	
				F	597	1540	2970	
			91	M	247	1040	3730	
				F	289	953	3100	
		40	1	M	1260	6440	22700	
				F	1750	6180	19900	
			91	M	1760	9220	22600	
				F	3780	20400	41700	

5.5. Toxicology

5.5.1. General Toxicology

Data:

13-Week Good Laboratory Practices (GLP) Twice Daily Oral Gavage Toxicity Study of Tucatinib in Sprague Dawley Rats Followed by a 28-Day Recovery Phase/8369684

Key Study Findings:

- No tucatinib-related mortality, changes in clinical or ophthalmic observations, or coagulation, or urinalysis parameters.
- Primary target organs of toxicity were gastrointestinal tract, liver, and reproductive organs.
- Non-adverse changes were observed in hematology (lower red cell mass, higher red cell distribution width, higher reticulocyte count, higher platelet, neutrophil, and monocyte counts) and clinical chemistry (higher aspartate aminotransferase [AST] and alanine aminotransferase [ALT] activity, and higher alkaline phosphatase [ALP] activity).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 6, 20, or 60 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% sodium carboxymethyl cellulose (CMC, sodium salt, medium viscosity) and 0.1% Poloxamer 188 in deionized water, pH 7 ± 0.1.
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	20
Age:	8 to 9 weeks
Satellite groups/ unique design:	3 vehicle and 9 treatment (TK satellite animals)

Methods	
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	No tucatinib-related mortality observed.
Clinical Signs	None.
Body Weights	Mean body weights were lower for males at 60 mg/kg/day, starting Day 4 of the dosing phase and persisting through the end of the dosing phase (12% lower than controls on Day 92 of the dosing phase). Body weight change during the recovery phase was similar to controls.
Hematology	Findings at ≥20 mg/kg/day included lower red cell mass (red blood cell count, hemoglobin concentration, and hematocrit), higher red cell distribution width at 60 mg/kg/day, and higher reticulocyte count in males at 60 mg/kg/day, females at ≥20 mg/kg/day. Additional minimal to mild hematology findings, suggestive of an inflammatory response, included higher platelet, neutrophil, and monocyte counts in females at 60 mg/kg/day. Hematology findings lacked microscopic correlates. Findings generally exhibited reversibility at the end of recovery phase.
Clinical Chemistry	Findings at ≥6 mg/kg/day included higher ASP activity (<2.5-fold control) in females at ≥20 mg/kg/day, higher ALT activity (<2.5 fold control) in males at 60 mg/kg/day and females at ≥6 mg/kg/day, and higher ALP activity (<2 fold control) in males at 60 mg/kg/day and females at ≥6 mg/kg/day, were suggestive of minor hepatocellular/hepatobiliary alteration, which may be related to minimal centrilobular hepatocyte hypertrophy and higher liver weights. Additional minimal to mild findings suggestive of pre-renal dehydration associated with decreased food consumption and/or body weight and possibly related to lower urine volume included higher creatinine, chloride, and phosphorus concentrations at 60 mg/kg/day.
Urinalysis	No changes.
Gross Pathology	None.

Organ Weights

Sex	**Male**				**Female**			
mg/kg/day	0	6	20	60	0	6	20	60
Liver								
Absolute Organ Weight (%)	-	-	-	-	7.5465 g	-2.8	5.8	6.9
Organ to Body Weight (%)	-	-	-	-	2.5624	2.3998	2.6200	2.9119*
Organ to Brain Weight (%)	-	-	-	-	364.0180	356.5683	388.1867	395.1218
Uterus/Cervix								
Absolute Organ Weight (%)	NA	NA	NA	NA	0.7829 g	5.9	-2.5	-28.3*
Organ to Body Weight (%)	NA	NA	NA	NA	0.2654	0.2712	0.2516	0.2021*
Organ to Brain Weight (%)	NA	NA	NA	NA	37.7942	40.4570	37.0333	27.5368*
Prostate								
Absolute Organ Weight (%)	1.4711 g	0.1	-3.2	-14.6	NA	NA	NA	NA

Parameters	Major findings								
	Organ to Body Weight (%)	0.2488	0.2594	0.2539	0.2409	NA	NA	NA	NA
	Organ to Brain Weight (%)	64.4283	65.7580	62.0158	55.1113*	NA	NA	NA	NA
Histopathology	Organ weight changes at terminal euthanasia: liver of females (≥20 mg/kg/day), uterus/cervix (60 mg/kg/day) and prostate gland of males (60 mg/kg/day). Changes reversed in recovery animals. Microscopic findings at terminal euthanasia: liver (centrilobular hepatocyte hypertrophy), ovaries (decreased corpora lutea, corpus luteum cyst and/or increased interstitial cells), uterus (atrophy), and vagina (mucification) of females (≥6 mg/kg/day) and in the mammary gland (lobular atrophy) of males (≥6 mg/kg/day). Changes fully recovered during the recovery phase except for partial recovery of the ovaries (decreased corpora lutea and increased interstitial cells) of females administered ≥20 mg/kg/day.								
Other evaluations	NA								

* P≤0.05

13-Week GLP Twice Daily Oral Gavage Toxicity Study of Tucatinib in Cynomolgus Monkeys Followed by a 28-Day Recovery Period/8369685:

Key Study Findings:

- No tucatinib-related findings for mortality, body weight, ophthalmology, physical examination observations, blood pressure, ECG, hematology, coagulation, urinalysis, microscopic, or macroscopic findings.
- Non-adverse increases in bilirubin and total cholesterol occurred in males and females during the dosing phase. Females had minimally increased creatinine concentrations at ≥20 mg/kg/day. Changes were not present at recovery sacrifice, indicating reversibility.
- Anatomical pathology findings were limited to increased liver weight in terminal sacrifice animals at 40 mg/kg/day, correlating with minimally increased total bilirubin concentration. Increased liver weights were non-adverse and reversed during the recovery period.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 5, 20, or 40 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) Tween® 80 (Polysorbate 80) in deionized water, pH 2.6 ± 0.1
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	6
Age:	27 to 42 months
Satellite groups/ unique design:	NA
Deviation from study protocol affecting interpretation of results:	No

Parameters	Major findings
Mortality	No tucatinib-related mortality occurred.
Clinical Signs	Fecal abnormalities (≥5 mg/kg/day). Considered adverse at 40 mg/kg/day as some animals experienced transient body weight loss, lean body condition, and/or blood in the stool. Veterinary treatment with azithromycin or enrofloxacin was required primarily during the first half of the study for 3 males and 3 females. Fecal abnormalities were not noted during the recovery phase.
Body Weights	Transient body weight loss (40 mg/kg/day).
Ophthalmoscopy	No tucatinib-related findings.
ECG	Tucatinib-related elevated heart rates (non-adverse) as detected by vital signs occurred on Days 2 and 92 of the dosing phase in males at ≥5 mg/kg/day; however, elevated heart rates were not noted during ECG assessment.
Hematology	No tucatinib-related findings.
Clinical Chemistry	Reversible, non-adverse increases in bilirubin and total cholesterol in dosing phase males and females, and minimally increased creatinine concentration in females at ≥20 mg/kg/day.
Urinalysis	No tucatinib-related findings.
Gross Pathology	No tucatinib-related findings.
Organ Weights	Reversible increased liver weights for terminal sacrifice animals administered 40 mg/kg/day.
Histopathology	No tucatinib-related findings.
Other evaluations	NA

28-day oral gavage studies of tucatinib in rats and monkeys followed by 28-day recovery periods:

28-day GLP studies were conducted prior to the 90-day studies outlined above.

- Sprague-Dawley rats were administered tucatinib at 20, 60, or 200/120 mg/kg/day. The 200 mg/kg/day dose was not tolerated (nonspecific and gastrointestinal toxicity) and was reduced to 120 mg/kg/day on Day 8. Observations at tolerated doses included minor changes in laboratory parameters and female reproductive organs.
- Cynomolgus monkeys were administered tucatinib at 20, 60, or 90 mg/kg/day. The 90 mg/kg/day was not tolerated (nonspecific clinical signs of toxicity); one animal at 60 mg/kg/day was also terminated early due to these clinical signs. Observations at tolerated doses included minor changes in laboratory parameters and increased liver and kidney weight ratios.

The Applicant's Position:

Tucatinib is a reversible, HER2-targeted, small molecule, TKI intended for the treatment of advanced cancers. Therefore, the toxicology program was designed in accordance with the International Council for Harmonisation (ICH) guidance "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH S9 and ICH S9 Q&A). All principal toxicology studies were conducted in accordance with GLP and currently accepted guidelines. The toxicity of tucatinib was adequately characterized, generally consistent with the primary pharmacology expected from inhibition of HER2 signaling, and supports its use in the target patient population.

High systemic exposures to tucatinib in rats and cynomolgus monkeys (at least 4-fold higher than human exposure at the maximum recommended clinical dose) were associated with mortality due to nonspecific and/or gastrointestinal toxicity. At tolerated doses, findings included gastrointestinal toxicity and changes in liver and reproductive organ parameters.

- Gastrointestinal toxicity was manifested by emesis and/or watery feces, had no associated histologic changes at tolerated doses, was reversible, and generally associated with lower body weights and/or body weight gain.
- At tolerated doses in rats and cynomolgus monkeys, reversible liver perturbations included generally minimal increases in serum markers of liver injury (including AST, ALT, and bilirubin), liver weight increases, and centrilobular hepatocyte hypertrophy. However, there were no associated hepatic histologic changes indicating hepatocellular injury in any animal (e.g., no hepatic degeneration, inflammation, fibrosis, or necrosis).
- At tolerated doses in rats only, reproductive organ findings included uterine atrophy, vaginal mucification, changes in corpora lutea, and decreased uterus/cervix weights in females, and lobular atrophy of the mammary gland and decreased prostate weights in males.

Regulatory Authorities Assessment:

13-Week rat study

In general, the regulatory authorities agree with the Applicant's assessment except that:

1) **No apparent treatment-related GI toxicity was observed at the doses tested in the study.**
2) **The changes in clinical chemistry including increased activity in AST and ALT are considered adverse effects.**

Additional noteworthy findings and study methods are listed in the tables below.

Methods	
Dose and frequency of dosing:	0, 6, 20, or 60 mg/kg/day, administered twice daily
Number/Sex/Group:	20, including 5/sex/group for recovery

Observations and Results: changes from control

Parameters	**Major findings**
Food Consumption	↓mean food consumption over each 1-week interval in males at 60 mg/kg/day (↓up to 20% comparing to the control) and reached statistical significance over 8 1-week intervals including the last 4 intervals. This correlated with the observed significantly lower (P< 0.05) mean body weights and lower mean body weight gain in this group.
Hematology	Main: Changes compared to the control -↓red cell mass (HD, erythrocytes, hemoglobin; ~↓4% on Day 54 and/or Day 93, male and female) -↑RETIC (on Day 54 and 93, HD↑≈19% in males, MD & HD 20-27% in females) -↑neutrophil (HD, ↑10% in males on Day 93, ↑43-71% in females on Day 54 and 93) -↑platelets (HD, ↑8% in males, 16-21% in females, on Day 54 and 93) Recovery day 28: Unremarkable

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Clinical Chemistry</td><td>Main:
Changes compared to the control
-↑AST (≥20 mg/kg/day in females, ↑100% on day 93)
-↑ALT (≥6mg/kg/day in females, dose dependent, ↑up to 142% on day 54 and 93)
Recovery day 28: Unremarkable</td></tr>
<tr><td>Organ Weights</td><td>Main: Change compared to control values (%) in rats
<table>
<tr><td></td><td colspan="2"></td><td colspan="2">Absolute change</td><td colspan="2"></td><td colspan="2">Relative change (to BW*)</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Dose (mg/kg/day)</td><td colspan="2">6</td><td colspan="2">20</td><td colspan="2">60</td><td colspan="2">6</td><td colspan="2">20</td><td colspan="2">60</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>Liver</td><td></td><td></td><td></td><td>6</td><td></td><td>7</td><td></td><td></td><td></td><td></td><td></td><td>14*</td></tr>
<tr><td>Uterus/Cervix</td><td>-</td><td></td><td>-</td><td></td><td>-</td><td>-28*</td><td>-</td><td></td><td>-</td><td></td><td>-</td><td>-24*</td></tr>
<tr><td>Prostate</td><td></td><td>-</td><td></td><td>-</td><td>-15*</td><td></td><td></td><td>-</td><td></td><td>-</td><td>-3</td><td>-</td></tr>
</table>
Blank: unremarkable; “- “: not applicable; *p<0.05

Recovery: unremarkable</td></tr>
<tr><td>Histopathology</td><td>Main: liver, ≥ 20 mg/kg/day, females (centrilobular hepatocyte hypertrophy, minimal)
ovaries, ≥ 20 mg/kg/day (decreased corpora lutea, corpus luteum cyst and/or increased interstitial cells, minimal to slight),
uterus, ≥ 6 mg/kg (atrophy, minimal to slight)
vagina, ≥ 20 mg/kg (mucification, slight)
mammary gland, ≥6 mg/kg/day, males (lobular atrophy, minimal to marked)
The observed changes were dose-dependent.
Recovery: partial recovery of changes in the ovaries, unremarkable for others</td></tr>
<tr><td>TK</td><td>AUC associated with observed toxicities and exposure multiples comparing to human:
Reproductive toxicity: Female: AUC_{12h}=536 ng.h/mL (6 mg/kg/day, females)
*Exposure multiples: 0.1
Liver toxicity: AUC_{12h}=4320 ng.h/mL (20 mg/kg/day, females)
*Exposure multiples: 1
*Compared to human exposure at the recommended dose of 300 mg, twice daily (AUC_{last} of 4724 ng.h/mL)</td></tr>
</table>

13-Week Monkey study

Methods	
Dose and frequency of dosing:	0, 5, 20, or 40 mg/kg/day, Twice daily
Number/Sex/Group:	6, including 2/sex/group for recovery

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Clinical Chemistry</td><td>
<table>
<tr><td></td><td colspan="6">Percentage deviation from control</td></tr>
<tr><td>Sex</td><td colspan="6">Male</td><td colspan="6">Female</td></tr>
<tr><td>Study Day</td><td colspan="3">55</td><td colspan="3">93</td><td colspan="3">55</td><td colspan="3">93</td></tr>
<tr><td>Dose (mg/kg/day)</td><td>5</td><td>20</td><td>40</td><td>5</td><td>20</td><td>40</td><td>5</td><td>20</td><td>40</td><td>5</td><td>20</td><td>40</td></tr>
<tr><td>CHOL</td><td></td><td></td><td>40*</td><td></td><td></td><td>9</td><td></td><td></td><td>21</td><td>19*</td><td></td><td>36*</td></tr>
<tr><td>TBIL</td><td></td><td></td><td></td><td></td><td></td><td>67</td><td></td><td></td><td></td><td></td><td>67*</td><td>100*</td></tr>
</table>
Blank-unremarkable; *p<0.05</td></tr>
</table>

<table>
<tr><td>Organ Weights</td><td>Main: Change compared to control values (%) in monkeys
<table>
<tr><td></td><td colspan="2"></td><td colspan="2">Absolute change</td><td colspan="2"></td><td colspan="2">Relative change (to BW*)</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Dose (mg/kg/day)</td><td colspan="2">5</td><td colspan="2">20</td><td colspan="2">40</td><td colspan="2">5</td><td colspan="2">20</td><td colspan="2">40</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>Liver</td><td>5</td><td></td><td></td><td></td><td>18*</td><td>20</td><td>6</td><td></td><td></td><td></td><td>18*</td><td>12</td></tr>
</table>
Blank: unremarkable; *p<0.05

Recovery: unremarkable</td></tr>
<tr><td>TK</td><td>AUC associated with observed toxicities and the calculation on exposure multiples comparing to human
GI toxicity: AUC_{12h}=14810 ng.h/mL (40 mg/kg/day, combined sexes).
*Exposure multiples: 3
Liver toxicity: AUC_{12h}=14810 ng.h/mL (40 mg/kg/day, combined sexes)
*Exposure multiples: 3
*Compared to human exposure at the recommended dose of 300 mg twice daily (AUC_{last} of 4724 ng.h/mL)</td></tr>
</table>

The 28-day rat and monkey toxicology studies were reviewed by FDA under IND 78304, the original IND submitted with tucatinib. Key study findings are listed below.

28-day rat study: Hematology and clinical chemistry effects were mainly observed in MD (60 mg/kg/day) and HD (200/120 mg/kg/day), and most indicative of inflammation and hepatotoxicity. The primary target organs are the hematolymphoid system (lymphoid depletion, MD, HD), the gastrointestinal tract (erosion and ulcerations, HD), skeletal muscle (males, all doses, myofiber degeneration/regeneration, hemorrhage), and the reproductive systems of both males (HD, testes degeneration/atrophy, oligospermia) and females (all doses, vaginal atrophy). The observed findings generally resolved at the end of a 4-week recovery period.

AUC associated with observed toxicities and the calculation on exposure multiples comparing to human:

GI toxicity (male and female):
AUC_{12h}=77600 ng.h/mL (HD, on Day 27)
[a]Exposure multiples: 16

Reproductive toxicity:
Males: AUC_{12h}=62800 ng.h/mL (HD, on Day 27)
[a]Exposure multiples: 13
Female: AUC_{12h}=4350 ng.h/mL (LD, on Day 27)
[a]Exposure multiples: 1

[a]Compared to human exposure at the recommended dose of 300 mg twice daily (AUC_{last} of 4724 ng.h/mL)

28-day monkey study: All HD (90 mg/kg/day) monkeys and 1/10 MD (60 mg/kg/day) monkeys were euthanized moribund before the end of the dosing phase of the study. A treatment-related increase in liver and kidney weights were seen in both males and females. The ratio of liver and kidney weights relative to body weights increased up to 24% and 35%, respectively, compared to the control groups. The changes in organ weights trended toward recovery after a 28-day recovery period. There were microscopic findings in the liver and kidneys including swelling and cytoplasmic rarefaction of hepatocytes and degeneration of tubular epithelium (kidney) in the euthanized early animals at HD.

General toxicology; additional studies

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
The regulatory authorities agree that additional general toxicology studies with tucatinib were not needed for the proposed indication.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Data:
Bacterial Reverse Mutation Assay/AB39LT.503. (b) (4)

Key Study Findings:
- Negative

Conducting Laboratory and Location: (b) (4)
GLP compliance: Yes
Test system: Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537 and Escherichia coli tester strain WP2 *uvr*A in the presence and absence of Aroclor-inducted rat liver S9 enzymes.

The Applicant's Position:
Under the conditions tested, tucatinib was not mutagenic.

Regulatory Authorities Assessment:
The regulatory authorities agree with the study results described above. The assays were conducted using concentrations up to 5000 µg/plate, and no appreciable toxicity was observed.

In Vitro Assays in Mammalian Cells

Data:

In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK+/-Mouse Lymphoma Assay)/AB39LT.704. (b) (4)

Key Study Findings:

- Negative

Conducting Laboratory and Location: (b) (4)
GLP compliance: Yes
Test system: Mouse lymphoma L5178Y TK+/- cell line; up to 4810 µg/mL; +/-S9

The Applicant's Position:
Under the conditions tested, tucatinib was negative for the induction of chromosomal aberrations.

Regulatory Authorities Assessment:
The regulatory authorities agree with the study results described above.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Data:

Mammalian Erythrocyte Micronucleus Test/AB39LT.123. (b) (4)

Key Study Findings:

- Negative

Conducting Laboratory and Location: (b) (4)
GLP compliance: Yes
Test system: ICR Mice; testing to 2000 mg/kg

The Applicant's Position:
Under the conditions tested, tucatinib was not clastogenic.

Regulatory Authorities Assessment:
The regulatory authorities agree with the study results described above. No data on the systemic exposures were provided.

Other Genetic Toxicity Studies

Data:
Two complementary (Q)SAR methodologies, one expert rule-based (DEREK Nexus, Lhasa Ltd.) and one statistical-based (SARAH Nexus, Lhasa Ltd.) determined tucatinib was not mutagenic.

The Applicant's Position:
The battery of in silico evaluations conducted for genetic toxicity were negative.

Regulatory Authorities Assessment:
The regulatory authorities agree with the Application's conclusions.

5.5.3. Carcinogenicity

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
The regulatory authorities agree that no carcinogenicity studies are warranted for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
The regulatory authorities agree that no standalone fertility and early embryonic development studies are warranted for the proposed indication. Effects of tucatinib on male and female reproductive organs were assessed in general toxicity studies in rats and monkeys. Tucatinib treatment induced reproductive toxicities including vaginal atrophy and changes in corpora lutea in female rats at ≥ 20 mg/kg/day in the 28-day study and at ≥ 6 mg/kg/day in 13-week study. The AUC_{12h} at 6 mg/kg/day in female rats was 536 ng.h/mL, approximately 11% of the AUC at the clinical recommended dose of 300 mg twice daily. In the 28-day rat study, treatment-related adverse histopathological changes were observed in the reproductive

systems of male rats (testes degeneration/atrophy, oligospermia) at 200/120 mg/kg/day. The AUC_{12h} of 120 mg/kg/day in male rats was 62800 ng.h/mL, approximately 13 times the AUC at the clinical recommended dose of 300 mg twice daily. Based on the nonclinical findings, tucatinib treatment may impair male and female fertility and other reproductive functions.

Embryo-Fetal Development

Data:

An Oral (Gavage) Dose Range-Finding Embryo-Fetal Development Study of Tucatinib in Rabbits/20144956

- External and visceral fetal abnormalities at maternal doses of ≥90 mg/kg/day and skeletal abnormalities at 90 and 120 mg/kg/day, including domed head malformations, severe brain dilation, incompletely ossified frontals and parietals, and a hole in the parietal region of the skull. Lack of fetal skeletal findings at 150 mg/kg/day was likely due to the increase in embryo/fetal mortality and reduced implantations in this group and/or small group size on this dose range-finding study.
- Maternal decreases in food consumption and reductions in maternal body weight gains, or losses in mean maternal body weights at ≥120 mg/kg/day, and increased late resorptions, total number of resorptions, percent post-implantation loss, and reduction of live fetuses and percent male fetuses at ≥90 mg/kg/day.
- The AUC_{12h} corresponding to the rabbit maternal dose (90 mg/kg/day) resulting in fetal toxicity is 1.8-fold higher than the clinical dose of 300 mg/dose administered BID in humans.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 60, 90, 120, and 150 mg/kg/day divided twice daily approximately 12 hours apart
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% sodium carboxymethyl cellulose (CMC, sodium salt, medium viscosity) and 0.1% Poloxamer 188 in deionized water, pH 7 ± 0.1
Species/Strain:	New Zealand White (b) (4) female rabbits
Number/Sex/Group:	6/group
Satellite groups:	None
Study design:	Dosing: Gestation days 7 to 19; Caesarian section: Gestation day 29.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	None related to test article
Clinical Signs	None

Body Weights	Decreased body weight gain during dosing at 120 and 150 mg/kg/day

Necropsy Findings
Cesarean Section Data

Daily Dose (mg/kg/day)		0 (Control)	60	90	120	150
Litters:	No. Litters Evaluated	5	6	5	5	6
	Mean No. Live Fetuses	10.0	11.2	7.2	8.2	9.7
	Mean No. Resorptions	0.4	0.5	1.8	2.6	1.0
	No. of Litters with Dead Fetuses	0	0	1	1	0
	Mean % Post-implantation Loss	3.08	4.29	19.77	20.96	11.28
	Mean Fetal Body Weight (g)	39.52	39.07	40.68	40.84	38.32
	Fetal Sex Ratios (% males)	51.62	49.39	34.81	35.50	37.10
	Total Affected Fetuses (Litters)	4 (3)	6 (4)	5 (2)	7 (2)	1 (1)
- No noteworthy findings.						

Necropsy Findings
Fetal/Offspring [malformations, variations, etc.]

Daily Dose (mg/kg/day)	0 (Control)	60	90	120	150
Fetal Anomalies:					
Gross External					
Head- Domed- Malformation					
No. Fetuses (%)	0 (0.00)	0 (0.00)	3 (15.00)	5 (20.00)	1 (2.08)
No. Litters (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	1 (16.7)
Total Affected Fetuses (Litters)	0 (0)	0 (0)	4 (2)	5 (1)	1 (1)
Visceral Anomalies					
Brain – Lateral Ventricle, Dilated (Severe)- Malformation					
No. Fetuses (%)	0 (0.00)	0 (0.00)	3 (15.00)	5 (20.00)	1 (2.08)
No. Litters (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	1 (16.7)
Brain–Third ventricle, Dilated (Severe)- Malformation					
No. Fetuses (%)	0 (0.00)	0 (0.00)	3 (15.00)	5 (20.00)	0 (0.00)
No. Litters (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)
Total Affected Fetuses (Litters)	0 (0)	0 (0)	5 (2)	5 (1)	2 (2)
Skeletal Anomalies					
Frontal – Incomplete Ossification- Variation					
No. Fetuses (%)	0 (0.00)	0 (0.00)	3 (15.00)	5 (20.00)	0 (0.00)
No. Litters (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)
Parietal – Incomplete Ossification- Variation					
No. Fetuses (%)	0 (0.00)	0 (0.00)	1 (5.00)	5 (20.00)	0 (0.00)
No. Litters (%)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)
Parietal – Hole- Variation					
No. Fetuses (%)	0 (0.00)	0 (0.00)	2 (10.00)	0 (0.00)	0 (0.00)
No. Litters (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Total Affected Fetuses (Litters)	4 (3)	6 (4)	5 (2)	7 (2)	1 (1)
- No noteworthy findings					

An Oral (Gavage) Dose Range-Finding Embryo-Fetal Development Study of Tucatinib in Rats/ 20160869

- Maternal effects at ≥90 mg/kg/day: reduction in mean maternal body weights, body weight gains, food consumption; decreased mean number of implantations, total number of fetuses, number of live fetuses; increase in total resorptions, mean post-implantation loss.
- Effects on embryo-fetal development and growth at ≥120 mg/kg/day: decreased mean fetal body weight and fetal ossification sites (decreases in the mean number of hindlimb tarsals and phalanges, forelimb phalanges and metatarsals); increased skeletal variations.
- AUC_{12h} corresponding to the rat maternal dose (120 mg/kg/day) resulting in fetal toxicity is 9.1-fold higher than with the clinical dose (300 mg/dose BID) in humans.

Conducting Laboratory and Location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 90, 120, and 150 mg/kg/day divided twice daily approximately 12 hours apart
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% sodium carboxymethyl cellulose (CMC, sodium salt, medium viscosity) and 0.1% Poloxamer 188 in deionized water, pH 7 ± 0.1
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	6/group
Satellite groups:	Toxicokinetics—3/group (control) and 6/group for tucatinib
Study design:	Dosing: Gestation days 7 to 17; Caesarian section: Gestation day 18.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	None related to test article
Clinical Signs	Fur loss/thin fur at ≥120 mg/kg/day
Body Weights	Mean maternal body weights were 93%, 89%, and 85% of controls on GD 21, and mean body weight gains were 85%, 73%, and 66% of controls for the overall study period (GD 7 to 21) at 90, 120, and 150 mg/kg/day, respectively.

Necropsy Findings
Cesarean Section Data

Daily Dose (mg/kg/day)		**0 (Control)**	**90**	**120**	**150**
Litters:	No. Litters Evaluated	5	6	6	6
	Mean No. Live Fetuses	13.6	11.2	11.7	10.7
	Mean No. Resorptions	0.0	0.8	0.2	0.7
	No. of Litters with Dead Fetuses	0	0	0	0
	Mean % Post-implantation Loss	0.00	7.47	1.28	6.13
	Mean Fetal Body Weight (g)a	5.91 g	-2.83	-11.02	-19.33
	Fetal Sex Ratios (% males)	45.19	59.70	52.74	51.37

Necropsy findings

Fetal/ Offspring [malformations, variations, etc]				
Daily Dose (mg/kg/day)	**0 (Control)**	**90**	**120**	**150**
Fetal Anomalies:				
Gross External	-	-	-	-
Visceral Anomalies	-	-	-	-
Skeletal Anomalies				
Incomplete ossified parietal (Variation)				
No. Fetuses (%)	0(0.00)	1(2.38)	0(0.00)	0(0.00)
No. Litters (%)	0(0.00)	1(16.7)	0(0.00)	0(0.00)
Ossified sternebra bipartite (Variation)				
No. Fetuses (%)	0(0.00)	1(2.78)	0(0.00)	0(0.00)
No. Litters (%)	0(0.00)	1(16.7)	0(0.00)	0(0.00)
Fused cervical arch (Malformation)				
No. Fetuses (%)	0(0.00)	1(2.78)	0(0.00)	0(0.00)
No. Litters (%)	0(0.00)	1(16.7)	0(0.00)	0(0.00)
Misshapen cervical arch (Variation)				
No. Fetuses (%)	0(0.00)	1(2.78)	0(0.00)	0(0.00)
No. Litters (%)	0(0.00)	1(16.7)	0(0.00)	0(0.00)
Unossified thoracic centrum (Variation)				
No. Fetuses (%)	0(0.00)	1(2.78)	0(0.00)	0(0.00)
No. Litters (%)	0(0.00)	1(16.7)	0(0.00)	0(0.00)
Nodulated rib (Variation)				
No. Fetuses (%)	0(0.00)	0(0.00)	1(2.78)	0(0.00)
No. Litters (%)	0(0.00)	0(0.00)	1(16.7)	0(0.00)
Incomplete ossified squamosal (Variation)				
No. Fetuses (%)	0(0.00)	0(0.00)	0(0.00)	1(3.33)
No. Litters (%)	0(0.00)	0(0.00)	0(0.00)	1 (16.7)
Incomplete ossified zygomatic				
No. Fetuses (%)	0(0.00)	0(0.00)	0(0.00)	1(3.33)
No. Litters (%)	0(0.00)	0(0.00)	0(0.00)	1 (16.7)
Full cervical supernumerary rib				
No. Fetuses (%)	0(0.00)	0(0.00)	0(0.00)	2(6.67)
No. Litters (%)	0(0.00)	0(0.00)	0(0.00)	1(16.7)
Short cervical supernumerary rib				
No. Fetuses (%)	0(0.00)	0(0.00)	1(3.33)	3(10.00)
No. Litters (%)	0(0.00)	0(0.00)	1(16.7)	2(33.3)
Ossified thoracic centrum bipartite				
No. Fetuses (%)	0(0.00)	0(0.00)	1(2.78)	2(6.11)
No. Litters (%)	0(0.00)	0(0.00)	1(16.7)	2(33.3)
Incomplete ossified sternebra				
No. Fetuses (%)	0(0.00)	1(2.78)	0(0.00)	4 (13.33)
No. Litters (%)	0(0.00)	1(16.7)	0(0.00)	1(16.7)
Short rib				
No. Fetuses (%)	0(0.00)	1(2.78)	0(0.00)	1(3.33)
No. Litters (%)	0(0.00)	1(16.7)	0(0.00)	1(16.7)
Total Affected Fetuses (Litters)				
Skeletal Variation	0(0)	3(3)	3(3)	11(3)
Skeletal Malformation	0(0)	1(1)	0(0)	0(0)
Fetal Ossification Sites a				
Hindlimb tarsals (reduced)	0.05	-48.15	-100.0	-100.0
Hindlimb phalanges (reduced)	6.71	8.10	-6.92	-23.24

	Forelimb phalanges (delayed)	8.37	-1.76	-1.02	-6.91
	Metatarsals (delayed)	4.98	-0.70	-2.82	-11.34

For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
- No noteworthy findings.

The Applicant's Position:
Tucatinib administered to pregnant dams caused teratogenicity in rabbits and embryo-fetal toxicity in rats.

In a preliminary embryo-fetal development study in rabbits, tucatinib caused embryo-fetal toxicity (external and visceral malformations; skeletal malformations) in the absence of significant maternal toxicity at ≥90 mg/kg/day. The AUC_{12h} at 90 mg/kg/day in rabbits was approximately the same as human subjects dosed with the recommended dose of 300 mg BID. These data indicate that tucatinib is a selective embryo-fetal toxicant in rabbits.

In a preliminary embryo-fetal development study in rats, tucatinib caused embryo-fetal toxicity (decreased fetal body weight and ossification sites and increased skeletal variations) at a dose that was higher than that which caused toxicity to dams (weight and food consumption effects). The AUC_{12h} at 120 mg/kg/day in rats was approximately 9.1x higher than that in human subjects dosed with the recommended dose of 300 mg BID.

Regulatory Authorities Assessment:
Rat embryo-fetal development study
The regulatory authorities note that according to the protocol, scheduled euthanasia occurred on GD21 for main study animals and on GD18 for toxicokinetic study animals.

The regulatory authorities agree with the Applicant's conclusion that:

- **Tucatinib caused maternal toxicity at ≥90 mg/kg/day, which consisted of reduction in body weight* and food consumption.**

*** The applicant provided changes in maternal body weights compared to control included the changes in fetal body weight. Gravid uterine weights were not examined in the study; therefore, the real maternal weight changes by subtracting gravid uterine weights from maternal weights can not be calculated.**

The regulatory authorities do not agree with the Applicant's statement (b) (4) **The submitted data indicate that:**

- **Tucatinib caused embryo-fetal toxicities at a lower dose of 90 mg/kg, including decreased fetal body weight, reduced number of live fetuses, reduction in fetal ossification sites and increases in skeletal variations.**
- **AUC_{12h} of 16400 hr*ng/mL corresponding to the maternal and embryo-fetal growth developmental toxicity at 90 mg/kg/day was approximately 3.5-fold higher than the AUC at the clinical dose of 300 mg/dose twice daily in humans.**

Additional noteworthy study results

Parameters | **Major findings**

Body Weights

Dose-dependent body weight loss during GD 7 to 10

120 mg/kg/day: -7 g (3% loss); 150 mg/kg/day: -10 g (4% loss)

↓ *body weight gains*

Body Weight Gains Compared to the Control (%)

Dose (mg/kg/day	90	120	150
GD 12 to 15	61	71	52
GD 15 to 18	86	88	76

During the postdose period (GD 18 to 21), there was no noteworthy improvement.

Food Consumption

↓*Mean maternal food intake*

Mean Maternal Food Intake Compared to the Control (%)

Dose (mg/kg/day	90	120	150
GD 7 to 10	91	57	41
GD 10 to 12	100	86	67
GD 12 to 15	88	78	64
GD 15 to 18	97	92	77
GD 7 to 18 (Dosing Period)	95	83	65
GD 18 to 21 postdose period	99	97	103
GD 7 to 21	**96**	**85**	**73**

Necropsy findings

Offspring

Necropsy Findings

Cesarean Section Data

Daily Dose (mg/kg/day)		**Deviation compared to the control (%)**		
	0 (Control)	**90**	**120**	**150**
No. Litters Evaluated	5	6	6	6
Mean No. Live Fetuses (male)	6.2	8		-11
Mean No. Live Fetuses (female)	7.4	-39.2	-25.7	-30.7
Mean Fetal Body Weight (male)	5.9		-8.8	-17.5
Mean Fetal Body Weight (female)	5.9	-7.6	-13.9	-21.6
Mean Fetal Body Weight (male+female)	5.9	-2.8	-11.0	-19.3

Blank: unremarkable

<table>
<tr><td></td><td>Fetal/ Offspring (malformations, variations)
All doses
↓fetal ossification sites (the mean number of hindlimb tarsals and phalanges, forelimb phalanges and metatarsals)
↑skeletal variations (incomplete ossified parietal, ossified sternebra bipartite, fused cervical arch, misshapen cervical arch, unossified thoracic centrum, nodulated rib, incomplete ossified squamosal, incomplete ossified zygomatic, full cervical supernumerary rib, short cervical supernumerary rib, ossified thoracic centrum bipartite, incomplete ossified sternebra, short rib</td></tr>
<tr><td>Toxicokinetics</td><td>*Mean toxicokinetic parameters for tucatinib and ONT-993 (metabolite) - Gestation Day 17
<table>
<tr><th rowspan="2">Analyte</th><th colspan="2">Dose level (mg/kg)</th><th rowspan="2">C_{max} (0-12) (ng/mL)</th><th rowspan="2">Dose Normalized C_{max}</th><th rowspan="2">AUC_{0-12h} ng.h/mL</th><th rowspan="2">Dose Normalized AUC_{0-12}</th><th rowspan="2">AUC_{0-24h} ng.h/mL</th><th rowspan="2">T_{max} (h)</th></tr>
<tr><th>Daily</th><th>Twice daily</th></tr>
<tr><td rowspan="3">tucatinib</td><td>90</td><td>45</td><td>2420</td><td>54</td><td>16400</td><td>365</td><td>50000</td><td>2</td></tr>
<tr><td>120</td><td>60</td><td>3840</td><td>64</td><td>31600</td><td>527</td><td>57900</td><td>2</td></tr>
<tr><td>150</td><td>7</td><td>9550</td><td>127</td><td>60600</td><td>808</td><td>136000</td><td>8</td></tr>
<tr><td rowspan="3">ONT-993</td><td>90</td><td>45</td><td>16</td><td>0.4</td><td>156</td><td>3.5</td><td>342</td><td>4</td></tr>
<tr><td>120</td><td>60</td><td>16</td><td>0.3</td><td>153</td><td>2.6</td><td>292</td><td>4</td></tr>
<tr><td>150</td><td>7</td><td>27</td><td>0.4</td><td>219</td><td>2.9</td><td>480</td><td>8</td></tr>
</table>
Tucatinib
• AUC and C_{max} increased more than dose proportionally.
• Tmax values ranging from 2 to 8 hours post dose.
ONT-993
• AUC and Cmax increased dose proportionally.
• T_{max} values ranging from 4 to 8 hours post dose.
*some of this data is presented by the Applicant in Section 5.4 above.</td></tr>
</table>

Rabbit embryo-fetal development study

The regulatory authorities agree with the Applicant's conclusions for the pilot embryo-fetal development study in rabbits. Additional noteworthy findings are included in the table below.

AUC_{12h} of 6370 hr*ng/mL corresponding to the embryo-fetal growth developmental toxicity at 90 mg/kg/day was approximately 1.3-fold higher than the AUC at the clinical dose of 300 mg/dose twice daily in humans.

Parameters	Major findings
Body Weights	≥ 120 mg/kg: ↓ intervals GD 7-10 and GD 7-19 (↓up to 5%).

<table>
<tr><td></td><td>Mean maternal body weights in treatment groups on GD 29 were comparable to that in control.</td></tr>
<tr><td>Food Consumption</td><td>Mean maternal food consumption was 81%, 62%, 49%, and 80.5% of the controls in the 60, 90, 120, and 150 mg/kg/day dose groups, respectively, for the interval of GD 7 to 20.
Food consumption improved during the postdose period.</td></tr>
<tr><td>Toxicokinetics</td><td>*Mean toxicokinetic parameters for Tucatinib in plasma - Gestation Day 19
<table>
<tr><th>Dose level mg/kg/dose</th><th>Dose level mg/kg/day</th><th>$C_{max(0-12)}$ (ng/mL)</th><th>Dose Normalized $C_{max(0-12)}$</th><th>AUC_{0-12h} ng.h/mL</th><th>Dose Normalized AUC_{0-12}</th><th>AUC_{0-24h} ng.h/mL</th><th>T_{max} (h)</th></tr>
<tr><td>30</td><td>60</td><td>819</td><td>27.3</td><td>1860</td><td>61.9</td><td>3560</td><td>1</td></tr>
<tr><td>45</td><td>90</td><td>2190</td><td>48.6</td><td>6370</td><td>141</td><td>12900</td><td>1</td></tr>
<tr><td>60</td><td>120</td><td>5720</td><td>95.4</td><td>29900</td><td>499</td><td>55400</td><td>1</td></tr>
<tr><td>75</td><td>150</td><td>6330</td><td>84.4</td><td>29500</td><td>394</td><td>55300</td><td>1</td></tr>
<tr><td colspan="8">• AUC and C_{max} increased more than dose proportionally as the doses increased from 60 mg/kg/day to 120 mg/kg/day; increased dose proportionally as the doses increased from 120 mg/kg/day to 150 mg/kg/day.
• T_{max} was 1 hours post dose on Gestation Day 19.
* some of this data is presented by the Applicant in Section 5.4 above.</td></tr>
</table></td></tr>
</table>

Prenatal and Postnatal Development

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
The regulatory authorities agree that no prenatal and postnatal development studies are warranted for the proposed indication.

5.5.5. Other Toxicology Studies

Data:
In vitro phototoxicity: Tucatinib showed absorbance in the UVA region of an ultraviolet-visible light absorbance scan, indicative of potential phototoxicity. Follow-up testing with the 3T3 Neutral Red Uptake Phototoxicity Test indicated tucatinib had a Photo-Irritant Factor of 7.3. Therefore, tucatinib is considered to have phototoxic potential.

In vivo phototoxicity: A GLP study was conducted to determine the potential phototoxic effects of tucatinib on the eyes and skin of Long-Evans female rats. Animals were administered 6 doses of 0, 3, 10, or 30 mg/kg by oral gavage every 12 hours (0, 6, 20, or 60 mg/kg/day) followed by a 90 minute exposure to UVB, UVA and visible light. The TK characteristics were also determined. There was no evidence of cutaneous phototoxicity or tucatinib-related ophthalmic or light microscopic findings indicative of ocular phototoxicity, therefore, the NOEL considered to be 60 mg/kg/day (30 mg/kg/dose). This dose level corresponded to C_{max} and AUC_{12h} values (after first and fifth dose) of 5380 and 6300 ng/mL, and 17,000 and 28,300 ng·hr/mL, respectively.

Evaluation of a (b) (4) *degradant and* (b) (4) *impurity:* (b) (4) degradant of tucatinib, and (b) (4) impurity, were qualified by in silico assessments for genotoxicity and in vivo dedicated rat toxicity studies.

In silico: Both compounds were evaluated by Derek and Leadscope and were found to be non-mutagenic.

In vivo: Two GLP studies were conducted in Sprague-Dawley rats to evaluate the potential toxicity of (b) (4) and (b) (4) when administered twice daily for 28 days. Doses for both studies were 1x, 3x, and 10x the human equivalent dose expected at the highest concentration to be qualified. End points were mortality, clinical observations, body weight, food consumption, clinical pathology, TK, gross necropsy findings, organ weights, and histopathology.

(b) (4): Rats were administered 0 (vehicle control), (b) (4) mg/kg/day divided in 2 daily doses. There were no test article-related observations for any parameter. Therefore, the NOEL after dosing (b) (4) by oral gavage daily for 28 days in rats is (b) (4) mg/kg/day.

(b) (4) Rats were administered 0 (vehicle control), (b) (4) mg/kg/day divided in 2 daily doses. There were no test article-related observations for any parameter. Therefore, the NOEL after dosing (b) (4) by oral gavage daily for 28 days in rats is (b) (4) mg/kg/day.

The Applicant's Position:

The in vivo phototoxicity study with tucatinib indicates that tucatinib has no phototoxic effect on pigmented or nonpigmented skin, or on the eye. The two 28-day toxicity studies conducted with an impurity and a degradant that may be found in the drug product qualify these molecules at levels above the ICH identification threshold.

Regulatory Authorities Assessment:

The regulatory authorities agree with the Applicant's conclusions.

Impurities/degradants

The proposed specification limits for impurities (b) (4) (NMT (b) (4)%), (b) (4) (NMT (b) (4)%), and (b) (4) (NMT (b) (4)%) in the drug substance are above the ICH Q3A qualification threshold of (b) (4)% w/w.

Impurities (b) (4)

Impurities (b) (4) were predicted to be non-mutagenic using QSAR prediction methodologies of DEREK (knowledge-based) and Leadscope (statistical-based). (b) (4) and (b) (4) were qualified by the 28-day GLP repeat-dose studies in rats and monkeys with tucatinib. Thus, the proposed specification limits are acceptable from the pharmacology/ toxicology perspective.

Impurity (b) (4)

Impurity (b) (4) is a process-related impurity identified using a new HPLC method in the scale-up batches. (b) (4) was predicted to be non-mutagenic based on QSAR prediction methodologies of DEREK (knowledge-based) and Leadscope (statistical-based). In a GLP 28-day repeat-dose toxicology study, no treatment-related toxicities were identified with (b) (4) doses up to (b) (4) mg/kg/day (b) (4) mg/m^2 human equivalent dose), which supports up to (b) (4) mg/day (b) (4) in a 60 kg patient. At the proposed specification limit of (b) (4) %, a 60 kg patient receiving 300 mg tucatinib twice daily would receive (b) (4) mg/day (b) (4) Therefore, the proposed specification limit of (b) (4) at (b) (4) % is qualified by the nonclinical data.

(b) (4): A Twice Daily 28-Day Oral Toxicity Study in Rats:

Key Study Findings:

- **Twice daily oral gavage administration of (b) (4) was tolerated at doses up to 2.47 mg/kg/day.**

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing*:	(b) (4) mg/kg/day, BID
Route of administration:	Oral gavage
Formulation/Vehicle:	5% v/v dimethyl sulfoxide, 45% v/v propylene glycol, 50% v/v deionized water, final pH of 4.0 ± 0.2
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	10
Age:	7 weeks old
Satellite groups/ unique design:	NA
Deviation from study protocol affecting interpretation of results:	No

***: Dose levels were selected based on multiples (approximately 1, 3, and 10x) of the potential human dose of (b) (4)**

Parameters	**Major findings**
Mortality	No treatment-related mortality occurred.
Clinical Signs	unremarkable
Body Weights	unremarkable

Ophthalmoscopy	unremarkable
ECG	not performed
Hematology	unremarkable
Clinical Chemistry	unremarkable
Urinalysis	unremarkable
Gross Pathology	unremarkable
Organ Weights	unremarkable
Histopathology	unremarkable

X	X

Wei Chen
Primary Reviewer

Tiffany Ricks
Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

Regulatory Authorities Assessment:

Tucatinib 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. The proposed dosing regimen is 300 mg tablets taken orally twice daily (BID) with or without food.

The primary evidence supporting the 300 mg BID is based on the results from a randomized, double-blinded, placebo-controlled study (HER2CLIMB) showing improvements in PFS (median of 7.8 month for tucatinib arm vs 5.6 month for placebo arm, with a HR of 0.544) and acceptable safety profile in tucatinib arm as compared to the placebo arm.

The clinical pharmacology review focused on the dose recommendation in patients with organ dysfunctions and drug-drug interactions. The use of tucatinib in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment, as capecitabine is contraindicated in patients with severe renal impairment in the current capecitabine label. The recommended starting dose is 200 mg orally twice daily in patients with severe hepatic impairment. Patients should avoid use of strong CYP2C8 inhibitors; however, if strong CYP2C8 inhibitor cannot be avoided, the recommended starting dose of tucatinib is 100 mg orally twice daily. Closely monitor for adverse reactions in patients with concomitant use of moderate CYP2C8 inhibitors. Avoid concomitant use of strong CYP3A4 inducers or moderate CYP2C8 inducers with tucatinib.

6.1.1. Recommendations:

The regulatory authorities have reviewed the information submitted in NDA213411. This NDA is approvable from a clinical pharmacology perspective. They key review issues with specific recommendations/comments are summarized below in Table 2.

Table 2: Key Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the pivotal Phase 2 study HER2CLIMB. The proposed dosing regimen of 300 mg BID is supported by improved PFS median of 7.8 month (95% CI: 7.5, 9.6) in tucatinib arm vs 5.6 month (95% CI: 4.2, 7.1) in placebo arm, with a HR of 0.544 (95% CI: 0.42, 0.705) in patients with locally advanced unresectable or metastatic HER2+ breast cancer,

Review Issue	Recommendations and Comments
	including in subjects with known brain metastases, who were previously treated with trastuzumab, pertuzumab, and T-DM1.
General dosing instructions	The proposed tucatinib dosing regimen of 300 mg BID is acceptable for approval from a clinical pharmacology perspective: • HER2CLIMB study show Tucatinib 300 mg BID has improved PFS, with acceptable safety profile • Tucatinib 300 mg BID tablet has comparable exposure with the Maximum Tolerated Dose (MTD) of 600 mg BID Power in Capsule (PIC) formulation. • Exposure response analysis suggest slight trend toward improved PFS with increased trough exposure. • In the early dose finding stage, the emergence of Grade 3 events (diarrhea, nausea, vomiting) reported after the DLT period at 350 mg dose level.
Dosing in patient with organ impairment	• No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh criteria). The regulatory authorities recommend reducing the starting dose for patients with severe hepatic impairment to 200 mg BID. • No dose adjustment is needed for patients with mild or moderate renal impairment (CLcr > 30 mL/min). • The use of tucatinib in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), given that there is no clinical data for tucatinib from patients with severe renal impairment (CLcr < 30 mL/min) and current capecitabine label suggested that capecitabine is contraindicated in patients with severe renal impairment.
Drug-drug interactions	*As victim* • Avoid concomitant use of strong CYP2C8 inhibitor. If concomitant use of strong CYP2C8 inhibitor is inevitable, the regulatory authorities recommends that the starting dose should be reduced to 100 mg BID. • Increase monitoring for adverse reactions with concomitant use of moderate CYP2C8 inhibitor. • Avoid concomitant use of strong CYP3A4 inducer or moderate CYP2C8 inducer. The regulatory authorities have no starting dose recommendation if concomitant use cannot be avoided. *As perpetrator* • Avoid concomitant use of tucatinib with (b) (4) CYP3A substrates. If concomitant use cannot be avoided, consider reducing the dosage of (b) (4) CYP3A substrates (b) (4) • Consider reducing the dosage of P-gp substrates, (b) (4) where minimal concentration changes may lead to serious or life-threatening adverse reactions.

Review Issue	Recommendations and Comments
Labeling	The proposed labeling recommendations are acceptable upon the Applicant's agreement to the regulatory authorties' suggested revisions to the label. The regulatory authorities have labeling recommendations on the following major labeling changes: • Reduce the starting dose in patient with severe hepatic impairment to 200 mg BID • Avoid concomitant use of strong CYP2C8 inhibitor. If concomitant use of strong CYP2C8 inhibitor is inevitable, the recommended starting dose should be reduced to 100 mg BID. • Increase monitoring for adverse reactions with concomitant use of moderate CYP2C8 inhibitor. • Add section 8.6 Renal Impairment to recommend Patients with severe renal impairment should avoid use of tucatinib in combination with capecitabine and trastuzumab, as capecitabine is contraindicated for such patients in the current capecitabine label.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:
The clinical pharmacology of tucatinib has been well-characterized. A total of 11 clinical studies (10 completed; 1 ongoing) provide information on the PK and pharmacodynamic properties of tucatinib.

Seven clinical studies in subjects without cancer were designed to characterize the clinical pharmacology of tucatinib. In these Phase 1 studies, single or multiple doses of tucatinib were administered to healthy male and female subjects and subjects with hepatic impairment. Four additional studies in subjects with advanced cancer or MBC provide supporting PK data for tucatinib in the indicated patient population.

In addition to the clinical pharmacology studies, a fit-for-purpose and mechanistic PBPK model for tucatinib was developed using available in vitro and in vivo data for tucatinib, using the SimCYP population-based simulator. Model verification and model updates were completed based on results from drug-drug interaction (DDI) studies ONT-380-012 and SGNTUC-020.

A population PK model and covariate analysis was developed using data from healthy subjects and subjects with cancer. A baseline patient factor covariate analysis of PK data and exposure-response analysis of HER2CLIMB data support the recommended dose of 300 mg tucatinib administered orally, BID, with or without a meal, on a continuous schedule.

Data:
NA

Regulatory Authorities Assessment:

The regulatory authorities generally agree with the applicant's position. The clinical pharmacology program in the current submission includes the following assessments:

- **Dose Selection in Cancer Patients**

The selection of the tucatinib dosing regimen of 300 mg BID in the pivotal HER2CLIMB study was primary based on results from studies ARRAY-380-101 and ONT-380-005:

  - **ARRAY-380-101: A phase 1 dose-escalation study of tucatinib monotherapy in subjects with advanced solid tumors. Tucatinib dose of 25, 50, 100, 200, 300, 500, 600, 650 and 800 mg BID were evaluated**
  - **ONT-380-005: A Phase 1b study in breast cancer patients. Tucatinib dose of 300 mg and 350 mg were evaluated, either as doublet combination (with capecitabine or trastuzumab), or as triplet combination (with both capecitabine and trastuzumab)**

- **Other Clinical Pharmacology Assessment in Healthy Subjects**

The rest of clinical pharmacology program was carried out in healthy subjects, encompassing the following assessments:

  - **Dedicated Hepatic Impairment: ONT-380-009**
  - **Drug Interaction: ONT-380-012; SGNTUC-020**
  - **Relative BA/BE: Array-380-102; Array-380-103**
  - **Food Effect; Omeprazole drug interaction: Array-380-103**
  - **Mass Balance: ONT-380-008**
  - **QT: ONT-380-011**
  - **Ethnicity: SGNTUC-015**

The results from the above studies were the basis for the dose recommendation in the general population and in subpopulations who are under the effect by intrinsic factors (such as renal and hepatic impairment) and extrinsic factors (such as food, drug interactions).

Furthermore, the applicant submitted PBPK and Population PK analyses, as follows:

- **PBPK analysis was aimed to evaluate the potential of tucatinib to inhibit CYP2C8, CYP2C9, P-gp, OCT2, OATP1B1/3 or UGT1A1 or the potential of tucatinib and ONT-993 to inhibit CYP3A4 or MATE1/2-K.**
- **The population PK model was developed with data from pooled PK data with the aforementioned studies except study HER2CLIMB. The goal of this analysis was to develop a population pharmacokinetic (PK) model for tucatinib to assess the sources of variability in tucatinib PK. An exploratory covariate analysis was performed with data from HER2CLIMB study to explore the relationship between tucatinib exposure and covariates of interest.**

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:
The recommended dose of tucatinib is 300 mg PO BID (in combination with trastuzumab (b) (4) and capecitabine 1000 mg/m^2 PO BID (b) (4) administered without regard to a meal.

Data:
The primary and key secondary results from the pivotal HER2CLIMB study indicated that 300 mg BID tucatinib in combination with trastuzumab and capecitabine resulted in a clinically meaningful reduction in the risk of disease progression and death. Exposure efficacy analyses indicated a trend towards increased PFS with increasing trough exposure, although the confidence intervals (CI) overlapped for all quartiles, and subjects in all quartiles experienced a treatment benefit. No trend was observed in the exposure-response relationship for incidence of adverse events of special interest (AESI) and Cycle 3 Day 1 trough tucatinib concentration in these low incidence events.

In the pivotal HER2CLIMB study, tucatinib was administered without regard to a meal. There was no meaningful impact of food on the PK of tucatinib.

The adverse event (AE) profile of tucatinib was favorable and adequately managed by protocol-mandated dose modifications (see Section 8.2.4). The median relative dose intensity (RDI) for tucatinib was 93.6%, whereas the mean RDI for tucatinib was 88.5% (standard deviation [STD] 13.6), indicating most subjects were able to receive the intended dose of tucatinib over their treatment duration. Furthermore, after dose hold, most subjects resumed tucatinib dosing at the same dose level Only 5.7% of subjects in the treatment arm discontinued tucatinib due to AE (Section 8.2.4).

Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's position. In the pivotal HER2CLIMB study, tucatinib 300 mg BID demonstrated favorable benefit-risk profile compared to placebo. Tucatinib in combination with capecitabine improved PFS by 2.2 months (median of 7.8 month for tucatinib arm vs 5.6 month for placebo arm, with HR of 0.544) with acceptable safety profile in patients with locally advanced unresectable or metastatic HER2+ breast cancer (Table 35, Table 36).

The tucatinib dose of 300 mg BID tablet for the general population is selected as it achieves a comparable exposure as the MTD (600 mg BID Powder In Capsule formulation). This dose selection is further supported by exploratory exposure response analysis with efficacy and safety data from the HER2CLIMB study. A slight trend towards increased PFS with increasing trough exposure, comparing PFS among C_{trough} quartiles, and between subgroups below and above median C_{trough}, suggesting a dose below 300 mg BID may compromise the efficacy. No

exposure response relationships are identified for safety. Increased incidence of grade ≥ 3 AE was observed at dose 350 mg BID during dose finding. Refer to section 6.3.2.1 for more details with regard to dose regimen evaluation.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:
The population PK covariate search supports (b) (4) (b) (4)

Data:

Special Populations

Patients with Hepatic Impairment: ONT-380-009 was a dedicated hepatic impairment study in subjects without cancer. Mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment had no clinically relevant effect on tucatinib exposure. Tucatinib AUC_{inf} and C_{max} increased <2-fold in hepatically impaired subjects versus subjects with normal hepatic function. (b) (4)

Patients with Renal Impairment: Study ONT-380-008 showed that < 5% of total radioactivity was excreted in urine, indicating that renal excretion of tucatinib is not a major route of elimination. Tucatinib elimination is predominantly mediated by metabolism and biliary excretion; (b) (4)

Intrinsic Factors

A population PK analysis showed that body weight (b) (4) did not have a clinically meaningful effect on tucatinib PK. Age, (b) (4) and race were not identified as predictors of tucatinib PK.

Using NCI organ dysfunction working group criteria, a baseline patient factor covariate analysis of PK data from HER2CLIMB was conducted. Weight and age did not meaningfully impact the PK of tucatinib, as the predicted range was <2-fold on tucatinib trough concentration (C_{trough}). Race, Eastern Cooperative Oncology Group (ECOG) performance status and baseline renal function were not significant predictors of tucatinib PK.

Regulatory Authorities Assessment:

Intrinsic Factors

The regulatory authorities generally agree with the Applicant's position on therapeutic individualization. However, the regulatory authorities does not agree with the applicant's proposal of (b) (4)

Instead, the regulatory authorities recommend reducing the starting dose to 200 mg BID in patients with severe hepatic impairment, based on the following rationale:

1) **an increase in median exposure and higher between subject variability in patients with severe hepatic impairment**
2) **hepatotoxicity is one of the most frequent TEAEs. The risk of adverse events is mitigated by reducing the dose from 300 mg BID to 200 mg BID in patients with severe hepatic impairment to match the exposure in patients with normal hepatic function. Refer to section 6.3.2.3 for more details.**

In addition, there are no clinical data to support the applicant's proposal of (b) (4) **Tucatinib is used as combination therapy with capecitabine, which is contraindicated in patients with severe renal impairment. Therefore, the use of tucatinib in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment.**

The Applicant conducted exploratory genotyping as part of the Drug-Drug Interaction Study ONT-380-012. Genotype-inferred CYP2C8 phenotypes were assigned based on published evidence. Comparison across 84 subjects (65= "extensive metabolizers"; 16= "extensive or intermediate metabolizers"; 2= "intermediate metabolizers", 1= "unknown") who received a single dose of 300 mg tucatinib on Day 1 of the study showed similar exposure to tucatinib. None of the subjects enrolled were assigned as the poor metabolizer phenotype. Based on the limited data from ONT-380-012, the impact of CYP2C8 polymorphisms on the exposure of tucatinib and ONT-933 is inconclusive.

The regulatory authorities agree that no dose adjustment for tucatinib is required for subpopulations based on other intrinsic factors such as age and race. Population PK analysis suggested that the effect on the tucatinib exposure by other population PK identified intrinsic covariates is not considered clinically meaningful and dose adjustments based on those covariates are not necessary (Figure 4, section 19.4. Population PK assessment).

Reviewer's note: In the population PK analysis, sex was confounded with combination therapy and study. As a result, sex was not included in the covariate search and the effect by sex on the tucatinib PK is unknown.

Extrinsic Factors

When 300 mg Tucatinib tablet is taken with a high-fat meal, C_{max} was unchanged while Tucatinib AUC_{inf} increased approximately 49%. The regulatory authorities agree with the Applicant's position that tucatinib can be given with or without food, given that tucatinib is

administrated without regard to food in the HER2CLIMB study and food effect study suggested no clinically meaningful change in exposure (Table 9).

Two formulations have been developed and utilized in the clinical trials: tablet and powder in capsule (PIC). Tablet formulation is the to-be-market formulation and was utilized in the pivotal HER2CLIMB study. Less than 10% increase in the relative bioavailability was observed for the tablet formulation as compared with the capsule formulation in the relative bioavailability study. On the other hand, population PK and covariate analysis suggest tablet formulation have higher bioavailability as compared to the capsule formulation (Figure 4). The regulatory authorities considered the formulation is not an issue, as the to-be-market formulation was utilized in the pivotal HER2CLIMB study and information derived from clinical trials with tablet formation was utilized to support the labeling.

The regulatory authorities agree with the Applicant's position that a proton pump inhibitor does not have a clinically meaningful effect on tucatinib PK, as suggested by minor tucatinib exposure change with concomitant administration of omeprazole (Table 10).

The regulatory authorities agree with the Applicant's position on the prevention or management of drug interaction issue, as follows:

- **Avoid concomitant use of strong CYP2C8 inhibitor; strong CYP3A4 or moderate CYP2C8 inducer**
- **Avoid concomitant use of (b) (4) CYP3A substrates and reduce the dose of P-gp substrate, (b) (4), where minimal concentration change may lead to serious or life-threatening toxicities.**

The above recommendations are supported by the results from the dedicated DDI study. However, the regulatory authorities also recommend reducing the starting dose to 100 mg BID for patients for whom coadministration with a strong CYP2C8 inhibitor cannot be avoided. The regulatory authorities do not have dose recommendations for patients for whom coadministration with a strong CYP3A4 or moderate CYP2C8 inducers cannot be avoided. This is due to the fact that the dose proportionality has not be evaluated with doses higher than 350 mg BID tablet, and that an increase in the tucatinib dose may lead to an increase in the rate of diarrhea, one of the most frequent TEAEs, and other GI tract toxicities.

The DDI effect with moderate CYP2C8 inhibitors was not evaluated in the clinical trial. Given the observed 3 fold increase of tucatinib AUC with gemfibrozil, a strong CYP2C8 inhibitor, the regulatory authorities recommend increasing monitoring for adverse reactions with concomitant use of moderate CYP2C8 inhibitors.

Refer to section 6.3.2.4 for more detailed evaluation on tucatinib dose regimen base on the effect by extrinsic factors.

Reviewer's note: During ORBIS discussion, Health Canada considered avoiding concomitant use of moderate CYP2C8 inhibitor and reducing the starting dose to 150 mg BID, based on the PBPK predicted 2-3 fold increase with concomitant use of moderate CYP2C8 inhibitor. FDA

acknowledged the rationale of this decision. After reevaluation, FDA would like to maintain the previous recommendation of 'increase monitoring for adverse reaction' without recommend 'avoiding concomitant use' or starting dose adjustment, with the following rationales:

FDA's clinical pharmacology team considered the applicant's PBPK modeling and simulation for moderate CYP2C8 is inconclusive, as there are uncertainties concerning the lower end of the estimated tucatinib exposure change. Based on the in vivo DDI study with gemfibrozil, the tucatinib exposure changes with concomitant use of a moderate CYP2C8 inhibitor can be 1 to 3 fold, rather than 2 to 3 fold.

The safety profile of tucatinib in the heavily treated patients in a third-line therapy is generally acceptable compared to the control arm, current strategy of dose modifications (reduction, interruption) effectively mitigate the safety concern. Given the possibility of sub-optimal exposure by reducing the dose, the efficacy may be compromised in this heavily treated patient population. Taken all the aforementioned benefit-risk profile into consideration, FDA decided to recommend the same dose of 300 mg BID dose but 'increase monitoring for adverse reaction' when moderate CYP2C8 inhibitors are concomitantly used.

6.2.2.3. Outstanding Issues

The Applicant's Position:
NA

Data:
NA

Regulatory Authorities Assessment:
The regulatory authorities have no outstanding issues requiring a PMR or PMC.

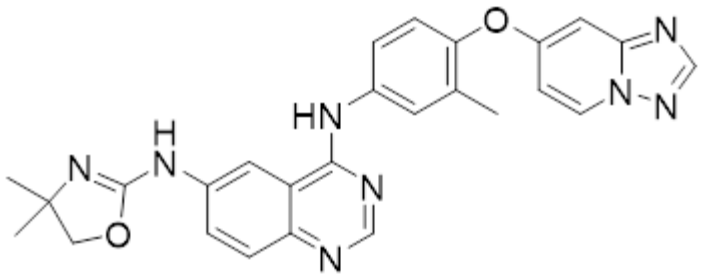
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
The general clinical pharmacology characteristics of tucatinib have been studied in healthy subjects and those with locally advanced, unresectable, or metastatic HER2+ BC. Single and multiple dose PK at the recommended dose of 300 mg BID were well-characterized in monotherapy in healthy subjects, and in combination with trastuzumab and capecitabine or trastuzumab emtansine (T-DM1) in subjects with BC.

Data:
General pharmacology and PK characteristics are summarized in Table 3.

Table 3: General pharmacology and pharmacokinetic characteristics of tucatinib

2a. General Information	
Chemical Structure and major physical and chemical properties	Chemical structure of the compound and molecular weight (MW) **Chemical Name:** (N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine (4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine **Molecular Formula:** $C_{26}H_{24}N_8O_2$  **Molecular Weight** (unsolvated free base): 480.52 g/mol Log P, pKa, solubility (in water and in buffers at different pH levels) **LogD (pH 7.4):** 3.82 **pKa:** 2.07 ± 0.05, 4.19 ± 0.03, 6.15 ± 0.14 **Solubility:** <pH 2.9 = >18.7 mg/mL; >pH 4.6 = <0.4 mg/mL
Proposed indication	Tucatinib is indicated 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 and formulation type and formulation strengths	Oral tablet Formulation Strengths: 50-mg and 150-mg tablets.
Planned dose	300 mg BID (tablet)
Mechanism of action	(b) (4) HER2 tyrosine kinase inhibition

2b. Dose and Adverse Events	
Therapeutic dose and exposure	Proposed clinical dosing regimen: 300 mg BID GMean (%CV) C_{max} and AUC for a single dose at the maximum proposed dose 300 mg tablet AUC_{inf}: 2480 h*ng/mL (38.5%) C_{max}: 410 ng/mL (42.3%) GMean (%CV) C_{max} and AUC at the steady state with the maximum proposed

2b. Dose and Adverse Events	
	clinical dosing regimen 300 mg tablet BID AUC_{tau}: 5234 h*ng/mL C_{max}: 630 ng/mL
Maximum tolerated dose	Clinical 600 mg BID powder in capsule 300 mg BID tablet Nonclinical data (13 week repeat-dose oral studies) Rat NOAEL: 60 mg/kg/day Cynomolgus monkey NOAEL: 20 mg/kg/day
Principal adverse events	Most common tucatinib adverse events Diarrhea, Nausea, Fatigue Dose limiting related adverse events Elevated liver transaminases

2c. PK Features		
Maximum dose tested	**Single Dose**	800 mg powder in capsule; 350 mg tablet
	Multiple Dose	800 mg BID powder in capsule; 350 mg BID tablet
Dose/exposure range tested in clinic (data from this IND and/or elsewhere)	**Single Dose**	Dose Range: 25-800 mg BID (powder in capsule formulation) 50-350 mg BID (tablet formulation) GMean (%CV) C_{max} and AUC: Powder in Capsule formulation (25 mg BID) C_{max}: 19.1 ng/mL (39.6%) AUC_{0-12}: 80.4 h*ng/mL (76.5%) Powder in Capsule formulation (800 mg BID) C_{max}: 876 ng/mL (31.2%) AUC_{0-12}: 3660 h*ng/mL (23.3%) Tablet formulation (50 mg BID) C_{max}: 73.8 ng/mL (54.9%) AUC_{inf}: 370 h*ng/mL (41.2%) Tablet formulation (350 mg BID) C_{max}: 743 ng/mL (44.1%) AUC_{0-6}: 2750 h*ng/mL (28.8%)
	Multiple Dose	Dose Range: 25–800 mg BID (powder in capsule formulation); 50–350 mg BID (tablet) GMean (%CV) C_{max} and AUC: Powder in Capsule formulation (25 mg BID) C_{max}: 35.8 ng/mL (35.4%) AUC_{0-12}: 187 h*ng/mL (29.3%) Powder in Capsule formulation (800 mg BID) C_{max}: 655 ng/mL (55.0%) AUC_{0-12}: 4480 h*ng/mL (94.7%) Tablet Formulation (50 mg BID)

2c. PK Features		
		Cmax: 88.8 ng/mL (82.7%) AUC_{inf}: 531 h*ng/mL (67.3%) Tablet Formulation (350 mg BID) C_{max}: 1483 ng/mL (71.1%) AUC_{0-6}: 5238 h*ng/mL (31.6%)
Range of linear PK	Powder in Capsule Formulation: 25 to 800 mg Tablet Formulation: 50 to 300 mg	
Accumulation at steady-state	300 mg BID (tablet): AUC=1.72-fold; C_{max}=1.52-fold	
Metabolites	There is no major metabolite in humans: • The predominant metabolite (ONT-993) accounted for 9.16% of total plasma radioactivity exposure in humans • Cytotoxic potency of ONT-993 is 2- to 3-fold less than that of tucatinib; the potency adjusted exposure of ONT-993 is <10% of total pharmacological activity	
Absorption	**Absolute/Relative Bioavailability**	Absolute BA: NA, tucatinib has not been administered intravenously to estimate F.
	T_{max}	Median (range) 2.00 hours (range: 1.00 to 4.00 hours) (300 mg tablet)
Distribution	**V_d/F or V_d**	Vss/F: 730 L (300 mg tablet)
	% bound	Mean (%CV) 97.1% bound in human plasma
Elimination	**Route**	Primary route; percent dose eliminated: Following administration of nominal 300 mg [^{14}C]-tucatinib single oral solution, 85.8% (mean) of dosed radioactivity recovered in feces Other routes: Following administration of 300 mg [^{14}C]-tucatinib single oral solution, 4.09% (mean) of dosed radioactivity recovered in urine
	$t_{½}$	Terminal Elimination: $t_{½}$: 14.9 hours (300 mg tablet) Effective: t½: 9.55 hours (300 mg tablet BID)
	CL/F or CL	CL/F: 57.3 L/h (300 mg tablet)

Metabolism	• by CYP450 ☒Yes ☐ No ☐ NA, if yes, specify
	  • CYP2C8 (~75%), CYP3A (~10%)
	• by Phase II enzymes ☐Yes ☒ No ☐ NA
	• by other enzyme systems ☒Yes ☐ No ☐ NA, if yes, specify
	  • Aldehyde Oxidase
	• inhibits CYP450 ☒Yes ☐ No ☐ NA, if yes, specify and provide K_i and/or IC_{50}.
	  • CYP3A Ki: 0.805 µM
	  • CYP3A K_I: 0.54 µM (metabolism-dependent inactivation)
	  • CYP2C8 Ki: 0.170 µM
	  • CYP2C9 Ki: 4.57 µM
	• inhibits Phase II enzymes ☒Yes ☐ No ☐ NA, if yes specify and provide K_i and/or IC_{50}.	

<table>
<tr><th colspan="3">2c. PK Features</th></tr>
<tr><td></td><td colspan="2">• UGT1A1 Ki: 1.81 µM
• induces CYP450 ☐Yes ☒ No ☐ NA, if yes specify</td></tr>
<tr><td>Transporters</td><td colspan="2">• by major transporters ☒Yes ☐ No ☐ NA, if yes, specify
• P-gp, BCRP
• inhibits major transporters ☒Yes ☐ No ☐ NA, if yes, specify and provide K_i and/or IC_{50}.
• OCT2 (metformin) IC_{50}: 14.7 µM
• MATE1 (metformin) IC_{50}: 0.340 µM
• MATE2-K (metformin) IC_{50}: 0.135 µM
• P-gp IC_{50}: 10-30 µM
• induces major transporters ☐Yes ☐ No ☒ NA, if yes specify</td></tr>
<tr><td rowspan="4">Intrinsic Factors</td><td>Age</td><td>Not clinically significant</td></tr>
<tr><td>Sex</td><td>Not clinically significant</td></tr>
<tr><td>Race</td><td>Not clinically significant</td></tr>
<tr><td>Hepatic and Renal Impairment</td><td><u>From the hepatic impairment Study ONT-380-009</u>
300 mg tablet (single dose); GMRs relative to healthy matched controls:
Mild: AUC_{inf} GMR: 0.99; C_{max} GMR: 1.04
Moderate AUC_{inf} GMR: 1.15; C_{max} GMR: 0.89
Severe: AUC_{inf} GMR: 1.61; C_{max} GMR: 1.17

No renal impairment study conducted due to minimal renal elimination (<5%)</td></tr>
</table>

<table>
<tr><th colspan="3">2c. PK Features</th></tr>
<tr><td rowspan="2">Extrinsic Factors</td><td>Drug interactions</td><td><u>Drug-drug interaction (DDI) studies with geometric mean difference in C_{max} and AUC (</u>300 mg tablet):
Impact of Other Drugs on Tucatinib
• CYP3A Inhibition (Itraconazole)
  • Tucatinib C_{max} increased approximately 1.3-fold
  • Tucatinib AUC_{inf} increased approximately 1.3-fold
• CYP3A/CYP2C8 Induction (Rifampin)
  • Tucatinib C_{max} decreased approximately 37%
  • Tucatinib AUC_{inf} decreased approximately 48%
• CYP2C8 Inhibition (Gemfibrozil)
  • Tucatinib C_{max} increased approximately 1.6-fold
  • Tucatinib AUC_{inf} increased approximately 3.0-fold
• Gastric pH Modulation (Omeprazole)
  • Tucatinib C_{max} decreased approximately 13%
  • Tucatinib AUC_{inf} decreased approximately 13%

Impact of Tucatinib on Other Drugs
• CYP3A Inhibition:
  • Midazolam C_{max} increased approximately 3.0-fold
  • Midazolam AUC_{inf} increased approximately 5.7-fold
• CYP2C8 Inhibition:
  • Repaglinide C_{max} increased approximately 1.7-fold
  • Repaglinide AUC_{inf} increased approximately 1.7-fold
• CYP2C9 Inhibition:
  • No effect on tolbutamide C_{max} or AUC
• P-gp Inhibition:
  • Digoxin C_{max} increased approximately 2.4-fold
  • Digoxin AUC_{inf} increased approximately 1.5-fold
• MATE1/2-K Inhibition:
  • Metformin C_{max} increased approximately 1.1-fold
  • Metformin AUC_{inf} increased approximately 1.4-fold</td></tr>
<tr><td>Meal Effects</td><td><u>Mean difference in C_{max} and AUC</u>
<u>Meal type (i.e., high-fat, standard, low-fat)</u>
300 mg tablet in the presence of a high-fat meal
• Tucatinib C_{max} was unchanged
• Tucatinib AUC_{inf} increased approximately 49%</td></tr>
<tr><td>Population PK Analyses</td><td colspan="2">• Body weight and albumin were identified as covariates; however, impact on tucatinib PK was not clinically meaningful
• Age, creatinine clearance, and race were not identified as covariates in the population PK model</td></tr>
</table>

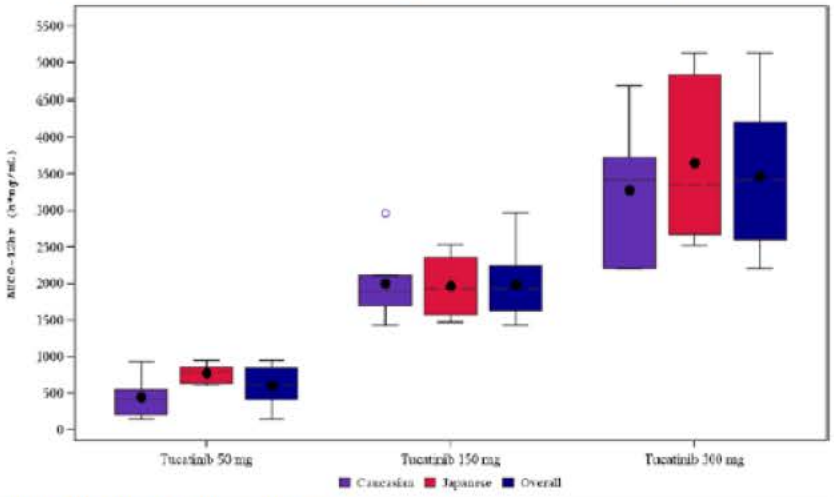
2d. Pharmacodynamic Features
• A thorough QT study has been completed and indicates tucatinib has no significant or clinically meaningful effect on QT prolongation. • Increased serum creatinine (30% mean increase) occurred within the first cycle of tucatinib, remained elevated but stable throughout treatment and were reversable upon discontinuation. These increases were due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
• All subjects in all quartiles experienced a meaningful treatment benefit relative to the control arm. • A trend toward increased PFS with increasing trough exposure, although the confidence intervals overlapped for all quartiles, and subjects in all quartiles experienced a numerically higher median PFS when compared to the control arm (5.6 months, 95% CI: 4.2, 7.1 months). • No trend observed on the exposure-response relationship for incidence of adverse events of special interest and Cycle 3 Day 1 trough tucatinib concentration in these low incidence events.

<u>Regulatory Authorities' Assessment</u>: The regulatory authorities agree with the applicant's assessment on general PK and PD properties as listed above, with the following additional information that was pertinent to the decision making:

Two formulations have been developed and utilized in the clinical trials: tablet and powder in capsule (PIC). Tablet formulation is the to-be-market formulation and was utilized in the pivotal HER2CLIMB study. The PK profile between the two formulations were bridged in the relative bioavailability study array-380-103, in which <10% increase in the relative bioavailability was observed for the tablet formulation as compared with the capsule formulation. On the other hand, population PK analysis suggests that tablet formulation has higher bioavailability than the capsule formulation (Figure 4).

Dose proportionality was demonstrated with PIC formulation, with PK data patients receiving single and repeated doses of 25 to 800 mg BID. Dose proportionality was also demonstrated over dose range of 50-300 mg BID for tablet formulation (Figure 1).

Figure 1: AUC_{tau} for Japanese and Caucasian Subjects over 50-300 mg BID Dose Range



Source: CSR of Study SGNTUC-015, Fig 11-6, Page No 59

6.3.2. Clinical Pharmacology Questions

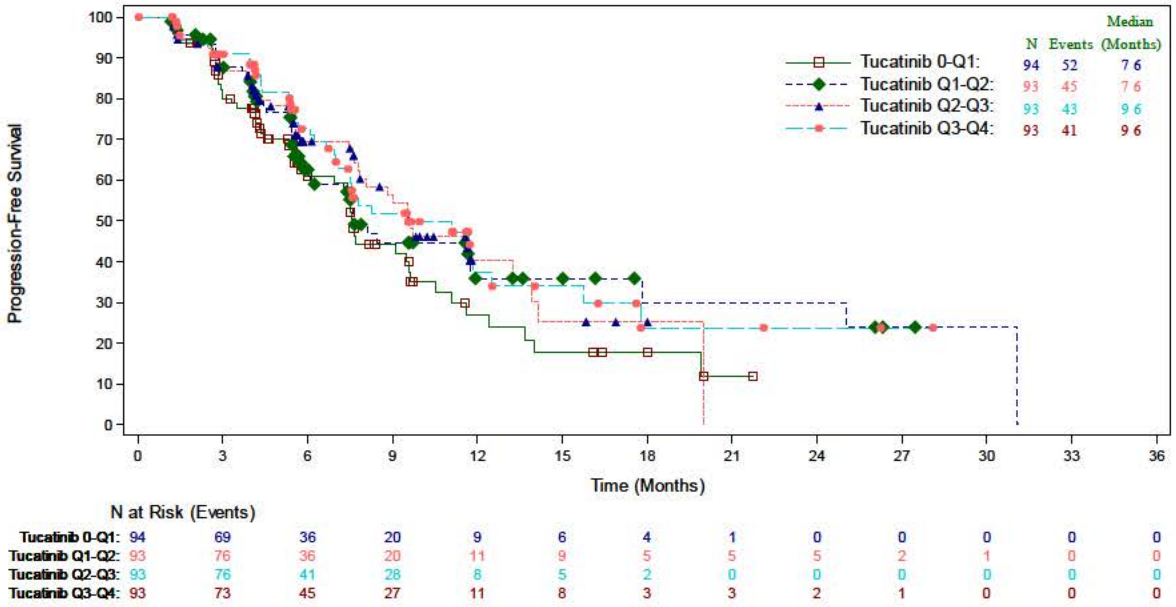
6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:
Yes. The primary evidence of effectiveness is provided by the findings of the HER2CLIMB trial. Exposure-efficacy analyses conducted as part of the clinical pharmacology program provide supportive evidence of effectiveness, and indicate a trend toward increased PFS with increased trough exposure; however, the CI overlapped for all quartiles and subjects in all quartiles experienced a meaningful treatment benefit relative to the control arm.

Data:
Exposure-Response Efficacy Analysis from HER2CLIMB: An initial exposure-efficacy analysis conducted using Cycle 3 Day 1 nominal trough concentration as the exposure metric indicated a trend toward increased PFS with increased trough exposure on the tucatinib arm, although the CIs overlapped for all quartiles, and subjects in all quartiles experience a meaningful treatment benefit relative to the control arm. This result is potentially confounded by high variability in Cycle 3 Day 1 trough concentrations and the exclusion of subjects that progressed or discontinued therapy prior to Cycle 3 Day 1.

Additional analyses evaluated the robustness of the PFS by quartiles of Cycle 3 Day 1 trough concentrations results by minimizing the impact of variability in subject exposure. Kaplan-Meier analyses of PFS using the quartiles of geometric mean exposure across all cycles demonstrated similar findings to the PFS analyses by Cycle 3 Day 1 (Figure 2). There was a trend toward increased PFS with increased trough exposure on the tucatinib arm (Table 4), although the CI overlapped for all quartiles, and subjects in all quartiles experienced a numerically higher median PFS versus the control arm (5.6 months, 95% CI: 4.2, 7.1 months).

Figure 2: Kaplan-Meier Plots for PFS per BICR by Quartiles of Average Tucatinib Trough Concentrations (PK Population)



Subjects in Tuc+Cap+Tra arm were categorized into quartiles based on the geometric means of tucatinib predose concentrations on C2D1, C3D1, C4D1, C5D1, and C6D1 using the overall quartiles of the geometric means in Tuc+Cap+Tra arm. Intervals used for categorization are inclusive of all upper bounds and exclusive of the lower bound, with the exception of 0 to Q1 (inclusive on both sides). Missing concentration values not included. BLOQ values imputed as 1/2 BLOQ (0.5 ng/mL) for calculation of quartiles. Q1, Q2, and Q3 values of the geometric means of tucatinib trough concentration in Tuc+Cap+Tra are 53.3 ng/mL, 142.1 ng/mL, and 268.8 ng/mL, respectively.
Source: m2.7.2 Figure 49

Table 4: PFS per BICR by Quartiles of Average Tucatinib Trough Concentrations (PK Set)

	Tuc+Cap+Tra (N=385)			
	Tucatinib 0–Q1 (N=94)	Tucatinib Q1–Q2 (N=93)	Tucatinib Q2–Q3 (N=93)	Tucatinib Q3–Q4 (N=93)
Median PFS (months) (95% CI)	7.6 (5.8, 9.6)	7.6 (6.0, 11.8)	9.6 (7.8, 13.2)	9.6 (7.5, 12.5)
Number of Events (%)	52 (55.3)	45 (48.4)	43 (46.2)	41 (44.1)
Number Censored (%)	42 (44.7)	48 (51.6)	50 (53.8)	52 (55.9)

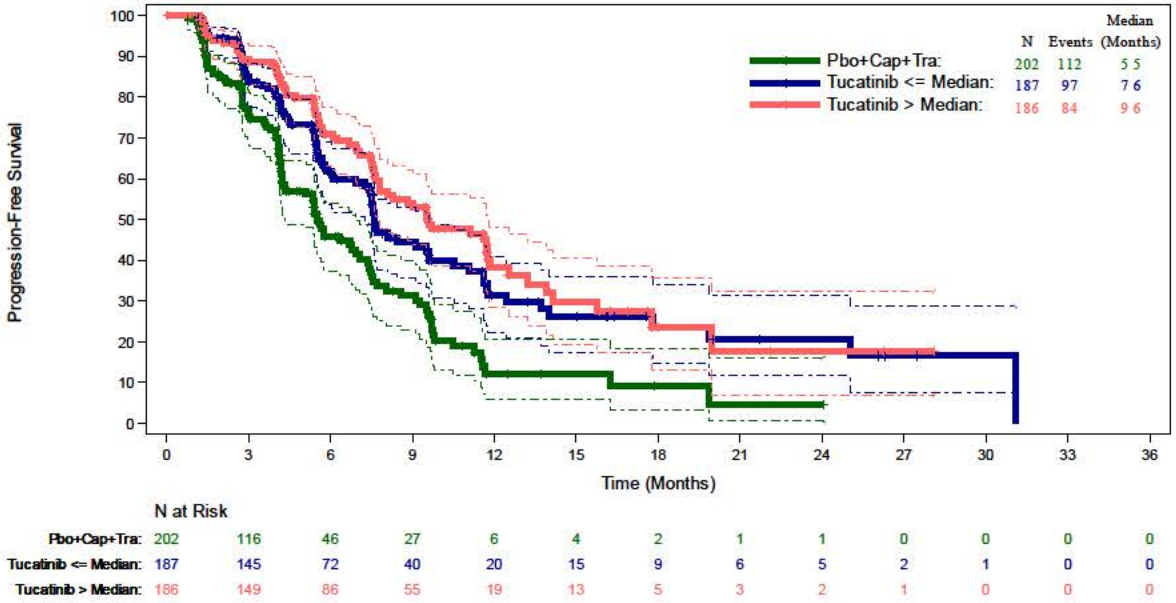
Subjects in Tuc+Cap+Tra arm categorized into quartiles based on the geometric means of tucatinib predose concentration on C2D1, C3D1, C4D1, C5D1, and C6D1, using the overall quartiles of the geometric means in Tuc+Cap+Tra arm. Intervals used for categorization are inclusive of all upper bounds and exclusive of the lower bound, with the exception of 0–1 (inclusive on both sides). Missing concentration values not included. BLOQ values imputed as 1/2 BLOQ (0.5 ng/mL) for the calculation of quartiles. Q1, Q2, and Q3 values of the geometric means of tucatinib trough concentration in Tuc+Cap+Tra are 53.3, 142.1 , and 268.8 ng/mL, respectively.

Regulatory Authorities Assessment:

The regulatory authorities agree with the applicant's assessment. In response to FDA's IR, the applicant conducted an alternative exploratory analysis with dichotomized C_{trough} using

median value, suggesting a slight trend toward improved PFS with increased C_{trough}. Both groups experienced a numerically higher median PFS versus the control arm (Figure 3).

Figure 3: Kaplan-Meier Plots for PFS per BICR by Median of Average Tucatinib Trough Concentrations



Source: Applicant's response to information request, eCTD sequence No 13

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. Tucatinib administered at 300 mg BID orally in combination with trastuzumab and capecitabine is appropriate for the treatment of patients with locally advanced unresectable or metastatic HER2+ BC, 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.

In the tucatinib development program, only the BID regimen has been evaluated in multiple dosing studies. The observed effective half-life of 9.55 hours and accumulation ratio of 1.72-fold support the BID regimen.

The proposed dosing regimen is further supported by the observed efficacy, safety, and PK data. (b) (4) AEs are effectively managed with dose modifications and supportive care as necessary. The relevant drug

interactions have been characterized, allowing for the development of labeling recommendations to avoid concomitant medications with a risk of pronounced DDI (Section 6.3.2.4).

Data:
Data supporting dosing in this patient population is in Sections 6.2.2.1 and 6.3.2.4 of the assessment aid.

Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's position that tucatinib at a dose of 300 mg BID achieves a positive benefit/risk profile in the general population. However, the regulatory authorities do not agree (b) (4) **Instead, the regulatory authorities recommend reducing the starting dose from 300 mg to 200 mg BID in patients with severe hepatic impairment. In addition, the regulatory authorities do not recommend the use of tucatinib in patients with severe renal impairment, as tucatinib is used as combination therapy with capecitabine, which is contraindicated in patients with severe renal impairment in the current label.**

The regulatory authorities concluded that tucatinib dose of 300 mg BID is acceptable for the general population based on the following information:

- **Favorable benefit-risk profile of tucatinib at a dose of 300 mg BID demonstrated in the pivotal HER2CLIMB study**

  Tucatinib 300 mg BID has shown improved PFS (median of 7.8 month for tucatinib arm vs 5.6 month for placebo arm, with HR of 0.544) for subjects with locally advanced unresectable or metastatic HER2+ breast cancer) and overall acceptable safety profile (Table 35, Table 36).

- **Acceptable rate of dose modifications in the pivotal HER2CLIMB study**

  The median relative dose intensity (RDI) for tucatinib was 93.6%, indicating most subjects were able to receive the intended dose of tucatinib over their treatment duration. Furthermore, after dose interruption, most subjects resumed tucatinib dosing at the same dose level. Only 5.7% of subjects in the treatment arm discontinued tucatinib due to an AE (Section 8.2.4).

- **Slight trend toward increased PFS with increased trough exposure on the tucatinib arm**

  Exploratory E-R analysis for efficacy based on subgroup analysis on PFS suggest a slight increase in PFS with increasing C_{trough}.

- **E-R relationship for safety was not identified; 350 mg dose level was shown to result in numerically higher grade ≥ 3 AEs as compared to 300 mg**

Exploratory E-R analysis for safety based on subgroup analysis on TEAEs did not identify correlation between C_{trough} and incidence of TEAEs (Table 5).

Table 5: Summary of TEAE by Quartiles of Average Tucatinib Ctrough in Study HER2CLIMB

	Tuc+Cap+Tra (N=385)				
	Tucatinib Q1 (N=94) n (%)	Tucatinib Q2 (N=93) n (%)	Tucatinib Q3 (N=93) n (%)	Tucatinib Q4 (N=93) n (%)	Pbo+Cap+Tra (N=197) n (%)
Any TEAE	93 (98.9)	93 (100)	93 (100)	93 (100)	191 (97.0)
≥Grade 3 TEAE	62 (66.0)	46 (49.5)	50 (53.8)	45 (48.4)	96 (48.7)
Any TE SAE	33 (35.1)	21 (22.6)	20 (21.5)	18 (19.4)	53 (26.9)
TEAE leading to death	2 (2.1)	2 (2.2)	1 (1.1)	0	6 (3.0)
Subjects who discontinued tucatinib/placebo due to TEAE	4 (4.3)	5 (5.4)	2 (2.2)	3 (3.2)	6 (3.0)
Subjects who discontinued capecitabine due to TEAE	14 (14.9)	8 (8.6)	3 (3.2)	8 (8.6)	18 (9.1)
Subjects who discontinued trastuzumab due to TEAE	4 (4.3)	6 (6.5)	2 (2.2)	1 (1.1)	5 (2.5)
Subjects with tucatinib/placebo dose reduction due to TEAE	36 (38.3)	16 (17.2)	12 (12.9)	14 (15.1)	21 (10.7)
Subjects with tucatinib/placebo dose hold due to TEAE	71 (75.5)	52 (55.9)	29 (31.2)	45 (48.4)	80 (40.6)

Source: Applicant's response to FDA's information request, eCTD sequence No. 22

In addition, exploratory E-R analysis for safety based on AUC and C_{max} with data from studies in subjects with cancer (studies 101, 004, 005) also suggest no evident association between tucatinib exposure (C_{max} and AUC) and Grade ≥3 TEAE, TE SAE (Table 6). This analysis does suggest correlation between C_{max} and AUC between dose modifications with the data from dose up to 800 mg BID dose. Given the dose reduction rate of 20% in the HER2CLIMB study, the regulatory authorities considered the selection of 300 mg dose acceptable.

Table 6: Subgroup Analysis with Safety Data from Studies 101, 004 and 005

	Tucatinib Exposure (Pooled from Studies 101, 004 and 005) N[a]=110			
	AUCtau		Cmax	
	n (%)	GM (CV%)	n (%)	GM (CV%)
Grade≥3 TEAE (Yes)	68 (61.8)	4804.3 (81.0)	68 (61.8)	586.0 (60.7)
Grade≥3 TEAE (No)	42 (38.2)	3678.4 (57.6)	42 (38.2)	451.1 (61.6)
TE SAE (Yes)	37 (33.6)	4620.5 (99.9)	37 (33.6)	554.9 (74.1)
TE SAE (No)	73 (66.4)	4202.4 (49.2)	73 (66.4)	518.2 (52.6)
TEAE leading to tucatinib dose reduction (Yes)	21 (19.1)	6141.5 (32.9)	21 (19.1)	801.8 (28.1)
TEAE leading to tucatinib dose reduction (No)	89 (80.9)	3997.1 (83.6)	89 (80.9)	481.0 (68.4)
TEAE leading to tucatinib dose hold (Yes)	46 (41.8)	5151.5 (44.2)	46 (41.8)	628.7 (45.4)
TEAE leading to tucatinib dose hold (No)	64 (58.2)	3834.9 (94.1)	64 (58.2)	469.2 (72.5)

Source: Applicant's response to FDA's information request, eCTD sequence No. 34.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

(b) (4)

Data:

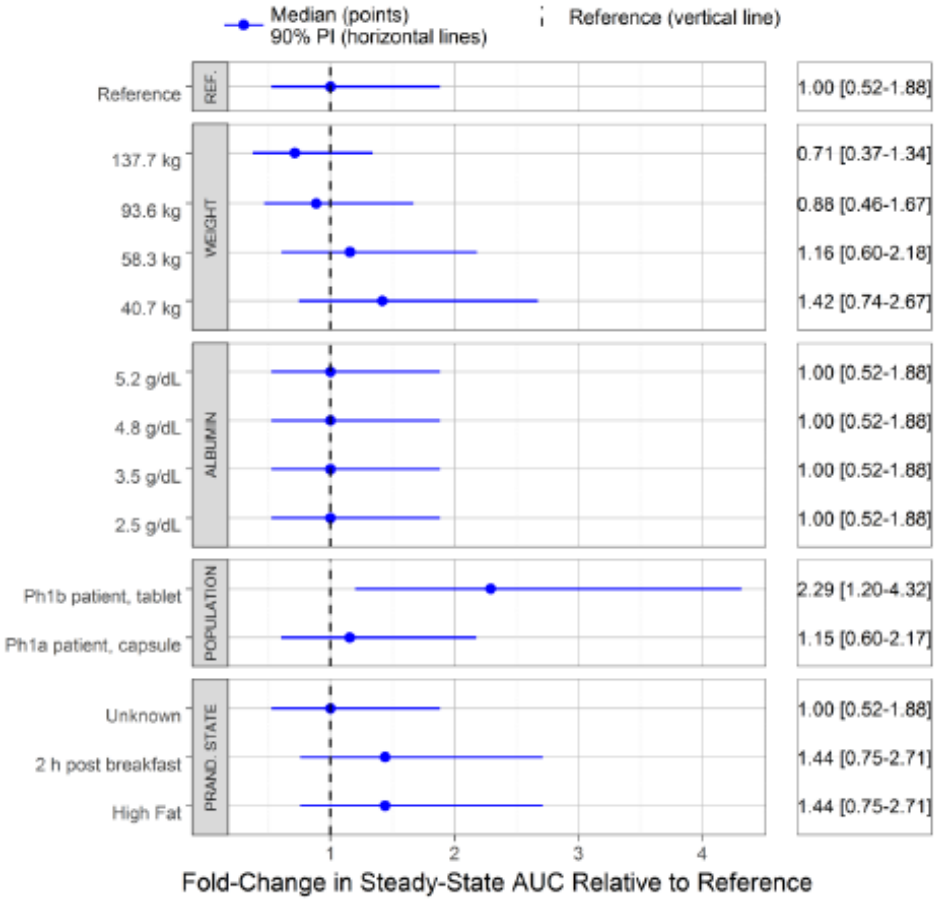
Data on tucatinib dosing or management based on intrinsic factors and in special populations are presented in Section 6.2.2.2 of the assessment aid.

Regulatory Authorities Assessment:

The regulatory authorities agree that no dose adjustment for tucatinib is required for subpopulations based on intrinsic factors such as age and race. Population PK analysis suggested higher tucatinib exposure (AUC and C_{max}) in subjects with mild/moderate hepatic dysfunction, decreased exposure with increasing body weight, and increased exposure with increasing age. However, the effect of aforementioned covariates on the tucatinib exposure is not considered clinically meaningful (Figure 4, population PK report, Appendix section 19.4), and dose adjustments based on those covariates are not necessary.

Reviewer's note: The effect of sex on tucatinib exposure is unknown as sex was confounded with combination therapy and study. Refer to section 6.2.2.2 and section 19.4 for more details.

Figure 4: Forest Plot of Covariate Effects on Tucatinib Steady-State AUC (Ratios)



In addition, clinical trial showing no clinical meaningful difference between Japanese and Caucasian population (Study SGNTUC-015, Figure 1).

The regulatory authorities' position on patients with hepatic impairment and renal impairment is as follows:

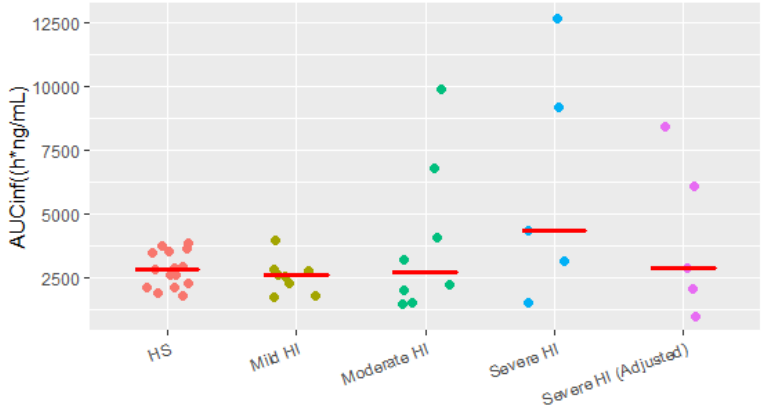
- **Patients with Hepatic Impairment:**

The regulatory authorities agree no dose adjustment for tucatinib is required for patient with mild or moderate hepatic impairment. However, the regulatory authorities recommend a starting dose reduction to 200 mg BID for patients with severe hepatic impairment, based on the following rationale:

- **The regulatory authorities noticed an approximate 1.6 fold increase in exposure and an increase between subject variability in subjects with severe hepatic impairment (Figure 5)**
- **Hepatotoxicity is one of treatment emergent adverse events (section 8.2.5.2). As a result, a conservative strategy is to match the exposure in severe hepatic impairment patients to the rest of cohorts, by reducing the dose to 200 mg BID in order to avoid**

the potential of worsening the hepatic impairment. The exposure observed in moderate hepatic impairment subjects and the exposure simulated (Figure 5, simulation base on the assumption of dose proportionality) in subjects with severe hepatic impairment are within the range of exposure observed with MTD dose of 600 mg BID with PIC formulation.

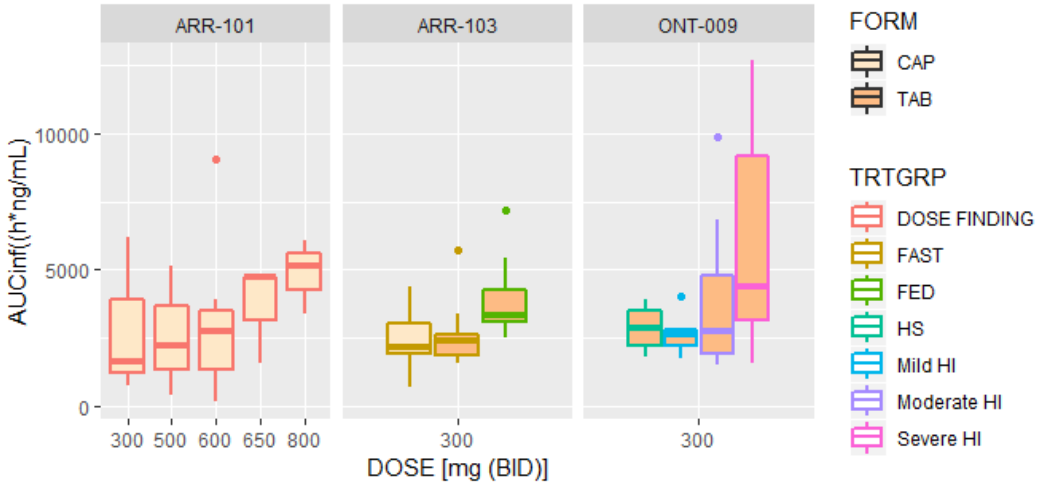
Figure 5: Tucatinib Exposure In Hepatic Impairment Subjects



Source: Reviewer's independent analysis

To evaluate the issue of high between-subject variability in moderate hepatic impairment cohort, the exposure was compared to exposure at MTD during dose finding stage and to that observed in the dedicated food effect study. The exposure range observed in the moderate hepatic impairment group was comparable to that achieved at MTD (600 mg BID, PIC formulation, Figure 6). As a result, the recommendation that no dose adjustment is required for patients with moderate hepatic impairment is acceptable.

Figure 6: AUC_{inf} distribution in Dosing Finding, Food Effect and Dedicated Hepatic Impairment Studies.



Source: Reviewer's independent analysis

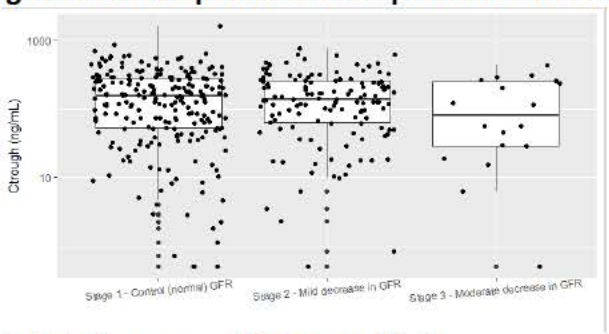
- **Patients with Renal Impairment:**

(b) (4)

The regulatory authorities do not recommend the use of tucatinib in combination with capecitabine and trastuzumab in patients with severe renal impairment, because capecitabine is contraindicated in patients with severe renal impairment and there is no clinical data for tucatinib from patients with severe renal impairment.

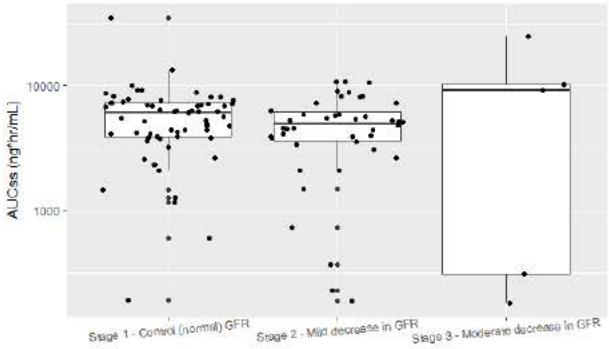
The regulatory authorities' position on no dose adjustment is required for patients with mild and moderate renal impairment is primary based on population PK and covariate analysis. In the population PK analysis with data from patients with mild and moderate renal impairment, creatinine clearance is not identified as clinical significant covariate during population PK and covariate analysis (normal (≥90 mL/min, n=206), mild dysfunction (60 - 89 mL/min, n=122), moderate dysfunction (30 - 59 mL/min, n=14), refer to detailed population PK analysis in Section. 19.40). Furthermore, no difference in tucatinib exposure was observed among renal function groups with pooled Phase I PK data (Figure 7and Figure 8).

Figure 7: Tucatinib Ctrough in Renal Impairment Groups from HER2CLIMB



Source: Reviewer's Independent Analysis; data source: eCTD Sequence NO. 34.

Figure 8: Tucatinib AUCs in Renal Impairment Groups from Phase I Trials



Source: Reviewer's Independent Analysis; data source: eCTD Sequence NO. 34.

Safety profiles among patients in renal impairment groups are evaluated by the regulatory authorities (Table 7). A numerical increase in the incidence of capecitabine dose modification and serious TEAE was observed in patients with moderate renal impairment. The addition of tucatinib to the capecitabine/trastuzumab did not shown increased incidence of AEs and dose modifications as compared to the placebo.

Table 7: Incidence of AEs and Dose Modifications in Renal Impairment Groups

Categories	Treatment ARM	Moderate Renal Impairment	Mild Renal Impairment	Normal Renal Function
Discontinuation of Tucatinib/Pbo	Pbo+Cap+Tra	0.09 (1 / 11)	0.06 (3 / 47)	0.01 (2 / 135)
	Tuc+Cap+Tra	0.05 (1 / 19)	0.07 (10 / 136)	0.05 (13 / 246)
Discontinuatn of apecitabine	Pbo+Cap+Tra	0.36 (4 / 11)	0.09 (4 / 47)	0.07 (10 / 135)
	Tuc+Cap+Tra	0.11 (2 / 19)	0.14 (19 / 136)	0.08 (20 / 246)
Dose Reduction of Tucatinib/Pbo	Pbo+Cap+Tra	0.36 (4 / 11)	0.06 (3 / 47)	0.07 (10 / 135)
	Tuc+Cap+Tra	0.26 (5 / 19)	0.18 (25 / 136)	0.17 (43 / 246)
Dose Reduction of Capecitabine	Pbo+Cap+Tra	0.64 (7 / 11)	0.36 (17 / 47)	0.38 (51 / 135)
	Tuc+Cap+Tra	0.53 (10 / 19)	0.61 (83 / 136)	0.53 (131 / 246)
Dose Interruption of Tucatinib/Pbo	Pbo+Cap+Tra	0.73 (8 / 11)	0.36 (17 / 47)	0.38 (51 / 135)
	Tuc+Cap+Tra	0.63 (12 / 19)	0.53 (72 / 136)	0.52 (127 / 246)
Dose Interruption of Capecitabine	Pbo+Cap+Tra	0.82 (9 / 11)	0.55 (26 / 47)	0.56 (75 / 135)
	Tuc+Cap+Tra	0.68 (13 / 19)	0.73 (99 / 136)	0.65 (160 / 246)
TEAE Toxicity Grade 3 +	Pbo+Cap+Tra	0.64 (7 / 11)	0.49 (23 / 47)	0.48 (65 / 135)
	Tuc+Cap+Tra	0.63 (12 / 19)	0.56 (76 / 136)	0.55 (135 / 246)
Serious TEAE	Pbo+Cap+Tra	0.45 (5 / 11)	0.26 (12 / 47)	0.27 (36 / 135)
	Tuc+Cap+Tra	0.26 (5 / 19)	0.25 (34 / 136)	0.26 (65 / 246)
Tucatinib/Pbo Withdrawn	Pbo+Cap+Tra	0.09 (1 / 11)	0.06 (3 / 47)	0.01 (2 / 135)
	Tuc+Cap+Tra	0.05 (1 / 19)	0.07 (9 / 136)	0.05 (13 / 246)
Capecitabine Withdrawn	Pbo+Cap+Tra	0.36 (4 / 11)	0.09 (4 / 47)	0.07 (10 / 135)
	Tuc+Cap+Tra	0.11 (2 / 19)	0.14 (19 / 136)	0.08 (20 / 246)
AE Toxicity Grade 5	Pbo+Cap+Tra	0.09 (1 / 11)	0.04 (2 / 47)	0.02 (3 / 135)
	Tuc+Cap+Tra	0 (0 / 19)	0.01 (2 / 136)	0.02 (6 / 246)

Source: Reviewer's independent analysis.

The current capecitabine label recommends reducing the dose of capecitabine by 25% in patients with moderate renal impairment and is contraindicated in patients with severe renal impairment. This recommendation is primarily based on the 85% and 258% higher exposure to FBAL (α-fluoro-β-alanine), and 47% and 71% higher exposure to 5'-DFUR in patients with moderate and severe renal impairment, respectively. An increase in incidence of serious AEs and grade 3+ AEs were observed in patients with severe renal impairment (PMID: 11935215). As a result, patients with severe renal impairment should avoid use of this drug combination as capecitabine is not indicated for such patients.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:
The effect of food on the PK of tucatinib was not clinically meaningful, thus, tucatinib may be administered without regard to a meal.

There are clinically relevant DDI with tucatinib, as described in the data section below. Tucatinib is a strong inhibitor of CYP3A and a weak inhibitor of P-gp. Tucatinib is predominantly eliminated by CYP2C8, and co-administration with strong CYP2C8 inhibitors strong CYP3A/CYP2C8 inducers should be avoided. Recommendations are presented in Table 8.

Table 8: Dosing Recommendations for Concomitant Use with Tucatinib

Drug Class	Dosing Recommendations
Strong CYP3A/CYP2C8 inducers	Avoid concomitant use
Strong CYP2C8 inhibitors	Avoid concomitant use
(b) (4) CYP3A substrate	Avoid concomitant use
(b) (4)	(b) (4)

Source: m2.7.2, Tables 49 and 50

Data:
Food-drug interaction: Following administration of a single dose of tucatinib in 11 subjects after a high-fat meal (~58% fat, 26% carbohydrate, and 16% protein), the mean AUC_{inf} increased by 1.5-fold, the T_{max} shifted from 1.7 to 4.0 hours, and C_{max} was unaltered. Relative to a fasted state, administration of tucatinib after a high fat meal did not meaningfully impact tucatinib. Tucatinib can be administered with or without a meal.

Drug-Drug interactions: The DDI study, ONT-380-012, assessed the effect of a CYP2C8 inhibitor (gemfibrozil), CYP3A inhibitor (itraconazole), and CYP2C8/3A inducer (rifampicin) on the PK of tucatinib. Strong inhibition of CYP2C8 by gemfibrozil increased tucatinib exposure by 3-fold. PBPK modeling indicated that CYP2C8 plays a major role (~75% of primary metabolism) in the elimination of tucatinib. Strong inhibition of CYP3A by itraconazole increased tucatinib exposure by just 1.3-fold, suggesting a minor role (~10% of primary metabolism) for CYP3A in the elimination of tucatinib. These observations were consistent with the observed 48% reduction in tucatinib exposure in response to the strong induction of CYP2C8/3A by rifampicin.

The DDI study, ONT-380-012, assessed the effect of tucatinib as the perpetrator on the PK of other drugs, including a CYP2C8 substrate (repaglinide), a CYP3A4 substrate (midazolam), and a P-gp substrate (digoxin). Tucatinib demonstrated strong inhibition of CYP3A, resulting in a 5.7-fold increase in midazolam exposure (AUC). Tucatinib demonstrated relatively weak inhibition of CYP2C8, resulting in a 1.7-fold increase in repaglinide exposure (AUC and C_{max}), and weak inhibition of P-gp, resulting in a 1.5-fold increase in AUC for digoxin exposure.

The DDI study, SGNTUC-020, assessed the effect of tucatinib as a perpetrator on the PK of metformin, a substrate of MATE1/2-K. Tucatinib demonstrated weak inhibition of the MATE1/2-K renal transporter resulting in a 1.4-fold increase in metformin exposure (AUC).

Regulatory Authorities Assessment:

Tucatinib as Victim

The regulatory authorities agree with Applicant's assessment on the food-drug interaction, based on the results from food effect study Array-380-103 showing that a high-fat meal increased the mean AUC_{inf} by 1.5-fold, shifted T_{max} from 1.7 to 4.0 hours, and did not affect C_{max} (Table 9).

Table 9: Statistical Analysis of Tucatinib PK Parameters (Food Effect)

	Treatment[a]	N	Geometric Mean	Ratio of Geometric Means (Fed/Fasted)	90% CI of Ratio	*P* Value[b]
AUC_{last} (hr*ng/mL)	C	11	3513.58	147.77	124.88–174.84	0.0018
	B	11	2377.82			
AUC_{inf} (hr*ng/mL)	C	11	3661.64	148.51	125.90–175.17	0.0015
	B	11	2465.60			
C_{max} (ng/mL)	C	11	478.93	107.73	85.36–135.96	0.5749
	B	11	444.57			

Abbreviation: CI, confidence interval.
[a] B = ARRY-380 tablets 300 mg, fasted.
C = ARRY-380 tablets 300 mg, fed.

Source: ARRAY-380-103, Table 9

The regulatory authorities agree with the Applicant's position that a proton pump inhibitor does not have a clinically meaningful effect on tucatinib PK, as suggested by results from study ARRAY-380-103 showing minor tucatinib exposure change by omeprazole 40 mg (Table 10).

Table 10: Statistical Analysis of Tucatinib PK Parameters (PPI Effect)

Formulation	Period	AUC_{inf} Ratio	AUC_{last} Ratio	C_{max} Ratio
Tucatinib tablets, fasted (N=11)	3	Reference	Reference	Reference
Omeprazole+Tucatinib tablets, fasted (N=9)	4	87.76 (74.00-104.09)	87.89 (73.79-104.70)	86.96 (66.80-113.21)

Source: ARRAY-380-103, Table 10

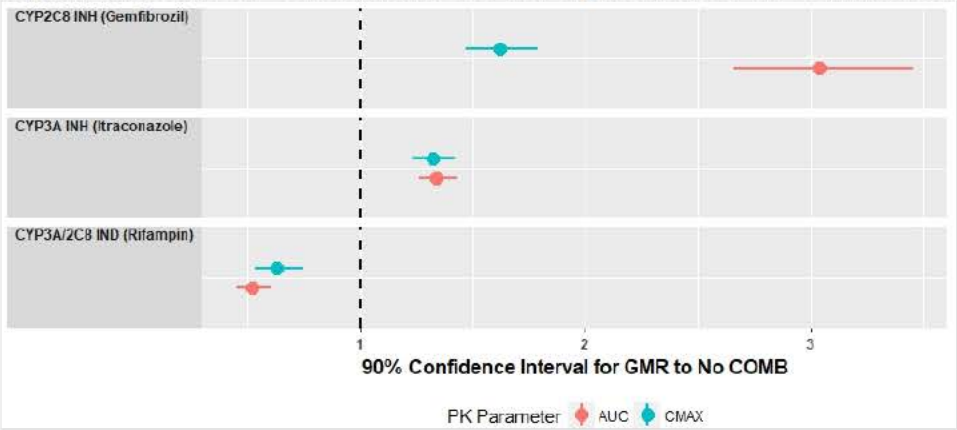
The regulatory authorities generally agree with the Applicant's assessment on the effect of CYP2C8 inhibitor (gemfibrozil), CYP3A inhibitor (itraconazole), and CYP2C8/3A inducer (rifampicin) on the PK of tucatinib (Figure 9).

In terms of a prevention/management strategy, the regulatory authorities agree with the applicant's proposal to avoid concomitant use of strong CYP2C8 inhibitor. In addition, the regulatory authorities recommend to reduce the starting dose of tucatinib to 100 mg BID when concomitant use of unavoidable, as the AUC was shown to increase by 3 fold when in combination with strong CYP2C8 inhibitor gemfibrozil, and dose proportionality has been

demonstrated below 300 mg BID dose (Figure 1).

The drug interaction for tucatinib with moderate CYP2C8 inhibitor has not been evaluated in the clinical trial. It is expected that the effect on the tucatinib by a moderate CYP2C8 inhibitor will be 1 to 3 fold, given that the strong CYP2C8 inhibitor gemfibrozil increased tucatinib AUC by 3 fold. As a result, FDA recommends increasing monitoring for adverse reactions with concomitant use of moderate CYP2C8 inhibitors.

Figure 9: Comparison between Concomitant Use of Perpetrators to No Combination



Source: Reviewer's Analysis

Reviewer's note: Refer to section 6.2.2.2 for more details with regard to the different opinions between FDA and HC on whether the concomitant use of moderate CYP2C8 should be avoided and whether an adjusted starting dose should be recommended.

The regulatory authorities agrees with the proposed recommendation to avoid concomitant use of strong CYP3A4 inducers or moderate CYP2C8 inducers. The regulatory authorities do not have a starting dose recommendation when concomitant use is unavoidable due to the following reasons:

1) **lack of adequate dose proportionality assessment beyond dose of 300 mg BID tablet**
2) **Insufficient clinical safety data at dose beyond 300 mg BID**
3) **Increase dose may lead to unacceptable AEs such as diarrhea and other GI toxicities**

As such, the regulatory authorities considered that the applicant's recommendation to avoid concomitant use of any strong CYP3A4 or moderate CYP2C8 inducer is acceptable.

Tucatinib as Perpentrator

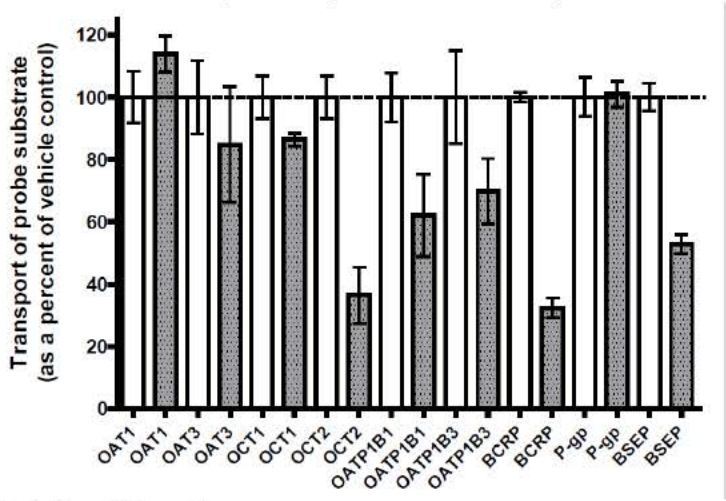
The regulatory authorities agree with the applicant's assessment on the DDI potential for tucatinib as the perpetrator on the PK of other drugs, including a CYP2C8 substrate (repaglinide), a CYP3A4 substrate (midazolam), a P-gp substrate (digoxin) and a substrate of MATE1/2-K (metformin). The regulatory authorities also agree with the applicant's position

on the prevention/management strategy: 1) recommend to avoid concomitant use of (b) (4) CYP3A substrates and 2) recommend to reduce the dose where minimal concentration change may lead to serious or life-threatening toxicities, (b) (4)

The regulatory authorities consider the likelihood of drug interaction with inhibitors of BCRP (tucatinib only), BSEP (tucatinib only), OAT2 (ONT-993 only) to be low.

The investigational drug has the potential to inhibit P-gp or BCRP in vivo if the investigational drug is administered orally, and the I_{gut} /IC_{50} or $K_i \geq 10$ where I_{gut} = dose of inhibitor/250 mL. Based on the in vitro drug interaction results (Figure 10), the 10 µM ONT-380 inhibited the transport of the probe substrates of BCRP and BSEP by 67.7% and 47.1%, respectively. For rough estimation, concentration of 10 µM can be roughly used as the estimation of IC_{50}. As a result, in our case, the 300 mg dose achieve {[300 mg/(480.52 g/mol)]/250 mL}/10 µM = 0.25 < 10. As such, the potential to inhibit P-gp or BCRP in vivo is considered low.

Figure 10: In vitro Inhibition of transporter by Tucatinib at 10 µm



Source: OPT-2014-020 Study Report, Figure 1

X	X
Huiming Xia	Pengfei Song
Primary Reviewer	Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:
An overview of clinical studies supporting the efficacy and safety of tucatinib is presented in Table 11.

Table 11: Clinical Studies Supporting the Efficacy and Safety of Tucatinib

Trial Identity [NCT No]	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Subjects Enrolled/ Dosed	Study Population	Centers/ Country
Controlled Study to Support Efficacy and Safety							
ONT-380-206 (HER2CLIMB) [NCT02614794]	Randomized, Double-Blinded, Placebo-Controlled, active comparator	Tuc (tablet) 300 mg or placebo PO BID, 21-day cycles Cape 1000 mg/m^2 PO BID for 14 days, 21-day cycles Tras by IV 8 mg/kg Day 1 Cycle 1, 6 mg/kg IV Day 1 subsequent cycles OR subcutaneous 600 mg every 21 days	Primary: PFS per BICR Alpha-controlled Secondary: OS, PFS in subjects with brain metastases per BICR, and confirmed ORR per BICR Other secondary: Confirmed ORR per investigator, DOR per BICR and investigator, CBR by BICR and investigator, PFS by investigator, safety and tolerability, PK, health economics	Study treatment until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.	612/601	Subjects with progressive locally advanced, unresectable or metastatic HER2+ BC and prior treatment with Tras, pertuzumab, and T-DM1, including subjects with history or presence of brain metastases not requiring immediate local therapy	155 sites in 15 countries (US, Canada, Denmark, Belgium, United Kingdom, France, Spain, Portugal, Germany, Switzer-land, Czech Republic, Austria, Italy, Israel, Australia)
Uncontrolled Studies to Support Efficacy and Safety							
ONT-380-005 [NCT02025192]	Phase 1b, Open-label, Uncontrolled	Tuc+Cape: Tuc (tablet) 300 mg or 350 mg PO BID and Cape 1000 mg/m^2 PO BID for 14 days; 21-day cycles Tuc+Tras: Tuc (tablet)	Primary: Incidence of AEs Secondary: PFS, ORR, DOR, CBR, DCR, BOR, incidence of isolated progression in brain), other safety endpoints, PK endpoints	Study treatment until unacceptable toxicity, disease progression,	60/60 Tuc+Cape: 11 Tuc+Tras: 22 Tuc+Cape+ Tras: 27	Subjects with progressive HER2+ MBC who have received prior treatment with	5 US sites

Trial Identity [NCT No]	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Subjects Enrolled/ Dosed	Study Population	Centers/ Country
		300 mg or 350 mg PO BID and Tras 8 mg/kg IV Day 1 Cycle 1, 6 mg/kg IV Day 1 subsequent cycles; 21-day cycles Tuc+Cape+Tras: Tuc (tablet) 300 mg PO BID, Cape 1000 mg/m^2 PO BID for 14 days, and Tras 8 mg/kg IV Day 1 Cycle 1, 6 mg/kg IV Day 1 subsequent 21-day cycles		withdrawal of consent, or study closure.		Tras and T-DM1 for metastatic disease	
ARRAY-380-101 [NCT00650572]	Phase 1, Open-label, Uncontrolled,	Tuc (PIC) Dose escalation: 25 to 800 mg PO BID 28-day cycles Expansion (at MTD): 600 mg PO BID, 28-day cycles	Dose-escalation Primary: Safety/tolerability, MTD per DLT Dose-escalation Secondary: PK, preliminary efficacy, biomarkers Expansion Phase Primary: Incidence/severity of AEs, clinical laboratory measurements, ECG, exposure-related PK, and biomarkers Expansion Phase Secondary: safety and efficacy, DOR, pharmacodynamics, PK, biomarkers	Study treatment until treatment discontinuation criteria were met	50/50 Dose-Escalation: 33/33 Expansion: 17/17	Subjects with advanced solid tumors	4 sites: 2 US 2 Canada
ONT-380-004 [NCT01983501]	Phase 1b, Open-label, Uncontrolled	Dose-escalation: Tuc (tablet) 300 mg or 350 mg PO BID and T-DM1 3.6 mg/kg IV on Day 1 of each	Primary: Incidence/severity of AEs and MTD/RP2D of Tuc + T-DM1 Secondary, Efficacy: PFS, ORR,	Study treatment until unacceptable toxicity,	57/57 Dose-Escalation: 15/15	Subjects with progressive HER2+ MBC and prior	11 sites: 7 US 4 Canada

Trial Identity [NCT No]	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Subjects Enrolled/ Dosed	Study Population	Centers/ Country
		21-day cycle Expansion (at MTD): Tuc (tablet) 300 mg BID and T-DM1 3.6 mg/kg IV on Day 1 of each 21-day cycle	DOR, CBR, DCR, BOR, and incidence of isolated CNS progression Secondary: Safety, tolerability, preliminary antitumor activity	disease progression, withdrawal of consent, or study closure.	Expansion: 42/42	treatment with Tras + taxane for metastatic disease	
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
ARRAY-380-102 [no NCT No.]	Open-label, Single dose,	300 mg Tuc PO in 4 formulations: 1) capsules (PIC) 2) micronized PIC 3) aqueous suspension 4) 20% Captisol® /apple juice solution	Primary: Plasma concentrations for ~24 hours following each of 4 oral formulations and noncompartmental PK parameters for Tuc and AR00440993. Relative bioavailability and intersubject and intrasubject variability in exposure-related PK parameters for all 4 formulations. Secondary: safety, tolerability and PK	Total 4 doses	14/14 for all parts	Healthy subjects	1 US site
ARRAY-380-103 [no NCT No.]	Open-label, Single-doses crossover	Tuc 300 mg PO in 4 treatment periods: 1) capsules (PIC; fasted) 2) tablets (fasted) 3) tablets (fed) 4) tablets (fasted) following omeprazole (40 mg) for 5 days	Primary: Plasma concentrations of Tuc and ONT-993 for ~24 hours for each single-dose. Non-compartmental PK parameters and relative bioavailability and inter- and intrasubject variability in Tuc exposure-related PK parameters for each of the 4 treatments Secondary: Safety and tolerability	Total 4 doses	12/12 1) 12 treated 2) 12 treated 3) 11 treated 4) 9 treated	Healthy subjects	1 US site

Trial Identity [NCT No]	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Subjects Enrolled/ Dosed	Study Population	Centers/ Country
ONT-380-008 [NCT03758339]	Phase 1, Open-label, Single Dose ADME	Single dose 300 mg of [^{14}C]-Tuc administered as an oral solution	Primary: PK for Tuc and ONT-993, and total radioactivity derived from the whole blood/plasma concentration-time profiles, from urine concentration-time profiles. PK for total radioactivity derived from feces.	Single dose	8/8	Healthy subjects	1 US site
ONT-380-009 [NCT03722823]	Open-label, Single-dose, Parallel-group	Tuc 300 mg PO	Primary: Hepatic function per PK from plasma concentration-time profiles Secondary: Safety and tolerability. PK endpoints of Tuc and ONT-993 derived from the plasma concentration-time profiles in subjects with impaired hepatic function compared to control subjects	Single dose	37/37 Hepatic function: Normal: 15 Mild impairment: 8 Moderate impairment: 8 Severe impairment: 6	Healthy and hepatically impaired subjects	4 US sites
ONT-380-011 [NCT03777761]	Phase 1, Randomized, Partially Double-blind, Placebo- and Positive-controlled	Treatment A: Tuc 300 mg PO Treatment B: Tuc matching placebo Treatment C: moxifloxacin 400 mg PO	Primary: Placebo-corrected change from baseline in QT Secondary: Change from baseline and placebo corrected change from baseline in HR, PR, and QRS. PK of Tuc and ONT-993 derived from the plasma concentration time profile. Safety/tolerability.	Total 9 doses	55/53	Healthy subjects	1 US site
ONT-380-012 [NCT03723395]	Phase 1, Open-label, Fixed-sequence,	Part A-E: Tuc 300 mg PO Part A: itraconazole 200 mg PO Part B: rifampin 600 mg PO	Primary: PK parameters derived from the plasma concentration time profiles Secondary: safety and	Total doses Part A: 2 Part B: 2 Part C: 2	116/114 Part A: 28/28 Part B: 28/28 Part C: 28/28	Healthy subjects	2 US sites

Trial Identity [NCT No]	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Subjects Enrolled/ Dosed	Study Population	Centers/ Country
	5-part, Drug-drug Interaction	Part C: gemfibrozil 600 mg PO Part D: repaglinide 0.5 mg PO, tolbutamide 500 mg, midazolam 2 mg PO Part E: digoxin 0.5 mg PO	tolerability Secondary, Parts D and E: PK parameters of Tuc and ONT-993 derived from the plasma concentration-time profiles	Part D: 20 (10 days BID) Part E: 28 (14 days BID)	Part D: 17/17 Part E: 15/13		
SGNTUC-015 [NCT03914755]	Open-label, Fixed-sequence	Tuc 50 mg PO Tuc 150 mg PO Tuc 300 mg PO	Primary: PK of Tuc and ONT-993 in Japanese and Caucasian subjects	Total 27 doses (13 days BID, 1 day QD)	36/36	Healthy subjects	1 US site
SGNTUC-020 [NCT03826602]	Phase 1, Open-label, Fixed-sequence Drug-drug Interaction	Tuc 300 mg PO metformin 850 mg PO iohexol 1500 mg IV	Primary: Effects of multiple BID oral doses of Tuc on the single-dose PK of metformin, a substrate of MATE1/2-K. Secondary: Safety and tolerability of combination, effects of Tuc on renal function Exploratory: PK of Tuc and ONT-993	Total 14 doses (7 days BID)	18/18	Healthy subjects	1 US site

Abbreviations: BC=Breast cancer; BICR=Blinded Independent Central Review; BID=twice daily; Cape=capecitabine; DLT=dose-limiting toxicity; HER2=human epidermal growth factor receptor-2; IV=intravenous; MTD=maximum tolerated dose; QD=once a day; PIC=powder in capsule; PK=pharmacokinetics; PO=oral; T-DM1=ado-trastuzumab emtansine; Tras=trastuzumab; Tuc=tucatinib
Source: M5.2

The Applicant's Position:

The primary evidence of efficacy and safety for tucatinib in combination with trastuzumab and capecitabine in HER2+ MBC is based on the ongoing, randomized, double-blind, placebo-controlled, active comparator, global HER2CLIMB study. This study enrolled 612 subjects at 155 sites globally. Subjects were randomized 2:1 to receive tucatinib or placebo in combination with trastuzumab and capecitabine.

Supportive evidence for efficacy and safety is provided by three studies:

- Study ONT-380-005, an ongoing study in subjects with progressive HER2+ MBC who have received prior treatments with both trastuzumab and T-DM1 for metastatic disease. Twenty-seven of the 60 subjects enrolled were assigned to the tucatinib triplet combination arm (tucatinib + trastuzumab + capecitabine).
- Study ONT-380-004, an ongoing study of tucatinib in combination with T-DM1 in subjects with HER2+ MBC. Of the 57 enrolled subjects at the data cutoff, 50 received tucatinib at 300 mg BID.
- Study ARRAY-380-101, a completed study of tucatinib monotherapy in subjects with advanced HER2+ solid tumors. Of the 50 subjects enrolled, 35 subjects had MBC and were efficacy-evaluable.

Supportive evidence for safety in healthy subjects is provided by eight additional studies: ARRAY-380-102, ARRAY-380-103, ONT-380-008, ONT-380-009, ONT-380-011, ONT-380-012, SGNTUC-015, and SGNTUC-020.

Regulatory Authorities Assessment:

The regulatory authorities agree with the applicant's description of the studies listed in Table 11 **above.**

The FDA's evaluation of efficacy and safety is primarily based on data from Study ONT-380-206 (HER2CLIMB). Study ONT-380-005 supplied secondary data to support efficacy and safety, and Study ARRAY 380-101 provided secondary data to support safety. The FDA's evaluation did not use data from Study ONT-380-004 because the treatment combination on this study was different than the treatment combination on HER2CLIMB. Data from this study would be less informative about the efficacy and safety profile of tucatinib in combination with trastuzumab and capecitabine.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Study HER2CLIMB (ONT-380-206)

Trial Design

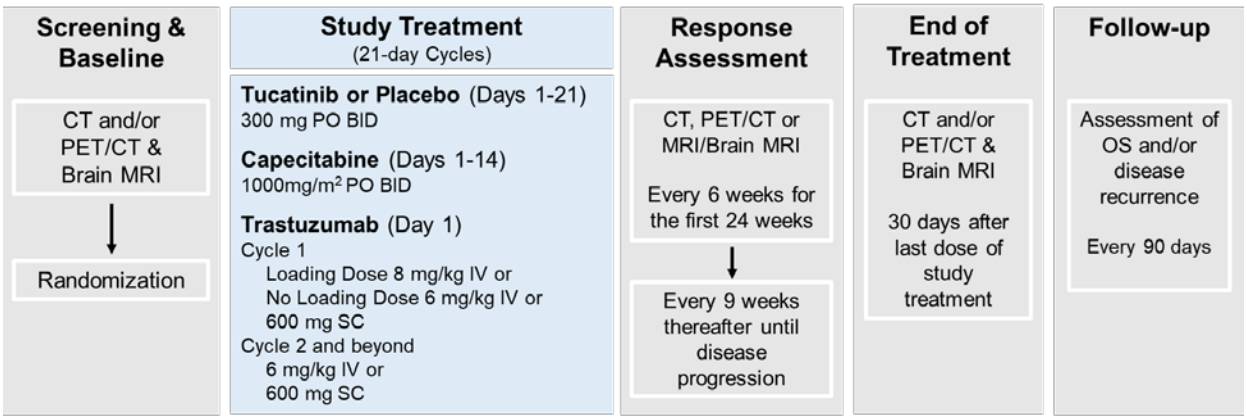
The Applicant's Description:

Basic Study Design:

HER2CLIMB is an ongoing randomized, double-blind, placebo-controlled, active comparator global study of tucatinib in combination with trastuzumab and capecitabine in subjects with locally advanced unresectable or metastatic HER2+ BC who had prior treatment with trastuzumab, pertuzumab, and T-DM1 in any setting. Subjects were randomized in a 2:1 ratio to receive tucatinib or placebo in combination with trastuzumab and capecitabine. The tucatinib arm includes subjects randomized to tucatinib + trastuzumab + capecitabine. The control arm includes subjects randomized to placebo + trastuzumab+ capecitabine.

Enrollment of ~600 subjects was planned for this study. Randomization was performed using a dynamic hierarchical randomization scheme and was stratified by presence or history of treated or untreated brain metastases (yes, no), ECOG PS (0, 1), and region of world (US, Canada, Rest of World). The study schema is shown in Figure 11.

Figure 11: HER2CLIMB Study Schema



Trial Location

This global study is being at 155 sites in 15 different countries, including the US, Canada, Denmark, Belgium, United Kingdom, France, Spain, Portugal, Germany, Switzerland, Czech Republic, Austria, Italy, Israel, and Australia.

Choice of Control Group

The control group is a placebo-controlled, active comparator arm. This provides a robust basis for determining the comparative effectiveness of tucatinib combined with trastuzumab and

capecitabine versus trastuzumab and capecitabine alone. All subjects received a treatment backbone trastuzumab plus capecitabine, a combination recommended in current treatment guidelines in this patient population for whom no single standard of care therapy exists. In the CEREBEL study, subjects treated with capecitabine plus trastuzumab had longer progression-free survival (PFS) compared with capecitabine plus lapatinib, another common therapeutic option in this setting. The CEREBEL study also demonstrated that the safety profile of trastuzumab plus capecitabine was similar to lapatinib plus capecitabine, but with a lower incidence of diarrhea, nausea, rash, and hyperbilirubinemia. The combination of trastuzumab plus capecitabine for the control treatment in this study allows a randomized, double-blinded study design for a more accurate assessment of the contribution of tucatinib to clinical outcomes. Furthermore, the use of capecitabine ensures that subjects in the control arm were treated with an active agent for central nervous system (CNS) disease.

Diagnostic Criteria

Subjects eligible for this study had progressive, locally advanced unresectable or metastatic HER2+ BC and prior treatment with 3 HER2-directed agents (trastuzumab, pertuzumab, and T-DM1 alone or in combination) in the neoadjuvant, adjuvant or metastatic setting. HER2 status was confirmed via centralized testing of archival tissue with an FDA-approved test prior to randomization.

Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Histologically confirmed HER2+ BC, with HER2+ defined by in situ hybridization, fluorescence in situ hybridization, or immunohistochemistry
- Previous treatment with trastuzumab, pertuzumab, and T-DM1
- Progression of locally advanced unresectable or MBC after last systemic therapy (as confirmed by investigator), or was intolerant of last systemic therapy
- Measurable or non-measurable disease assessable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- At least 18 years of age at time of consent
- ECOG PS 0 or 1

CNS Inclusion – Based on screening contrast brain magnetic resonance imaging (MRI), subjects must have had 1 of the following:

- No evidence of brain metastases
- Untreated brain metastases not needing immediate local therapy. For subjects with untreated CNS lesions >2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor was required prior to enrollment
- Previously treated brain metastases
- Brain metastases previously treated with local therapy was either stable since treatment or progressed since prior local CNS therapy, provided there was no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator

- Subjects treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during study screening were eligible to enroll if all of the following criteria were met:
    - Time since whole brain radiation therapy was ≥21 days prior to first dose of treatment, time since stereotactic radiosurgery was ≥7 days prior to first dose of treatment, or time since surgical resection was ≥28 days
    - Other sites of disease assessable by RECIST v1.1 were present

Key Exclusion Criteria – Previously treated with:

- Lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity)
- Neratinib, afatinib, or other investigational HER2/EGFR or HER2 TKI at any time
- Capecitabine (or other fluoropyrimidine [e.g., 5-fluorouracil]) for metastatic disease (except in cases where capecitabine was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity)

CNS Exclusion – Based on screening brain MRI, subjects must not have had:

- Any untreated brain lesions >2.0 cm in size, unless medical monitor approved enrollment
- Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg of dexamethasone (or equivalent). Subjects on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) were eligible with discussion and approval by the medical monitor
- Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may have posed risk to subject (e.g., brain stem lesions). Subjects who underwent local treatment for such lesions identified by screening contrast brain MRI may have still been eligible for the study based on criteria described under CNS inclusion criteria described above.
- Known or suspected leptomeningeal disease as documented by the investigator

Dose Selection

Selection of the tucatinib dosing regimen for HER2CLIMB was based on the recommended Phase 2 dose (RP2D) from the Phase 1b dose-escalation study of tucatinib in combination with trastuzumab and capecitabine in subjects with advanced HER2+ BC (ONT-380-005).

The dosing regimen of capecitabine in both arms of the HER2CLIMB study was 1000 mg/m^2 BID on Days 1 to 14 of a 21-day cycle, which was previously evaluated in ONT-380-005, and is the approved dose for combination therapy with lapatinib. Similar efficacy has been demonstrated with this dose (1000 mg/m^2) versus the single-agent approved dose of 1250 mg/m^2 BID, with less toxicity (Rossi 2007). For subjects in the control arm who received trastuzumab plus

capecitabine without tucatinib, this capecitabine dose was within the single-agent dose range (1000–1250 mg/m^2) recommended in the widely adopted national (US) guidelines for treatment of BC. When given as a single agent at the lower dose of 1000 mg/m^2, capecitabine has similar efficacy and higher overall dose intensity than 1250 mg/m^2 due to the frequent dose interruptions and reductions in subjects started at the higher dose (Bajetta 2005; Pivot 2015).

The dosing regimen of trastuzumab in HER2CLIMB was also evaluated in ONT-380-005, and is the commonly used single-agent dose in clinical practice when administered on a 21-day cycle.

Study Treatments

Tucatinib was given orally at 300 mg BID of each 21-day cycle. Trastuzumab was given IV or subcutaneously. IV trastuzumab was administered as an 8 mg/kg loading dose followed by 6 mg/kg every 21 days; the loading dose was not required for subjects who had received trastuzumab within 4 weeks of Cycle 1 Day 1. Subjects treated with subcutaneous trastuzumab receive 600 mg every 21 days. Capecitabine was given at 1000 mg/m^2 PO BID on Days 1–14 of each 21-day cycle.

Assignment to Treatment

Subjects were randomized 2:1 to the tucatinib or placebo arms using an Interactive Response Technology system. The randomization scheme controlled for the following stratification factors:

- Presence or history of treated or untreated brain metastases (Yes, No)
- ECOG PS (0, 1)
- Region of world (US, Canada, Rest of World)

The presence or history of brain metastases was based upon investigator assessment of screening MRI and clinical history. Patients with a documented history of prior brain metastases or unequivocal presence of brain lesions on screening MRI were considered a “Yes” for stratification purposes, and subsequent efficacy assessments. Patients with brain lesions of equivocal significance on screening MRI were also be considered a “Yes” for purposes of stratification and follow-up.

The dynamic hierarchical randomization scheme included specifications for a biased-coin assignment when the imbalance at a given hierarchical level (overall treatment group balance, then treatment group balance within each of the listed stratification factors) exceeded a specified threshold.

Blinding

This was a double-blind trial. Placebo tablets did not contain the active ingredient but were identical in appearance to active tablets to maintain blinding. Patients, site investigators and personnel, the sponsor (except for designated Clinical Drug Safety personnel), and all other individuals involved in monitoring, data management, and/or conduct of the trial were blinded. Subject level response was determined by a blinded independent central review (BICR).

Furthermore, the known safety profile of tucatinib at the time of the study had no remarkable features compared to placebo that might unblind the investigator to treatment assignment.

Unblinded data, including deaths, discontinuations, dose reductions, AEs (serious and non-serious) were monitored regularly by an independent data monitoring committee (IDMC). The independent data coordinating center preparing outputs for the IDMC was unblinded and had access to the overall randomization scheme.

Dose Modification, Dose Discontinuation

The HER2CLIMB protocol allowed for dose modifications of tucatinib, placebo and/or capecitabine. Dose re-escalation was not allowed. Dose modifications of tucatinib or placebo due to AEs are summarized in Table 12. Dose modifications of capecitabine are summarized in Table 13. There were no dose reductions permitted for trastuzumab.

Study drugs were discontinued if a delay >6 weeks was required due to treatment-related toxicity unless the delay was approved by the medical monitor. Subjects who discontinued either trastuzumab or capecitabine (but not both) were able to remain on study treatment. Subjects who discontinued tucatinib or placebo, or both trastuzumab and capecitabine were not allowed to remain on study treatment.

Table 12: Dose Modifications of Tucatinib or Placebo and Trastuzumab for Clinical Adverse Events Other Than Left Ventricular Dysfunction Related to Either Tucatinib or Placebo and/or Trastuzumab, or Hepatocellular Toxicity,* HER2CLIMB

Clinical Adverse Event	Related to Tucatinib or Placebo	Related to Trastuzumab
≥Grade 3 AEs other than Grade 3 fatigue lasting ≤3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities which return to ≤Grade 1 within 7 days	Hold until severity ≤Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤Grade 1 or pretreatment level. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITHOUT optimal use of anti-emetics or antidiarrheals	Hold until severity ≤Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITH optimal use of anti-emetics or antidiarrheals	Hold until severity ≤Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤Grade 1 or pretreatment level. Restart without dose reduction.
Grade 4 nausea, vomiting, or diarrhea regardless of use of anti-emetics or antidiarrheals	Do not administer until severity ≤Grade 1. Reduce to next lowest dose level.	Do not administer until severity ≤Grade 1. Restart without dose reduction.
Grade 3 rash WITHOUT optimal use of topical corticosteroids or anti-infectives	Hold until severity ≤Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.

Clinical Adverse Event	Related to Tucatinib or Placebo	Related to Trastuzumab
Grade 3 rash WITH optimal use of topical corticosteroids or anti-infectives	Hold until severity ≤Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤Grade 1 or pretreatment level. Restart without dose reduction.
Grade 4 rash regardless of use of topical corticosteroids or anti-infectives	Hold until severity ≤Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤Grade 1 or pretreatment level. Restart without dose reductions.

a. No dose modifications are required for alopecia
*Note that if the AE in question does not recover to the Grade required for restarting study medication as outlined in the table, the patient may need to discontinue the drug completely. Patients requiring a hold of tucatinib for > 6 weeks must discontinue study treatment, unless a longer delay is approved by the medical monitor
Source: Protocol, Table 7-2

Table 13: Dose Modification of Tucatinib or Placebo and Capecitabine for Liver Function Abnormalities, HER2CLIMB

Liver Function Abnormalities	Action for tucatinib or placebo, Regardless of Relationship to Drug	Capecitabine
Grade 2 elevation of ALT and/or AST (>3–≤5 x ULN)	Dose modification not required	If abnormalities are considered related to capecitabine, please follow guidelines. If abnormalities are not considered related to capecitabine, modifications are not mandated but may be made at the discretion of the investigator.
Grade 3 elevation of ALT and/or AST (>5–20 x ULN)	Hold until severity ≤Grade1. Restart at next lowest dose level	
Grade 4 elevation of ALT and/or AST (>20 x ULN)	Discontinue drug	
Elevation of ALT and/or AST (>3 x ULN) AND Bilirubin (>2 x ULN)	Discontinue drug	
Grade 2 elevation of bilirubin (>1.5–3 x ULN)	Hold until severity ≤Grade 1. Restart at same dose level	
Grade 3 elevation of bilirubin (>3– ≤10 x ULN)	Hold until severity ≤Grade 1. Restart at next lowest dose level	
Grade 4 elevation of bilirubin (>10 x ULN)	Discontinue drug	

ULN=upper limit of normal
Source: HER2CLIMB protocol, Table 7-4

Administrative Structure

An IDMC monitored subject safety of and provided an ongoing clinical assessment of the study treatment's evolving safety profile as the trial progressed. The IDMC reviewed blinded and unblinded data that included deaths, discontinuations, dose reductions, AE, events of special interest, and serious adverse events (SAEs). The IDMC met on a regular basis and made recommendations to the sponsor regarding the conduct of the trial. Real-time clinical management was on the basis of investigator assessment.

Procedures and Schedule

Imaging for response evaluation was performed at screening within 4 weeks before randomization, every 6 weeks (based on Cycle 1 Day 1) through Week 24, and then every 9 weeks through end of study drug treatment. Vital signs, samples for hematology, clinical

chemistry, liver functions, and PK tests were collected during screening, on Day 1 of every cycle until the end of treatment, and again at the 30-Day follow-up visit. AEs (per NCI CTCAE version 4.03) were recorded continuously until 30 days after the last dose of study treatment.

Dietary Restrictions/Instructions

There were no dietary restrictions. Tucatinib/placebo could be taken with or without a meal. Per Protocol, capecitabine was to be taken with a meal, based on prescribing information.

Concurrent Medications

Concomitant medications were listed and coded using the World Health Organization Drug Dictionary (WHODRUG) v Sep 2018 B2 and summarized for each treatment arm by preferred term (PT) and treatment arm using counts and percentages. Concomitant systemic corticosteroids, antidiarrheals as well as concomitant procedures were also summarized and listed.

To minimize the risk of potential DDI, concurrent use of strong CYP2C8 inhibitors or inducers, and concurrent use of strong CYP3A4 inhibitors or inducers with tucatinib, was not allowed. If the use of (b) (4) CYP3A substrates was unavoidable, dose reduction of CYP3A substrates (b) (4) as described in the medication's prescribing information was recommended.

Treatment Compliance

Compliance was assessed on a patient-by-patient basis. The pharmacist or designee recorded the number of tucatinib or placebo tablets dispensed to each individual patient and the number of tablets returned to the clinic at the end of each cycle. Data regarding the administration and dose of trastuzumab, as well as the number of tablets of capecitabine taken was also collected by the site after each cycle. Dose modifications and interruptions of any study drug were documented in the source documents and the electronic case report form (eCRF).

Rescue Medication

NA

Subject Completion, Discontinuation, or Withdrawal

Subjects continued to receive treatment until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. Subjects with isolated CNS progression per RECIST v1.1 were considered to have had a PFS event; however, these subjects had the option to continue study treatment after receiving local CNS directed therapy per investigator discretion until second disease progression with approval from the study medical monitor. If study treatment was discontinued for reasons other than disease progression per RECIST v1.1 or death, subjects continued follow-up with radiographic assessments. Computed tomography (CT), positron emission tomography (PET)/CT and/or MRI, and contrast brain MRI (only in subjects with known brain metastases) were performed approximately every 9 weeks until disease progression per RECIST v1.1, death, withdrawal of consent, or study closure (Figure 12). Review of medical records, public records, or public platforms may have been used to obtain long-term

follow-up information if reasonable efforts for contact or in-person assessment were unsuccessful.

Regulatory Authorities Assessment:

The regulatory authorities generally agree with the applicant's description of the HER2CLIMB protocol with the following clarifications and additions:

- **Confirmation of HER2+ status occurred at a central laboratory using ASCO/CAP guidelines.**
- **Patients received trastuzumab as per standard of care and could receive trastuzumab IV or subQ. Patients could receive trastuzumab or trastuzumab biosimilars.**
- **Diarrhea is an area of overlapping toxicity between tucatinib and capecitabine. The HER2CLIMB protocol did not require anti-diarrheal prophylaxis. If diarrhea occurred, attribution to either tucatinib or capecitabine or both, and dose interruption/modification of one or both drugs were at the investigator's discretion. The protocol also did not include treatment guidelines for management of diarrhea.**
- **Patients with brain metastases at baseline, including those with equivocal lesions, had an MRI-brain as part of their imaging assessment on the same schedule as the non-CNS re-staging scans (every 6 weeks for the first 24 weeks and then every 9 weeks until progression).**
- **Patients without brain metastases at baseline did not undergo MRI-brain as part of their re-staging imaging throughout the study. They had an MRI-brain at their end-of-treatment (EOT) visit.**
- **If a patient had isolated CNS progression, this was recorded as a progression event. The patient could remain on study treatment at discretion of the investigator following local therapy.**
- **There was no crossover from placebo to tucatinib permitted at progression.**

Study Endpoints

The Applicant's Description:

Primary Endpoint

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 occurs first.

Surrogate Endpoints

NA

Composite Endpoints
NA

Secondary and Other Relevant Endpoints
Alpha controlled key secondary endpoints:

- OS, defined as the time from randomization to death from any cause
- $PFS_{BrainMets}$ using RECIST v1.1 based on BICR
- ORR (RECIST v1.1), defined as the proportion of subjects with confirmed complete response (CR) or confirmed partial response (PR), as determined by BICR

Other secondary endpoints:

- PFS, defined as the time from randomization to investigator-assessed documented disease progression (per RECIST v1.1), or death from any cause, whichever occurs first
- ORR (RECIST v1.1) as determined by the investigator
- Duration of response (DOR) by RECIST v1.1 as determined by BICR
- DOR (RECIST v1.1) as determined by the investigator
- Clinical benefit rate (CBR) by RECIST v1.1 as determined by BICR
- CBR (RECIST v1.1) as determined by the investigator

Safety Endpoints:

- AEs
- Clinical laboratory assessments
- Vital signs and other relevant safety variables
- Frequency of dose holding, dose reductions, and discontinuations of capecitabine
- Frequency of dose holding, dose reductions, and discontinuations of tucatinib
- Frequency of dose holding and discontinuations of trastuzumab

Pharmacokinetic Endpoints:

- Plasma concentrations of tucatinib and metabolite ONT-993

Heath Economics and Outcomes:

- Cumulative incidence of health resource utilization (HRU), including length of stay, hospitalizations, and emergency department visits
- Health-related quality of life/health status (HRQoL), assessed using the European Quality of Life 5-Dimensional-5L (EQ-5D-5L) instrument

Regulatory Authorities Assessment:
The study endpoints described above by the applicant are acceptable. The primary endpoint is PFS as assessed by BICR using RECIST v1.1. The key secondary endpoints with alpha allocation are OS, $PFS_{brainmets}$ per BICR using RECIST v1.1, and ORR per BICR using RECIST v1.1.

$PFS_{brainmets}$ refers to PFS in the subgroup of patients with brain metastases at study baseline. The progression event could occur in the body or brain.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Statistical Analysis Plan (SAP), version 1, was finalized on 07 Aug 2019, prior to analysis of the primary endpoint. There were no amendments. Key analysis populations defined include:

- The intent-to-treat (ITT) analysis set: All randomized subjects.
- ITT-PFS: The first 480 subjects randomized (320 in the tucatinib arm; 160 in the control arm). This population was used to analyze the primary endpoint of PFS per BICR.
- ITT-OS: All randomized subjects (N=612; 410 in the tucatinib arm, 202 in the control arm). This population was used to analyze the key secondary endpoints of OS and confirmed ORR.
- ITT-$PFS_{BrainMets}$: All randomized subjects with target and/or non-target parenchymal brain lesions (per RECIST 1.1) at baseline or who have a history of brain metastases, or with brain lesions of equivocal significance on screening MRI based on screening data in the clinical database (N=291; 198 in the tucatinib arm, 93 in the control arm). This population was used to analyze the key secondary endpoint of $PFS_{BrainMets}$ per BICR.
- Safety: All randomized subjects who received at least 1 dose of study treatment (tucatinib/placebo, capecitabine, or trastuzumab) (N=601; 404 in the tucatinib arm, 197 in the control arm). Subjects were evaluated by the study treatment actually received. This population was used to analyze safety and HRU.

The primary analysis of PFS per BICR used the ITT-PFS population. The two treatment groups were compared using a stratified log-rank test controlling for the randomization stratification factors. The p-value for this test was calculated using a re-randomization procedure to reflect the dynamic hierarchical allocation scheme used in the study randomization. A Cox proportional-hazards model taking into account the stratification factors was used to estimate the treatment arm hazard ratio (HR) and its 95% CI. Kaplan-Meier estimates of the median and corresponding 95% CIs were also computed for each treatment arm. As pre-specified in the SAP, Canada and the US were combined for stratified and subgroup analyses due to the small proportion of subjects (6.7%) randomized from Canada.

To maintain strong control of the family-wise type I error rate at 0.05, PFS per BICR was tested at the 0.05 level first in the ITT-PFS population, and then the key secondary endpoints of OS and $PFS_{BrainMets}$ were tested using the group sequential Holm variable (GSHv) procedure, followed by the test of confirmed ORR.

The analysis of OS and $PFS_{BrainMets}$ was performed using the same statistical methods as the primary endpoint of PFS per BICR.

Comparison of confirmed ORR per BICR between the 2 treatment arms was performed using a 2-sided Cochran-Mantel-Haenszel (CMH) test controlling for study stratification factors.

Analyses of other secondary endpoints (PFS and ORR per investigator, DOR, and CBR) were not subject to formal type I error.

Subgroup analyses:
Subgroup analyses were performed for the primary endpoint and key secondary efficacy endpoints (OS and $PFS_{BrainMets}$) based on demographics and disease characteristics specified in the SAP. Subgroup analyses were conducted using conventional stratified log rank statistical methods (i.e., not rerandomization methods), as well as stratified Cox proportional hazards regression model.

Prespecified subgroups included:

- History of parenchymal brain metastases or brain metastases at baseline (Yes, No):
- Geographic Region: North America, Rest of World
- ECOG PS: 0 vs. 1 as recorded in eCRF at baseline
- Age: <65 vs. ≥65 years
- Race: White, African-American, others
- Hormone Receptor Status (Negative, Positive)

Interim Analyses: No interim analyses for efficacy were planned for the primary endpoint. One formal interim analysis for superiority was planned for the key secondary endpoint of $PFS_{BrainMets}$ and 2 formal interim analyses for superiority were planned for the key secondary endpoint of OS if the primary analysis for PFS was statistically significant.

Control of Multiplicity: To maintain strong control of the family-wise type I error rate at 0.05, the PFS was tested at the 0.05 level in the ITT-PFS set. If significant, the key secondary endpoints were to be tested using the GSHv procedure (Ye 2013).

The initial α split between $PFS_{BrainMets}$ and OS was α=0.03 and α=0.02, respectively. If one was statistically significant, the α would be passed to the other endpoint. Each endpoint will be tested at the interim analysis and again at the final analysis, if not rejected at the interim analysis.

Based on the observed information fraction of 71% and total alpha of 0.03, according to the Lan-DeMets O'Brien-Fleming spending function, the 2-sided alpha level at this interim analysis for $PFS_{BrainMets}$ was 0.0080. Similarly, based on the observed information fraction of 60% and total alpha of 0.05, the 2-sided alpha level at this interim analysis for OS was 0.0074.

If both $PFS_{BrainMets}$ and OS are statistically significant, ORR will be formally compared with the 2 arms using a 2-sided α of 0.05.

Missing Data: As described in the SAP, partial dates were imputed as the 15th day of the month if only the day was missing, or July 1st of the year if both day and month were missing.

Regulatory Authorities Assessment:

FDA reviewed the SAP prior to submission of this NDA and found it to be acceptable, but note the following:

1. **The sample size increased from 480 to 600 under protocol version 8 to enroll more patients with brain metastases, but the primary analysis of PFS by BICR is conducted in the first 480 patients. The applicant notes that this was to avoid potential bias from early progression events in the overall population as many patients may have short follow-up. FDA found this approach acceptable.**
2. **The stratified log-rank p-value for the primary and secondary analyses were calculated using a re-randomization procedure to account for the dynamic randomization scheme used. This was consistent with FDA recommendations.**
3. **The test for ORR by BICR was to be done in the subset of subjects with measurable disease in the ITT-OS population which may lead to imabalance in baseline characteristics between arms.**
4. **Although the subgroups were pre-specified, no alpha was allocated to any subgroup analyses other than the evaluation of the secondary endpoint $PFS_{BrainMets}$ in the ITT-$PFS_{BrainMets}$ population, which is a subset of the ITT-OS population.**
5. **Both the secondary endpoints (OS and $PFS_{BrainMets}$) were statistically significant at their first interim analyses, so no further formal testing for OS or $PFS_{BrainMets}$ is planned.**

Protocol Amendments

The Applicant's Description:

The original HER2CLIMB protocol from 11-Aug-2015, was amended 9 times during the study. All amendments were implemented prior to unblinding. None of the changes impacted trial integrity or interpretation of results. Table 14 describes the key changes in each amendment.

Table 14: Summary of Key Changes in Protocol Amendments, HER2CLIMB

Version	Date	Key Changes	Rationale
1	11-Aug-2015	Not Applicable (original protocol)	Not Applicable (original protocol)
2	25-Sep-2015	A planned interim analysis of PFS as the primary endpoint was removed.	FDA Recommendation that interim analysis may not provide an accurate or reproducible estimate of the treatment effect size to support demonstration of efficacy if using this trial to support drug approval.
3	26-Jan-2016	Inclusion criteria amended to remove the numerical size limits on certain CNS metastases.	To exclude high-risk patients who might be better served with local CNS therapy based on clinical scenario rather than specific numeric limits

Version	Date	Key Changes	Rationale
4	21-Mar-2016	Unblinding procedure in the event of a concerning drug related safety event was revised.	Removed requirement for investigators to obtain Sponsor's approval prior to unblinding in the case of concerning drug-related safety events.
5	06-Jul-2016	Assessment criteria used for the primary endpoint (PFS) was changed from RANO-BM to RECIST v1.1.	RECIST v1.1 is an established set of criteria with regulatory precedent, whereas RANO-BM is a newer less validated set of criteria.
6	29-Nov-2016	Increased number of subjects from ~180 to 480.	To provide greater statistical power to the primary and key secondary endpoints.
		Changed the order of hierarchical testing of the secondary endpoints PFS in subjects with brain metastases and OS.	To match the change in order of endpoints and based upon an in-person meeting with FDA
		Updated randomization stratification for region.	To reflect the change in number of regions updated in the same amendment.
		Cardiac failure added to the safety plan for cardiotoxicity.	To provide a safety plan to assess risk of cardiac failure
7	30-Aug-2017	Removed the requirement of prior therapy with a taxane.	The intent of requiring prior therapies with pertuzumab, trastuzumab, and T-DM1 was to ensure that patients had an opportunity to receive standard of care HER2 therapies prior to entering the study. While taxanes are usually given in combination with pertuzumab and trastuzumab, some patients have contraindications to taxanes and are given alternative cytotoxic or hormonal therapies instead in combination with pertuzumab, and these patients would now be eligible for the study.
		Added HRQoL and health economics objectives.	To allow assessment of HRQoL and health economics outcomes.
		Removed formal interim analyses of primary endpoint.	FDA recommendation that interim analysis may not provide an accurate or reproducible estimate of the treatment effect size to support demonstration of efficacy if using this trial to support drug approval
		Added a list of potential sensitive substrates for UGT1A1.	To enumerate sensitive substrates for UGT1A1 that should be used with caution with tucatinib.
8	12-Nov-2018	Seattle Genetics became the Study Sponsor	--
		Increased number of subjects from 480 to 600 and the length of enrollment to 48 months.	To increase the sample size to provide greater to power for the endpoints $PFS_{BrainMets}$ and OS.
		Amended the statistical testing from a hierarchical to parallel structure for key secondary endpoints of $PFS_{BrainMets}$ and OS.	Given the importance of OS as a clinical endpoint, this allowed for testing of OS in a parallel structure with the other key secondary endpoint, $PFS_{BrainMets}$
9	28-Feb-2019	Amended to reflect the potential interaction of tucatinib with sensitive CYP3A substrates.	Findings from study ONT-380-012 indicated a potential DDI. Prior to amendment, protocol stated sensitive CYP3A substrates enzymes should be used with caution in combination with tucatinib based on results from in vitro studies.

Version	Date	Key Changes	Rationale
10	25-Mar-2019	Updated the timing of the PFS primary analysis and second interim analysis of OS and $PFS_{BrainMets}$.	Based on an agreement with FDA, timing of the PFS primary endpoint analysis was changed to be based on number of events in the first 480 randomized subjects and complete enrollment of all subjects. Additional clarification added for timing of second interim analysis of OS if $PFS_{BrainMets}$ was statistically significant at first analysis and if OS was not statistically significant at first interim analysis.
		Added details to timing and scope of sponsor unblinding for primary analysis.	To account for updated timing of primary analysis of primary endpoint.
		Timing of PFS primary endpoint revised based on events and complete enrollment for the study.	Enrollment completion anticipated in close proximity to PFS events and enabled interim analysis of key secondary endpoints based on all enrolled subjects.

Source: ONT-380-206 CSR, Table 1

Regulatory Authorities Assessment:

The regulatory authorities generally agree with the applicant's description of key protocol changes. Additional key procotol revisions and protocol revisions related to sample size are detailed below.

- **The applicant considered patients with isolated CNS progression as having a progression event. However, patients could remain on study following local therapy in protocol amendment 5.**
- **The applicant expanded eligibility to all patients exposed to prior pertuzumab or T-DM1, regardless of the setting or timing, in protocol amendments 5 and 6.**
- **The applicant expanded eligibility to patients on low, stable doses of steroids in protocol amendments 5 and 6.**
- **The applicant changed the sample size from 180 patients to 480 patients to increase statistical power for the primary and key secondary endpoints in protocol amendment 6.**
- **The applicant added health-related quality of life (HRQoL) and health utilization secondary endpoints in protocol amendment 7, after 282 patients were already enrolled.**
- **The applicant Increased the sample size from 480 patients to 600 patients to increase statistical power for the key secondary endpoints in protocol amendment 8.**
- **The applicant clarified that the primary endpoint, PFS by BICR, would be assessed in the first 480 patients enrolled, not in all ~600 patients enrolled, in protocol amendment 10.**

8.1.2. Pivotal Study HER2CLIMB (ONT-380-206) Results

Compliance with Good Clinical Practices

Data:
Investigator site (Table 15) and service provider (Table 16) audits were conducted by Seattle Genetics, Inc. to assess compliance with Good Clinical Practice (GCP) and the HER2CLIMB protocol.

Table 15: Investigator Site Audits, HER2CLIMB

Investigator	Audit Location	Audit Dates
Rashmi Murthy, MD	UT-MD Anderson Cancer Center 1155 Pressler St. Houston, TX 77030	17 to 19-Oct-2017
Nancy Lin, MD	Dana-Farber Cancer Institute 450 Brookline, Avenue Boston, MA 02215	29 to 30-Nov-2017
Erika Hamilton, MD	Tennessee Oncology 250 25th Avenue N., Suite 100 Nashville, TN 37203	12 to 14-Dec-2017
Philippe Bedard, MD	University Health Network Princess Margaret Hospital 610 University Avenue Toronto, ON M5G 2M9	14 to 15-Dec-2017
Sara Hurvitz, MD	University of California, Los Angeles 10945 Le Conte Avenue, Suite 3360, Los Angeles, CA 90024	25 to 26-Jan-2018
Virginia Borges, MD	University of Colorado Cancer Center 12648 East 17th Avenue Aurora, CO 80045	28 Feb to 01-Mar-2018
Elisavet Paplomata, MD	Winship Cancer Institute of Emory University 1365 Clifton Road NE, Suite C3012, Atlanta, GA 30308	23 to 24-Apr-2018 03-May-2018
Jigarkumar Parikh, MD	Georgia Regents University Cancer Center, 1411 Laney Walker Blvd, AN-22001Augusta, GA 30912	22 to 23-May-2018
Tanya Wahl, MD	Swedish Cancer Center 1221 Madison Street Seattle, WA 98104	27 to 28-Aug-2018
Mafalda Oliveira, MD	Hospital General Vall D'Hebron Passeig Vall d'Hebron 119-129 Barcelona, 08100 (Spain)	25 to 27-Sep-2018
Tobias Arkenau, MD	Sarah Cannon Research Institute UK 93 Harley Street London W1G 6AD, UK	14 to 15-Jun-2018

Investigator	Audit Location	Audit Dates
Sara Giordano, MD	Medical University of South Carolina Hollings Cancer Center (HCC) 173 Ashley Avenue Room, BSB 104, MSC 635, Charleston, SC 29425	6 to 8-Jun-2018
Prof. Richard Greil, MD	Uniklinikum Salzburg, Landeskranhaus Universitatklinik fur Innere Medizin III der PMU, Mullner Hauptstrasse 48, A-5020 Salzburg, Austria	22 to 24-Oct-2018
Prof. Sherene Loi, MD	Peter MacCallum Cancer Centre Clinical Trials Unit 305 Gratten Street, Melbourne Victoria, 3000 Australia	19 to 21-Nov-2018
Vandana Abramson, MD	Vanderbilt University Medical Center Clinical Trials Shared Resources Office 3322 West End Avenue Nashville, TN 37203	18 to 19-Jun-2019
Lisa Carey, MD	University of North Carolina Chapel Hill Lineberger Comprehensive Cancer Center, 3909 Old Clinic Building Chapel Hill, NC 27599	30 Jul to 01-Aug-2019

Source: HER2CLIMB audit certificate

Table 16: Service Provider Audits, HER2CLIMB

Service Provider	Audit Location	Audit Dates
(b) (4)		

Service Provider	Audit Location	Audit Dates
(b) (4)		

CRO=Clinical Research Organization; eTMF=electronic trial master file; IDMC=Independent Monitoring Committee; IMP=Investigational Medicinal Products investigational medicinal product XXX; PK=Pharmacokinetics
Source: HER2CLIMB audit certificate

The Applicant's Position:
The study protocol was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (World Medical Association 2013). The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with the Declaration of Helsinki, the ICH GCP, and applicable regional regulations/guidelines.

Regulatory Authorities Assessment:
Theregulatory authorities agree with the applicant that this study followed the guidelines put forth in the Declaration of Helsinki and the ICH GCP.

Financial Disclosure

Data:
As defined in 21 the Code of Federal Regulations (CFR) 54.2b, 3 investigators had significant equity interests in Seattle Genetics (e.g., stock and/or stock options) that exceeded USD $50,000 in value.

(b) (6) was a Sub-Investigator at site (b) (6) when the study was sponsored by Cascadian and discontinued this role in (b) (6), prior to the transfer of study

sponsorship to Seattle Genetics following acquisition. [redacted] became an employee of Seattle Genetics in [redacted] and was granted stock options and/or restricted stock units that exceeded $50,000 in value. [redacted] did not work on the HER2CLIMB study as an employee of Seattle Genetics, and therefore Seattle Genetics has assessed that this arrangement did not introduce bias in the study results.

[redacted], a Principal Investigator at site [redacted], declared equity interest in Seattle Genetic that exceeded $50,000 in value on [redacted] collected at the time of the transfer of study sponsorship to Seattle Genetics following acquisition. There were only [redacted] subjects enrolled at this site out of a total enrollment of 612. Based on the minimal enrollm nt at this site, the blinded, randomized study design, and the use of BICR assessment of the primary and alpha-controlled secondary endpoints, Seattle Genetics assessed that [redacted] continued participation would not introduce bias in the study results.

[redacted] was a Sub-Investigator at site [redacted] when the study was sponsored by Cascadian and discontinued [redacted] role in [redacted], prior to the transfer of study sponsorship to Seattle Genetics following acquisition. [redacted] was granted stock options and/or restricted stock units that exceeded USD $50,000 in value as compensation for [redacted] has also received $126,307 in [redacted] fees and expenses. [redacted] did not work on the HER2CLIMB study as a [redacted] and therefore Seattle Genetics has assessed that this arrangement did not introduce bias in the study results.

No other listed investigators, BICR or IDMC members participating in the HER2CLIMB study reported having significant equity interest in Seattle Genetics.

The Applicant's Position:

The potential impact of financial interests is minimized by the blinded, multi-center study design, assessment of the primary endpoint of PFS by BICR [redacted] and safety review by the IDMC. Response assessments performed by [redacted] were made independently of Seattle Genetics, its designees, or any site involved in this clinical study.

Regulatory Authorities Assessment:

One sub-investigator under Cascadian Therapeutics, Inc. became an employee of Seattle Genetics, Inc. following study transfer to Seattle Genetics, Inc. Another sub-investigator under Cascadian Therapeutics, Inc. was a [redacted]. Both sub-investigators discontinued involvement with HER2CLIMB prior to study transfer to Seattle Genetics, Inc. and their sites were responsible for [redacted] patients

One principal investigator under both Cascadian Therapeutics, Inc. and Seattle Genetics, Inc. declared a significant equity interest (>$50,000) in Seattle Genetics following study transfer and continued study involvement. [redacted] site enrolled [redacted] patients.

The regulatory authorities agree with the applicant's assessment that these financial interests are unlikely to impact the results of HER2CLIMB. This is based on the small number of patients impacted, the nature of the study (blinded and randomized), and the use of a BICR to evaluate the primary endpoint.

Patient Disposition

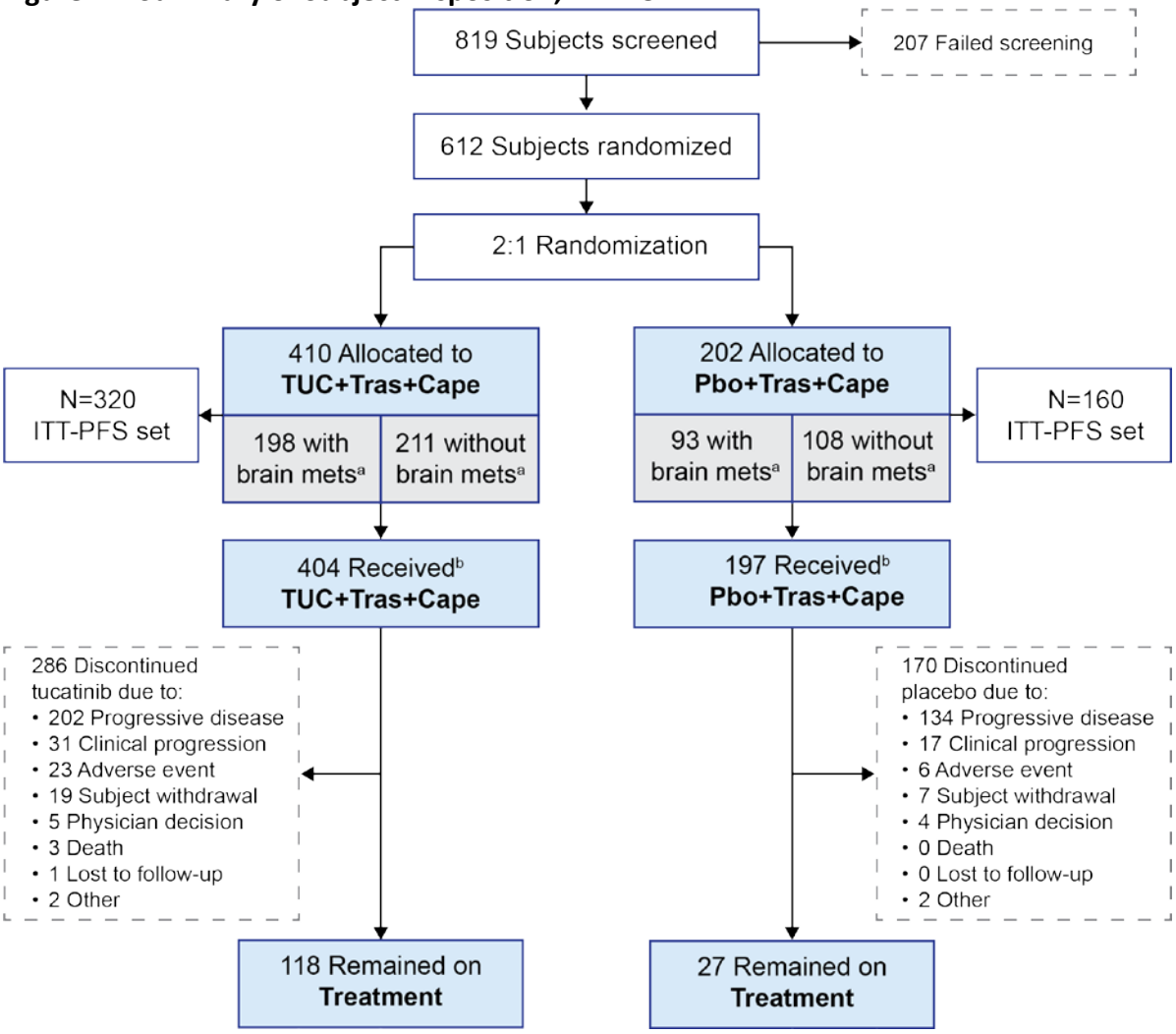
Data:

A summary of the subject disposition presented in Figure 12. A total of 612 subjects were randomized from 23-Feb-2016 to 03-May-2019 in a 2:1 ratio to receive tucatinib or placebo in combination with trastuzumab and capecitabine. As of the as 04-Sep-2019 data cutoff, 145 subjects (24%) remain on study treatment; 118 (29%) in the tucatinib arm, and 27 (13%) in the control arm.

The main reason for subject discontinuation from study treatment was progressive disease (PD) (202 subjects [70.6%] in the tucatinib arm and 134 subjects [78.8%] in the control arm). A total of 148 subjects (36.1%) in the tucatinib arm and 85 subjects (42.1%) in the control arm entered long term follow-up.

Of the 410 subjects on the tucatinib arm, 35.1% are off study versus 44.6% of the 202 subjects on the control arm; the primary reason for study discontinuation on both arms was death. The majority of deaths in both treatment arms were due to PD.

Figure 12: Summary of Subject Disposition, HER2CLIMB



Cape=capecitabine; Tras=trastuzumab; Tuc=tucatinib
a. Based on EDC data. Two subjects did not have baseline brain MRI; 1 randomized to tucatinib arm, 1 to control arm
b. Six subjects randomized to the tucatinib arm and 5 subjects to the control arm did not receive study treatment.
Source: ONT-380-206 CSR Table 14.1.1.2, Table 14.1.1.3, Table 14.1.1.1, Table 14.1.1.5

The Applicant's Position:

The majority of subjects in both arms of the study are off treatment. This is an indication of the maturity of the data. Among subjects off-study, disease progression was the most common cause. Study discontinuation due to AE, consent withdrawal, or loss to follow-up occurred infrequently.

Regulatory Authorities Assessment:

The regulatory authorities agree with the applicant's assessment of patient disposition on HER2CLIMB. In response to an Information Request (IR) dated February 18, 2020, the

applicant provided additional information about patients with isolated CNS progression on HER2CLIMB. There were 48 patients (11.7%) on the tucatinib arm and 36 patients (17.8%) on the control arm with isolated CNS progression. On the tucatinib arm, 21 patients continued treatment after isolated CNS progression, and on the control arm, 9 patients continued treatment.

Presence or history of treated or untreated brain metastases, ECOG performance status, and region of world were stratification factors in this study. Stratification factor values were collected at randomization using a randomization and trial supply management (RTSM) system and at baseline using the electronic data capture (EDC) system. The RTSM values were used for the stratified randomization to treatment arms and the primary and secondary analyses were also conducted using these values. The EDC values at baseline were used to define patient subgroups. We note that concordance was high between the values collected by the two systems (RTSM and EDC): 89.7% for ECOG performance status and 97.5% for presence or history of treated or untreated brain metastases as shown in Table 17. There were no discordances for region of world.

Table 17: Concordance between RTSM and EDC values for Stratification Factors

Presence or history of treated or untreated brain metastases					ECOG Performance Status				
	Tuc+Cap+Tras (N=410)		Pbo+Cap+Tras (N=202)			Tuc+Cap+Tras (N=410)		Pbo+Cap+Tras (N=202)	
At Randomization by RTSM, n (%)					At Randomization by RTSM, n (%)				
At Baseline by EDC, n (%)	Yes	No	Yes	No	At Baseline by EDC, n (%)	0	1	0	1
Yes	196 (47.8)	2 (0.5)	91 (45.0)	2 (1.0)	0	183 (44.6)	21 (5.1)	88 (43.6)	6 (3.0)
No	3 (0.7)	208 (50.7)	6 (3.0)	102 (50.5)	1	23 (5.6)	183 (44.6)	13 (6.4)	95 (47.0)
Not Available	0	1 (0.2)	0	1 (0.5)					

Source: ADaM dataset ADSL

Protocol Violations/Deviations

Data:
Table 18 summarizes important protocol deviations (IPD).

Table 18: Summary of Protocol Deviations, HER2CLIMB

	Tuc+Cap+Tras (N=410) n (%)	Pbo+Cap+Tras (N=202) n (%)	Total (N=612) n (%)
Any important protocol deviations[a]	14 (3.4)	7 (3.5)	21 (3.4)
Reason for important protocol deviation[a]			
Other[b]	5 (1.2)	3 (1.5)	8 (1.3)
Dosing	4 (1.0)	0	4 (0.7)
Inclusion/exclusion criterion	1 (0.2)	3 (1.5)	4 (0.7)
Missed assessment	3 (0.7)	0	3 (0.5)
Safety	0	2 (1.0)	2 (0.3)
Consent (ICF)	1 (0.2)	0	1 (0.2)

Cap=capecitabine; Tras=trastuzumab; Tuc=tucatinib
a. Subjects may have been counted in more than one category
b. Other category includes deviations related to blinding, prohibited therapy, and treatment continuation after progression.
Source: ONT-380-206 CSR Table 15

The Applicant's Position:
HER2CLIMB had a low number of IPDs overall and the proportion was similar on both treatment arms. None were assessed as having a meaningful impact on the overall study outcome.

Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's assessment that there were few major protocol deviations- 3.4% of patients on the tucatinib arm and 3.5% of patients on the placebo arm. These were unlikely to affect the study results.

Table of Demographic Characteristics

Data:
Demographics and subject characteristics in all analysis populations of HER2CLIMB are summarized in Table 19.

Table 19: Demographics, HER2CLIMB

	ITT-PFS		ITT-OS		$ITT\text{-}PFS_{BrainMets}$	
	Tuc+Cap+Tra (N=320) n (%)	Pbo+Cap+Tra (N=160) n (%)	Tuc+Cap+Tra (N=410) n (%)	Pbo+Cap+Tra (N=202) n (%)	Tuc+Cap+Tra (N=198) n (%)	Pbo+Cap+Tra (N=93) n (%)
Age (years)						
Mean (STD)	53.9 (11.3)	54.0 (10.4)	53.8 (11.3)	54.2 (10.4)	52.4 (11.5)	52.8 (11.1)
Median	54	54	55	54	53	52

	ITT-PFS		ITT-OS		ITT-PFS$_{BrainMets}$	
	Tuc+Cap+Tra (N=320) n (%)	Pbo+Cap+Tra (N=160) n (%)	Tuc+Cap+Tra (N=410) n (%)	Pbo+Cap+Tra (N=202) n (%)	Tuc+Cap+Tra (N=198) n (%)	Pbo+Cap+Tra (N=93) n (%)
Min, Max	27, 80	25, 78	22, 80	25, 82	22, 75	25, 75
Age Category, n (%)						
<65 years	252 (78.8)	132 (82.5)	328 (80.0)	168 (83.2)	166 (83.8)	77 (82.8)
≥65 years	68 (21.3)	28 (17.5)	82 (20.0)	34 (16.8)	32 (16.2)	16 (17.2)
Sex, n (%)						
Male	3 (0.9)	2 (1.3)	3 (0.7)	2 (1.0)	1 (0.5)	1 (1.1)
Female	317 (99.1)	158 (98.8)	407 (99.3)	200 (99.0)	197 (99.5)	92 (98.9)
Race, n (%)						
Asian	17 (5.3)	3 (1.9)	18 (4.4)	5 (2.5)	9 (4.5)	3 (3.2)
Black or African American	30 (9.4)	13 (8.1)	41 (10.0)	14 (6.9)	17 (8.6)	9 (9.7)
White	225 (70.3)	125 (78.1)	287 (70.0)	157 (77.7)	132 (66.7)	67 (72.0)
Other	3 (0.9)	2 (1.3)	3 (0.7)	2 (1.0)	3 (1.5)	1 (1.1)
Unknown	45 (14.1)	17 (10.6)	61 (14.9)	24 (11.9)	37 (18.7)	13 (14.0)
Ethnicity, n (%)						
Hispanic or Latino	31 (9.7)	11 (6.9)	37 (9.0)	14 (6.9)	16 (8.1)	9 (9.7)
Not Hispanic or Latino	283 (88.4)	146 (91.3)	362 (88.3)	184 (91.1)	176 (88.9)	84 (90.3)
Not Available	6 (1.9)	3 (1.9)	11 (2.7)	4 (2.0)	6 (3.0)	0
ECOG PS[a], n (%)						
0	159 (49.7)	76 (47.5)	204 (49.8)	94 (46.5)	92 (46.5)	38 (40.9)
1	161 (50.3)	84 (52.5)	206 (50.2)	108 (53.5)	106 (53.5)	55 (59.1)

Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib

a The last non-missing value before or on the day of first dose of study treatment

Source: ONT-380-206 CSR Table 3, Table 7, Table 10

The Applicant's Position:

Demographics and subject characteristics were similar across the ITT-PFS, ITT-OS, and ITT-PFS$_{BrainMets}$ populations, as well as between arms in each population.

The ITT-PFS population was used to analyze the primary endpoint of PFS per BICR and includes the first 480 subjects randomized in the trial (320 tucatinib arm, 160 control arm). The ITT–OS population (all randomized subjects) was used to analyze the key secondary endpoints of OS and confirmed ORR. The ITT-PFS$_{BrainMets}$ population (all randomized subjects with brain metastases) was used to analyze the key secondary endpoint of PFS$_{BrainMets}$ per BICR.

Overall, the demographics and baseline characteristics of subjects in HER2CLIMB are representative of the HER2+ MBC patient population at large and are well balanced between treatment arms.

Regulatory Authorities Assessment:

The applicant defined three analysis populations: ITT-PFS, ITT-OS, and ITT-PFS$_{brainmets}$, to assess the primary and key secondary endpoints in HER2CLIMB. The ITT-PFS populaton included the first 480 patients randomized, the ITT-OS population included all 612 patients randomized, and the ITT-PFSbrainmets population included the 291 patients with brain metastases at baseline.

The regulatory authorities generally agree with the applicant's presentation of demographic information. In the overall ITT population (n=612), the median age was 54, and there was representation of patients younger than 45 years (22%, 134/612) and older than 65 years (19%, 116/612). Male patients were eligible for HER2CLIMB and 5 male patients enrolled onto this study.

Only patients with an ECOG performance status of 0 or 1 were eligible for HER2CLIMB. The regulatory authorities note that there may be patients, including those with brain metastases, who were candidates for systemic therapy and would have met all other eligibility criteria for HER2CLIMB but had an ECOG performance status of 2. Demographics and ECOG PS were similar among the three analysis populations: ITT-PFS, ITT-OS, and ITT-PFSbrainmets, and balanced between the two treatment arms.

The study population was generally representative of a US population and 54% (331/612) of patients were enrolled in the US.

Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Baseline disease characteristics in all analysis populations of HER2CLIMB are summarized in Table 20. In the ITT-PFS$_{BrainMets}$ population (N=291), 77.3% of subjects were previously treated for brain metastases; 70.1% received prior radiotherapy and 15.8% had prior surgery. At study entry, 17.9% of subjects in ITT-PFS$_{BrainMets}$ population had radiographically progressing brain metastases since their most recent surgery/radiotherapy and 59.5% had radiographically stable brain metastases since their most recent surgery/radiotherapy.

Table 20: Baseline Disease Characteristics and Disease History, HER2CLIMB

	ITT-PFS		ITT-OS		ITT-PFS$_{BrainMets}$	
	Tuc+Cap+Tra (N=320) n (%)	Pbo+Cap+Tra (N=160) n (%)	Tuc+Cap+Tra (N=410) n (%)	Pbo+Cap+Tra (N=202) n (%)	Tuc+Cap+Tra (N=198) n (%)	Pbo+Cap+Tra (N=93) n (%)
Time from primary diagnosis to randomization (months)[a]						
n	305	155	391	196	190	91
Mean (STD)	59.3 (43.1)	66.3 (58.8)	59.9 (43.0)	69.3 (62.2)	62.3 (44.1)	66.7 (50.1)
Median	46.6	44.9	48.1	49.1	49.7	50.2
Min, Max	7.0, 234.8	8.7, 397.8	7.0, 234.8	8.7, 447.5	12.0, 234.8	10.7, 238.9
Time from metastatic diagnosis to randomization (months)[a]						
n	315	157	405	199	197	93
Mean (STD)	31.6 (26.1)	34.8 (28.6)	32.5 (25.5)	34.6 (27.5)	34.0 (24.6)	37.6 (30.8)
Median	25.8	27.7	26.5	27.7	28.6	30.4
Min. Max	0.3, 181.3	1.5, 194.1	0.3, 181.3	1.0, 194.1	3.9, 181.3	1.5, 194.1
Disease status at study entry, n (%)						
Locally advanced unresectable	1 (0.3)	2 (1.3)	1 (0.2)	2 (1.0)	0	0
Metastatic	319 (99.7)	158 (98.8)	409 (99.8)	200 (99.0)	198 (100)	93 (100)
Histology, n (%)						
Estrogen/progesterone receptor status						
Positive for either or both	190 (59.4)	99 (61.9)	243 (59.3)	127 (62.9)	107 (54.0)	59 (63.4)
Negative for both	126 (39.4)	61 (38.1)	161 (39.3)	75 (37.1)	88 (44.4)	34 (36.6)
Other	4 (1.3)	0	6 (1.5)	0	3 (1.5)	0
Stage at initial diagnosis, n (%)						
Stage 0-III	211 (65.9)	90 (56.2)	264 (64.4)	122 (60.4)	118 (59.6)	53 (57.0)
Stage IV	108 (33.8)	67 (41.9)	143 (34.9)	77 (38.1)	77 (38.9)	39 (41.9)
Not available	1 (0.3)	3 (1.9)	3 (0.7)	3 (1.5)	3 (1.5)	1 (1.1)
Sites of Metastatic Disease n (%)						
Subjects with history of brain metastases or brain metastases at study entry	148 (46.3)	71 (44.4)	198 (48.3)	93 (46.0)	198 (100)	93 (100)
Subjects with non-CNS metastatic	313 (97.8)	157 (98.1)	402 (98.0)	198 (98.0)	192 (97.0)	90 (96.8)

	ITT-PFS		ITT-OS		ITT-PFS$_{BrainMets}$	
	Tuc+Cap+Tra (N=320) n (%)	Pbo+Cap+Tra (N=160) n (%)	Tuc+Cap+Tra (N=410) n (%)	Pbo+Cap+Tra (N=202) n (%)	Tuc+Cap+Tra (N=198) n (%)	Pbo+Cap+Tra (N=93) n (%)
disease at study entry						
Lung	160 (50.0)	82 (51.3)	200 (48.8)	100 (49.5)	104 (52.5)	53 (57.0)
Liver	108 (33.8)	64 (40.0)	137 (33.4)	78 (38.6)	75 (37.9)	40 (43.0)
Bone	178 (55.6)	85 (53.1)	223 (54.4)	111 (55.0)	125 (63.1)	59 (63.4)
Skin or Subcutaneous	49 (15.3)	23 (14.4)	58 (14.1)	28 (13.9)	21 (10.6)	8 (8.6)
Number of prior lines of systemic therapy						
Mean (STD)	4.1 (1.8)	4.0 (2.0)	4.0 (1.8)	4.0 (1.9)	—[b]	—
Median	4.0	4.0	4.0	4.0	—	—
Min, Max	2, 14	2, 17	2, 14	2, 17	—	—
Number of prior lines of systemic therapy in the metastatic setting						
Mean (STD)	3.1 (1.6)	3.1 (1.7)	3.1 (1.6)	3.0 (1.6)	—	—
Median	3.0	3.0	3.0	3.0	—	—
Min, Max	1, 14	1, 13	1, 14	1, 13	—	—

Cap=capecitabine; Pbo=placebo; Tra=trastuzumab; Tuc=tucatinib
a. Missing day is imputed with Day 15 of that month
b. Not analyzed.
Source(s): m2.7.3, Table 5, Table 9, ONT-380-206 CSR, Table 8, Table 14.1.2.2b

The Applicant's Position:

Overall, the ITT-PFS, ITT-OS, and ITT-PFS$_{BrainMets}$ populations had similar baseline characteristics that were balanced between treatment arms and representative of patients with locally advanced unresectable or metastatic HER2+ BC. Subjects were heavily-pretreated, with a median of 4 prior lines of systemic therapy in the ITT-PFS and ITT-OS populations; 3 of these prior lines of therapy were in the metastatic setting. Approximately half of the subjects had a history of brain metastases and a majority had lung or liver metastases, disease characteristics that are associated with poorer prognosis. Of note, HER2CLIMB included subjects with untreated new or progressing brain metastases who are generally excluded from clinical trials.

Regulatory Authorities Assessment:

In the overall ITT-OS population (n=612 patients), 60.5% had hormone receptor (HR)-positive disease, 35.9% had de novo metastatic disease, and 69.3% had visceral metastases. Patients had received a median of 3 (range 1-14) prior lines of systemic therapy in the metastatic setting.

The regulatory authorities agree with applicant that baseline disease characteristics were similar among the three analysis populations: ITT-PFS, ITT-OS, and ITT-PFS$_{brainmets}$, and well-balanced between the two treatment arms. More details on patients with brain metastases and prior therapies are below.

Brain metastases

Patients with breast cancer and brain metastases represent a substantial unmet medical need. In HER2CLIMB, patients with brain metastases made up 48% (291/612) of the overall ITT-OS population.The regulatory authorities disagree with the applicant's description of the different brain metastases subpopulations within the ITT-PFS$_{brainmets}$ group. The applicant submitted an information amendment on February 6, 2020 stating that a programming error led to misclassification of some patients with "treated and stable" and "treated and progressing" brain metastases at baseline. The FDA verified the new frequencies of patients in the baseline brain metastases subcategories and that the programming error did not impact other data.

The corrected information is that of the 291 patients in the PFS$_{brainmets}$ population, 40% had previously treated and stable brain metastases, 37% had previously treated and progressing brain metastases, and 23% had untreated brain metastases. Patients with different brain metastases characteristics were balanced between the two arms as seen in Table 21 below.

Table 21: Baseline brain metastases classification, ITT-PFS$_{brainmets}$, HER2CLIMB

	ITT-PFS$_{brainmets}$	
	Tuc+Cap+Tra (N=198) n (%)	**Pbo+Cap+Tra (N=93) n (%)**
Baseline brain metastases		
Treated and stable	80 (40)	37 (39)
Treated and progressing	74 (37)	34 (36)
Untreated	44 (22)	22 (23)

Source: Information amendment from applicant dated February 6, 2020 and ADaM dataset CNSDATE

Patients with equivocal brain lesions made up a small percentage of the overall PFS$_{brainmets}$ group. There were 24/198 (12%) patients with equivocal brain lesions on the tucatinib arm, and 15/93 (16%) patients on the placebo arm.

Prior trastuzumab, pertuzumab, and T-DM1

The HER2CLIMB eligibility criteria specified that patients must be exposed to trastuzumab, pertuzumab, and T-DM1, but this could be in any treatment setting. Table 22 shows the

treatment setting(s) for prior trastuzumab, pertuzumab, and T-DM1 by treatment arm in the ITT-OS populaton.The two treatment arms were well-balanced in terms of these prior therapies.

Table 22: Treatment settings for prior trastuzumab, pertuzumab, and T-DM1, ITT-OS, HER2CLIMB

	ITT-OS	
	Tuc+Cap+Tra (N=410) n (%)	**Pbo+Cap+Tra (N=202) n (%)**
Prior trastuzumab		
(Neo) adjuvant only	25 (6)	14 (7)
Metastatic only	233 (57)	129 (64)
Both neoadjuvant and metastatic	152 (37)	59 (29)
Prior pertuzumab		
(Neo) adjuvant only	38 (9)	16 (8)
Metastatic only	354 (86)	174 (86)
Both neoadjuvant and metastatic	17 (4)	11 (5)
Prior T-DM1		
(Neo) adjuvant only	3 (0.7)	4 (2.0)
Metastatic only	406 (99)	198 (98)
Both neoadjuvant and metastatic	1 (0.2)	0 (0)

Source: Table 14.1.2.4a in the ONT-380-206 Clinical Study Report and ADaM dataset ADCM

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
NA

The Applicant's Position:
Compliance was assessed on a subject-by-subject basis. To ensure treatment compliance according to the study protocol, dose modifications were documented in the clinical database and concomitant therapies were recorded in the eCRF. Following analysis of the primary endpoint, additional post-hoc analyses on concomitant antidiarrheal medication were performed across treatment arms. Details on treatment-emergent diarrhea and concomitant antidiarrheal medication is presented in Section 8.2.8 of the assessment aid.

Regulatory Authorities Assessment:
Permissible concomitant medications included gonadotropin releasing hormone (GnRH) agonists. These are not standard-of-care in a HER2-positive breast cancer population, and only 19 patients [16 in the tucatinib arm and 3 in the placebo arm] were exposed to these on

study. The regulatory authorities do not believe that this would have an impact on study results.

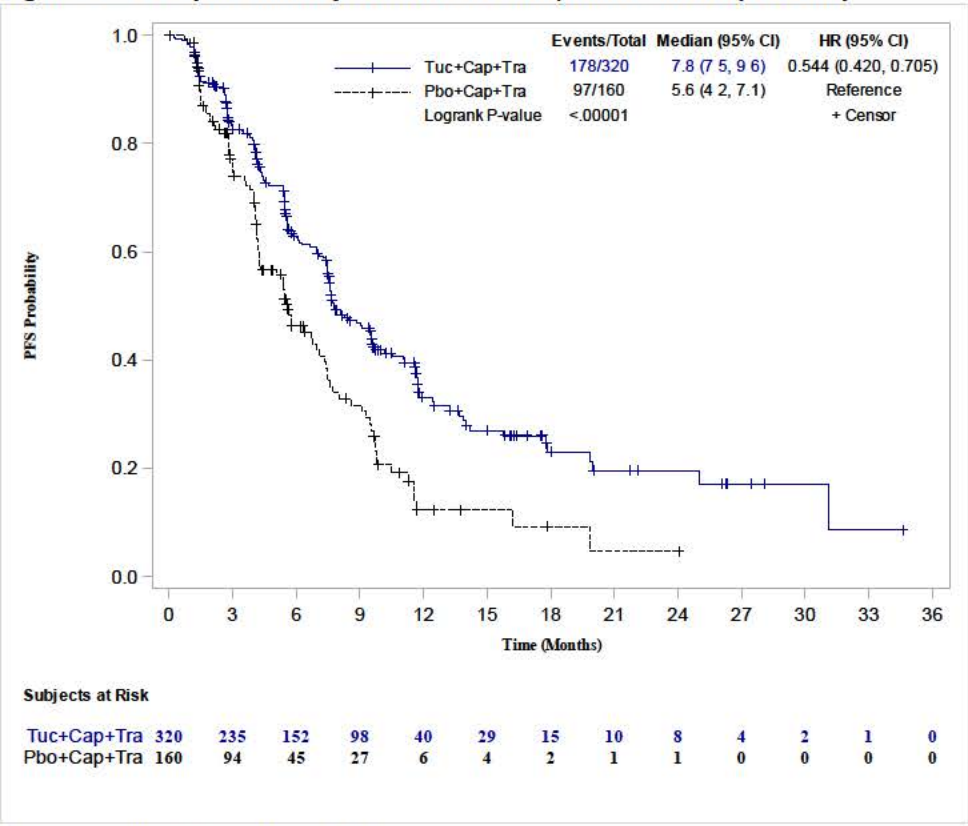
Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

PFS: With a median PFS follow-up of 10.4 months, the primary analysis of PFS per BICR demonstrated that treatment in the tucatinib arm was superior to the control arm, with a 46% reduction in the risk of disease progression or death (Figure 13). The median PFS per BICR was 7.8 months in the tucatinib arm versus 5.6 months in the control arm (Figure 13).

The 6-month PFS was 62.9% (95%CI: 56.9%, 68.4%) for the tucatinib arm and 46.3% (95% CI: 37.2%, 54.9%) for the control arm; the 12-month PFS was 33.1% (95% CI: 26.6, 39.7) versus 12.3% (95% CI: 6.0, 20.9). Results in the control arm were consistent with other contemporary trials in similar clinical settings using chemotherapy with trastuzumab or lapatinib (Rugo 2019; Saura 2019), even with a large proportion of subjects with brain metastases enrolled.

Figure 13: PFS per BICR by Treatment Arm, HER2CLIMB (ITT-PFS)

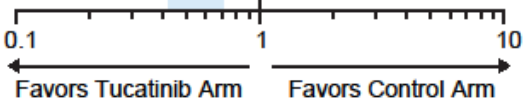


Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
Hazard Ratio computed with Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization. Two-sided p-value based on stratified log rank test and re-randomization procedure (Rosenberger and Lachin, 2002).
Source: ONT-380-206 CSR, Figure 3

Subgroup Analysis of PFS: All subgroups analyzed, including hormone receptor status, demonstrated a PFS benefit consistent with the overall outcome (Figure 14).

Figure 14: PFS per BICR by Subgroups, HER2CLIMB (ITT-PFS)

Subgroups	Event / N (%)	HR (95% CI)
ITT-PFS Population	**275/480**	**0.54 (0.42, 0.71)**
Age		
≥65 years	51/96	0.59 (0.32, 1.11)
<65 years	224/384	0.54 (0.41, 0.72)
Race		
White	206/350	0.57 (0.42, 0.77)
Non-white	69/130	0.46 (0.26, 0.82)
Hormone receptor status		
ER and/or PR positive	172/289	0.58 (0.42, 0.80)
ER and PR negative	103/191	0.54 (0.34, 0.86)
Baseline brain metastasis		
Y	138/219	0.46 (0.31, 0.67)
N	136/260	0.62 (0.44, 0.89)
ECOG		
0	134/235	0.56 (0.39, 0.80)
1	141/245	0.55 (0.38, 0.79)
Region		
North America	179/307	0.57 (0.41, 0.78)
Rest of world	96/173	0.51 (0.33, 0.79)



Hazard ratio was calculated from cox regression model considering stratified factors from randomization.
'Race Non-White' included subjects with race other than white.
'Hormone receptor status: ER and PR negative' included subjects without positive estrogen or positive progesterone.
'Baseline brain metastasis: Y' included subjects with a history of brain metastases or presence of brain metastases or brain lesions of equivocal significance on screening MRI per EDC data.
Source: ONT-380-206 CSR, Figure 4

Sensitivity analysis of PFS: The results of all sensitivity analyses were consistent and supported the primary analysis of PFS per BICR (Table 23).

Table 23: Summary of PFS Sensitivity Analysis per BICR, HER2CLIMB (ITT-PFS)

	Nominal Stratified Log-rank P-value[a, c]	Stratified Hazard Ratio[b, c] (95% CI)
Sensitivity analysis 1	<0.00001	0.538 (0.418, 0.694)
Sensitivity analysis 2	<0.00001	0.543 (0.422, 0.700)

	Nominal Stratified Log-rank P-value[a, c]	Stratified Hazard Ratio[b, c] (95% CI)
Sensitivity analysis 3	<0.00001	0.555 (0.435, 0.708)
Sensitivity analysis 4	<0.00001	0.550 (0.426, 0.710)

Sensitivity Analysis 1 (Ignoring Missing Assessments of Disease Response): analysis for PFS time by ignoring the missing assessments in censoring scheme.
Sensitivity Analysis 2 (Imputing Missing Assessments of Disease Response): analysis for PFS time by imputing event time for subjects with missing assessments in censoring scheme.
Sensitivity Analysis 3 (New therapy before PD/death): analysis for PFS time by ignoring all new anti-cancer therapies in censoring scheme.
Sensitivity Analysis 4 (New radiation before PD/death): analysis for PFS time by ignoring all new radiation therapies in censoring scheme.

a Two-sided P-value calculated from stratified log-rank test and re-randomization procedure. (Rosenberger and Lachin, 2002).
b Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra.
c Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization.

Source: m5.3.5.1, CSR ONT-380-206, Table 14.2.1.4

PFS Without the Re-randomization Procedure: A planned sensitivity analysis of PFS was performed using a stratified, log-rank test based on the actual randomized treatment assignment (i.e., without the re-randomization procedure) for the first 480 randomized subjects. This analysis was consistent with the primary efficacy analysis using the re-randomization procedure (nominal P<0.00001).

The Applicant's Position:
The primary analysis of PFS per BICR demonstrated that the addition of tucatinib to the combination of trastuzumab and capecitabine resulted in a statistically significant and clinically meaningful improvement of PFS overall. All subgroups analyzed demonstrated a PFS benefit consistent with the overall outcome, with similar HR across subgroups. Sensitivity analyses were supportive, including analyses based on investigator assessment.

Regulatory Authorities Assessment:
The regulatory authorities generally agree with the results and conclusions presented in this section. The primary analysis of PFS by BICR showed a statistically significant improvement favoring the tucatinib arm with a two-sided re-randomization p-value less than the pre-specified alpha level of 0.05. The stratified PFS hazard ratio was 0.54 (95% CI: 0.42, 0.71). As a sensitivity analysis, FDA calculated the stratified PFS hazard ratio based on actual stratification values collected by EDC at baseline, which was consistent at 0.55 (95% CI: 0.42, 0.71). The unstratified hazard ratio was 0.59 (95% CI: 0.46, 0.75), which was also fairly consistent.

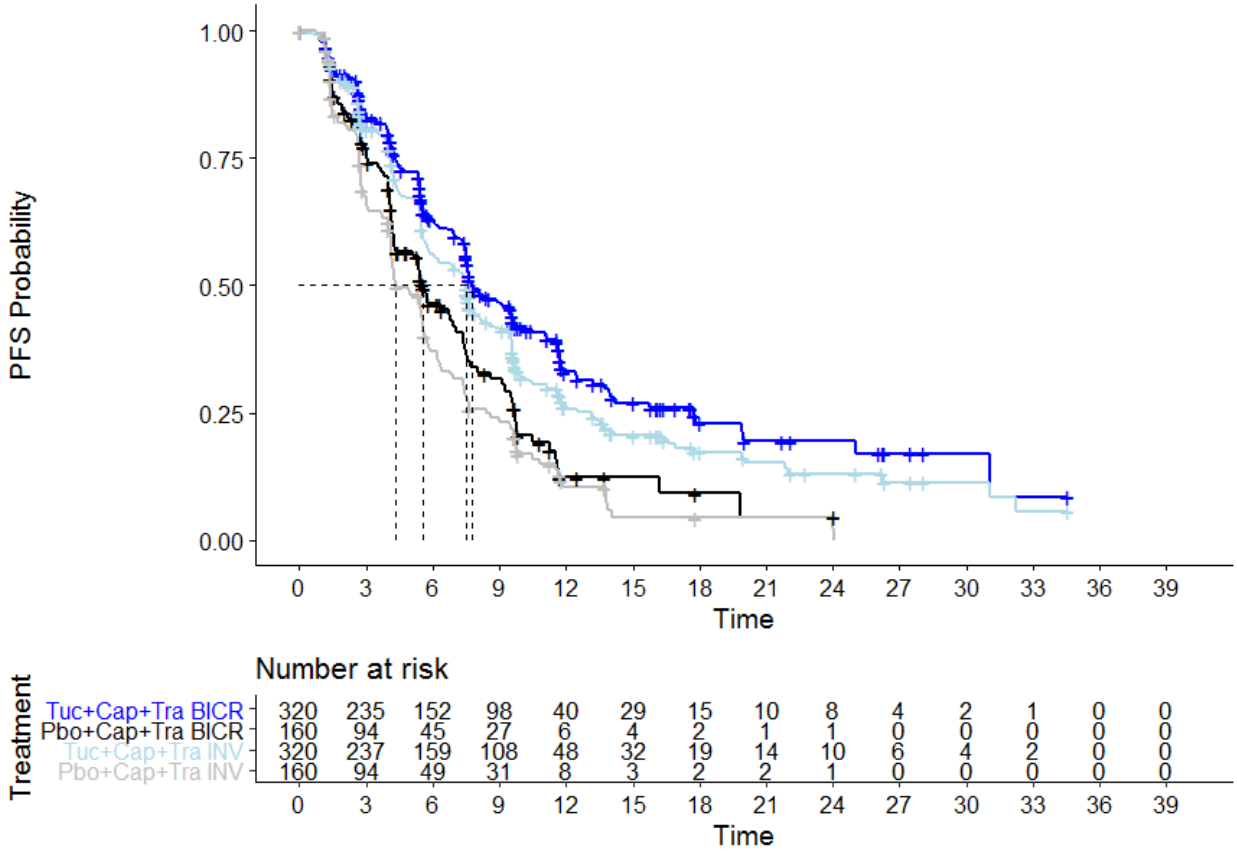
The applicant also presented the 6-month and 12-month PFS rates by arm, which are considered exploratory. The point estimate of event rates at a fixed time point for a time-to-event endpoint can be misleading because it does not represent the entire effect size of the

treatment and the chosen landmark time is arbitrary. We note that 23.1% of patients (20.0% on the tucatinib arm and 29.4% on the placebo arm) were censored prior to 6 months and 36.5% of patients (36.3% on the tucatinib arm and 36.9% on the placebo arm) were censored prior to 12 months, so these estimates may not be robust.

The subgroup analyses presented showed that there were no outlier subgroups, but the results from these analyses are considered exploratory only. The multiple sensitivity analyses conducted by the applicant considered different censoring schemes and ways to handle missing assessments. Results were all consistent with the primary analysis, but the p-values should be interpreted as nominal as noted.

Investigator-assessed PFS was consistent with the primary endpoint of BICR-assessed PFS. The stratified hazard ratio for investigator-assessed PFS in the ITT-PFS population was 0.56 (95% CI: 0.45, 0.70), favoring the tucatinib arm, with a median PFS of 7.5 months (95% CI: 6.0, 7.9) on the tucatinib arm and 4.3 months (95% CI: 4.1, 5.6) on the placebo arm. Figure 15 shows the Kaplan-Meier curves for PFS by investigator plotted with PFS by BICR.

Figure 15: Kaplan-Meier plot of PFS by INV and BICR in the ITT-PFS Population



Source: ADaM data set ADTTE

Concordance between BICR and investigator-assessed PFS was 73.8% on the tucatinib arm and 73.1% on the placebo arm in the ITT-PFS population. There was a larger number of PFS events by investigator (226 on the tucatinib arm and 128 on the placebo arm) than by BICR (178 on the tucatinib arm and 97 on the placebo arm). The majority of the discordances were due to a patient having an event by investigator and censored by BICR prior to starting new anti-cancer treatment. To further address this issue, we sent an information request to the applicant to conduct a sensitivity analysis of PFS considering initiation of new therapy as an event in the ITT-PFS population. Results by both BICR and investigator are shown in Table 24 and were consistent with the primary analysis. We note that in the primary analysis of PFS by BICR, 75 patients on the tucatinib arm and 47 patients on the placebo arm were censored for new anti-cancer therapy prior to PD or death. When initiation of new therapy was counted as a PFS event in this sensitivity analysis, there were an additional 71 events on the tucatinib arm and 46 events on the placebo arm, with 5 patients censored due to the new therapy being initiated after two or more missing assessments.

Table 24: PFS Sensitivity Analysis with Initiation of New Therapy as an Event

	BICR		Investigator	
	Tuc+Cap+Tras (N=320)	Pbo+Cap+Tras (N=160)	Tuc+Cap+Tras (N=320)	Pbo+Cap+Tras (N=160
PFS Event (progression, death, or new anti-cancer therapy), n (%)	249 (77.8)	143 (89.4)	249 (77.8)	146 (91.3)
Median PFS (months) (95% CI)	7.1 (5.7, 7.6)	4.2 (4.1, 5.4)	6.9 (5.6, 7.6)	4.2 (4.0, 5.4)
Stratified HR (95% CI)	0.53 (0.43, 0.66)		0.56 (0.45, 0.69)	

Source: IR Response from applicant dated February 25, 2020

Data Quality and Integrity

Data:
NA

The Applicant's Position:
There are no issues regarding data integrity and submission quality.

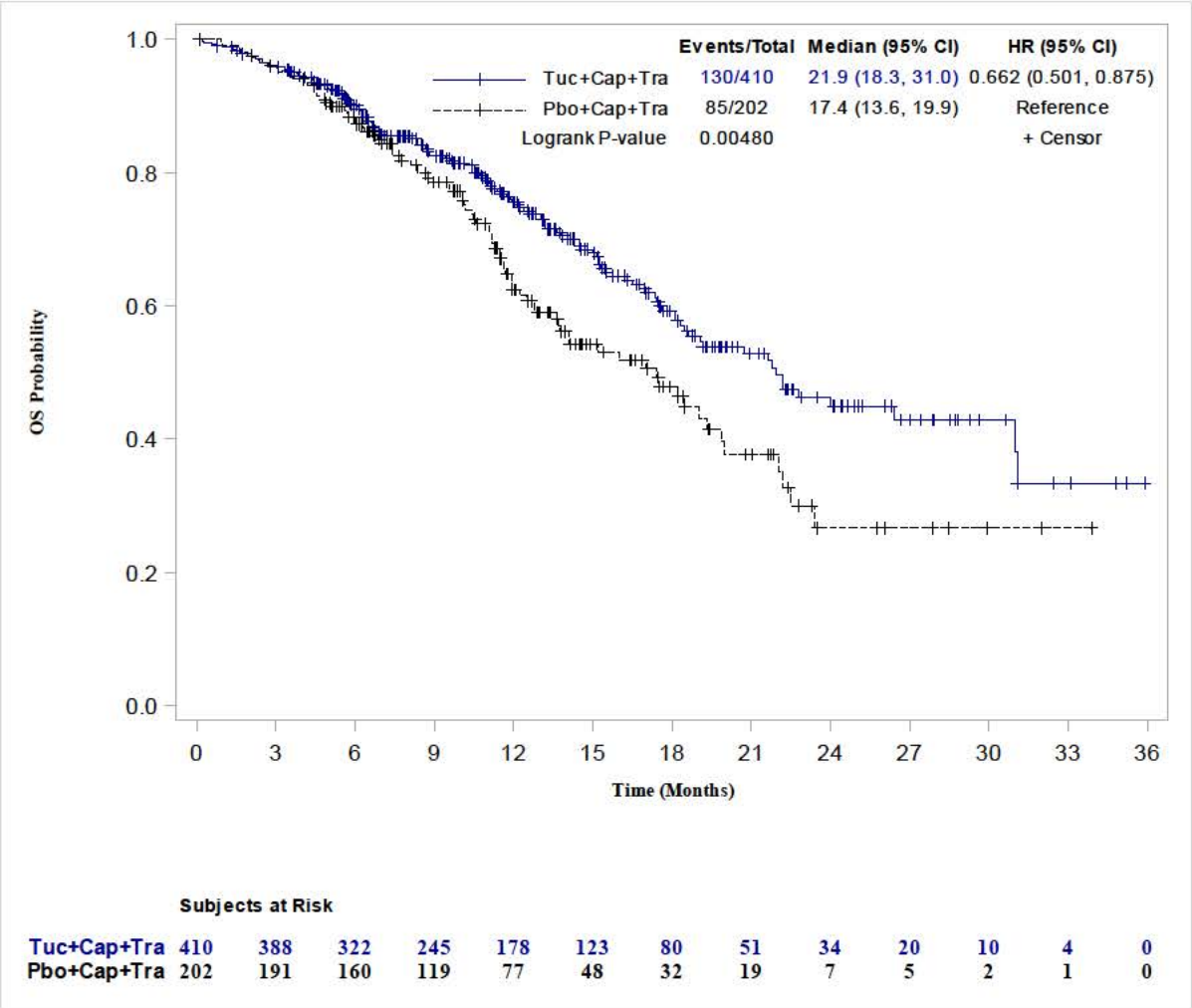
Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:

Alpha-controlled Key Secondary Endpoint – OS: With a median of 14 months of OS follow-up, OS was significantly prolonged in the tucatinib arm versus the control arm, with a 34% reduction in the risk of death versus the control arm (Figure 16). The median OS was 21.9 versus 17.4 months for the tucatinib and control arms, respectively (Figure 16).The 1-year OS was 75.5% (95% CI: 70.4, 79.9) and 62.4% (95% CI: 54.1, 69.5) for the tucatinib and control arms, respectively, and the 2-year OS was 44.9% (95% CI: 36.6, 52.8) and 26.6% (95% CI: 15.7, 38.7).

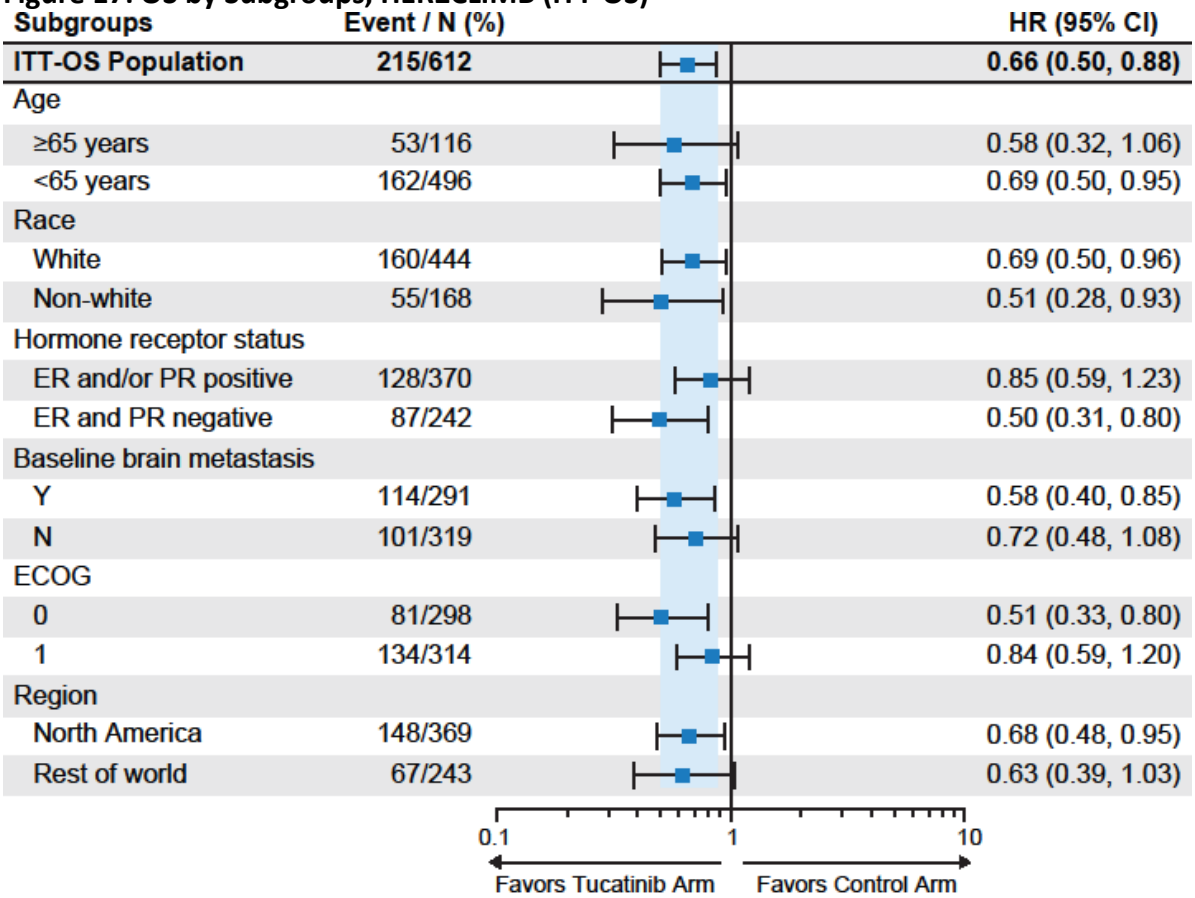
Figure 16: OS by Treatment Arm, HER2CLIMB (ITT-OS)



Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
Statistically significant after adjustment for multiplicity. The threshold for statistical significance was 0.0074.
Hazard ratio was computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization.
Two-sided p-value based on stratified log-rank test and re-randomization procedure (Rosenberger and Lachin, 2002).
Source: ONT-380-206 CSR, Figure 5

OS by Subgroup: All subgroups analyzed, including baseline brain metastasis status, demonstrated an OS benefit consistent with the overall outcome (Figure 17).

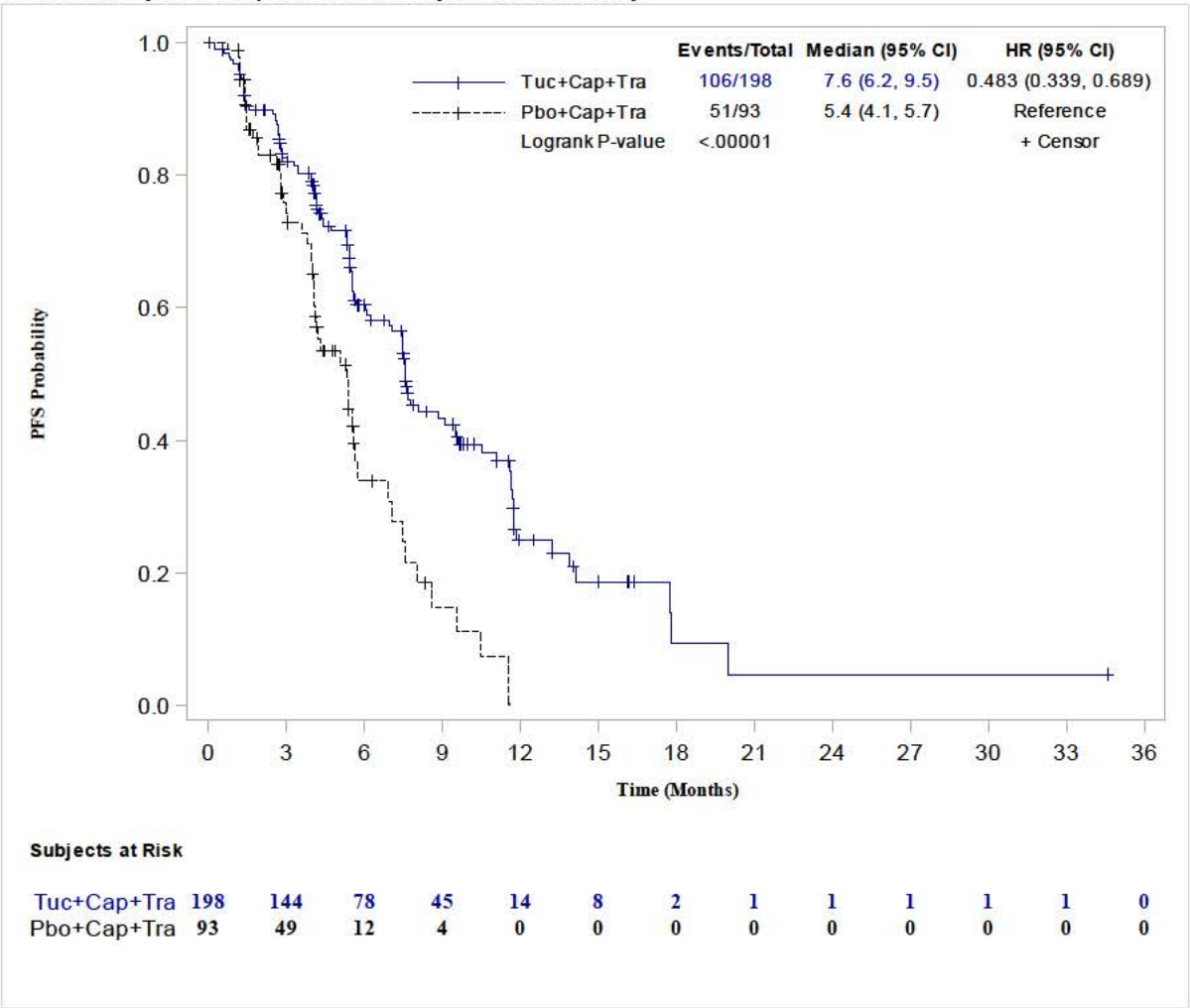
Figure 17: OS by Subgroups, HER2CLIMB (ITT-OS)



Hazard ratio was calculated from cox regression model considering stratification factors from randomization.
Source(s): ONT-380-206 CSR, Figure 6

Alpha-controlled Key Secondary Endpoint - PFS per BICR in ITT-PFS$_{BrainMets}$ population: In the PFS$_{BrainMets}$ population, there was a 52% reduction in the risk of disease progression on the tucatinib arm. The median PFS$_{BrainMets}$ was 7.6 months in the tucatinib arm versus 5.4 months in the control arm (Figure 18). The 6-month PFS$_{BrainMets}$ was 60.4% (95% CI: 52.4, 67.5) and 33.9% (95% CI: 21.0, 47.2) for the tucatinib and control arms, respectively, and the 1-year PFS$_{BrainMets}$ was 24.9% (95% CI: 16.5, 34.3) for the tucatinib arm; the 1-year PFS$_{BrainMets}$ could not be calculated for the control arm because no subjects remained at risk for an event.

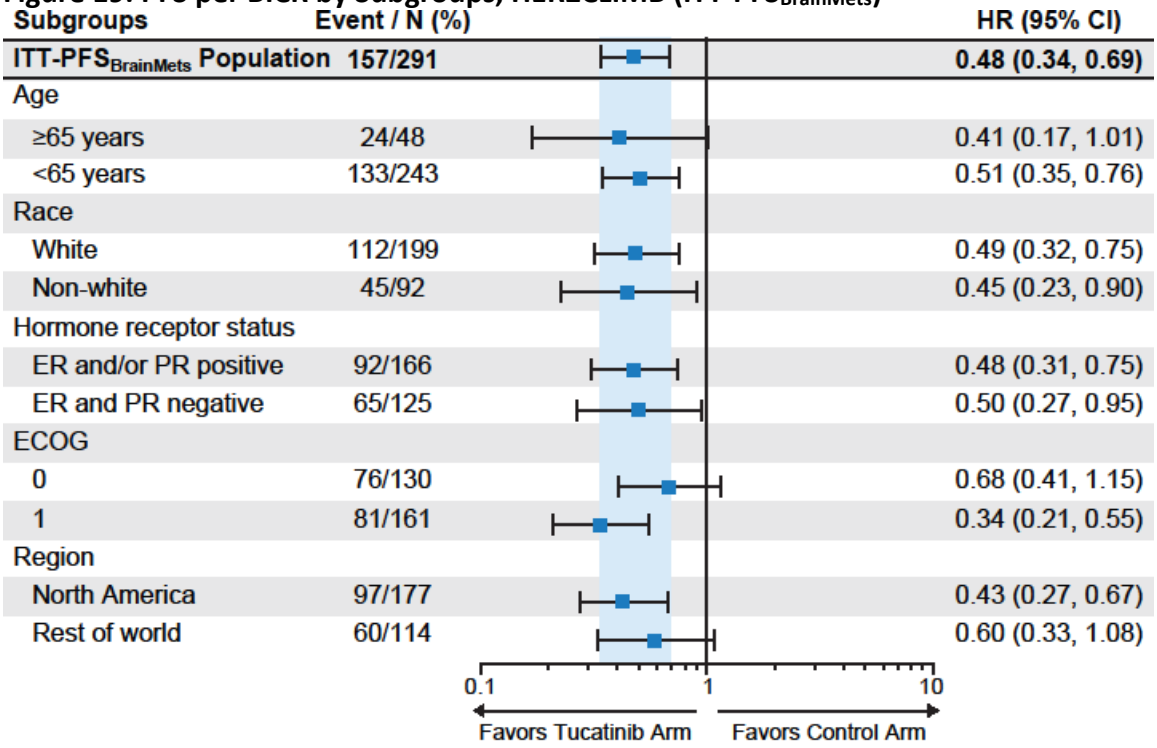
Figure 18: PFS per BICR, HER2CLIMB (ITT-PFS$_{BrainMets}$)



Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
Statistically significant after adjustment for multiplicity. The threshold for statistical significance was 0.0080.
Hazard ratio was computed from the Cox proportional hazards model using stratification factors (ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization.
Two-sided p-value based on stratified log rank test and re-randomization procedure (Rosenberger and Lachin, 2002).
Source: ONT-380-206 CSR, Figure 7

PFS by Subgroup per BICR in the ITT-PFS$_{BrainMets}$: All subgroups of subjects with brain metastases demonstrated a PFS benefit consistent with the overall outcome (Figure 19).

Figure 19: PFS per BICR by Subgroups, HER2CLIMB (ITT-PFS$_{BrainMets}$)



Hazard ratio is calculated from cox regression model considering stratification factors from randomization.
Source: ONT-380-206 CSR, Figure 8

Key Secondary Endpoint – Confirmed ORR by BICR (ITT-OS): Confirmed ORR per RECIST v1.1 was analyzed in the ITT-OS population for subjects with measurable disease per BICR at baseline (82.9% in the tucatinib arm and 84.7% in the control arm). Only response assessments before first documented PD or new anti-cancer therapies were considered. Best confirmed objective response for subjects with measurable disease at baseline in the ITT-OS population are summarized in Table 25. Treatment with tucatinib in these subjects resulted in a significantly higher confirmed ORR versus subjects in the control arm.

Table 25: Confirmed ORR per BICR, HER2CLIMB (Measurable Disease Set, ITT-OS)

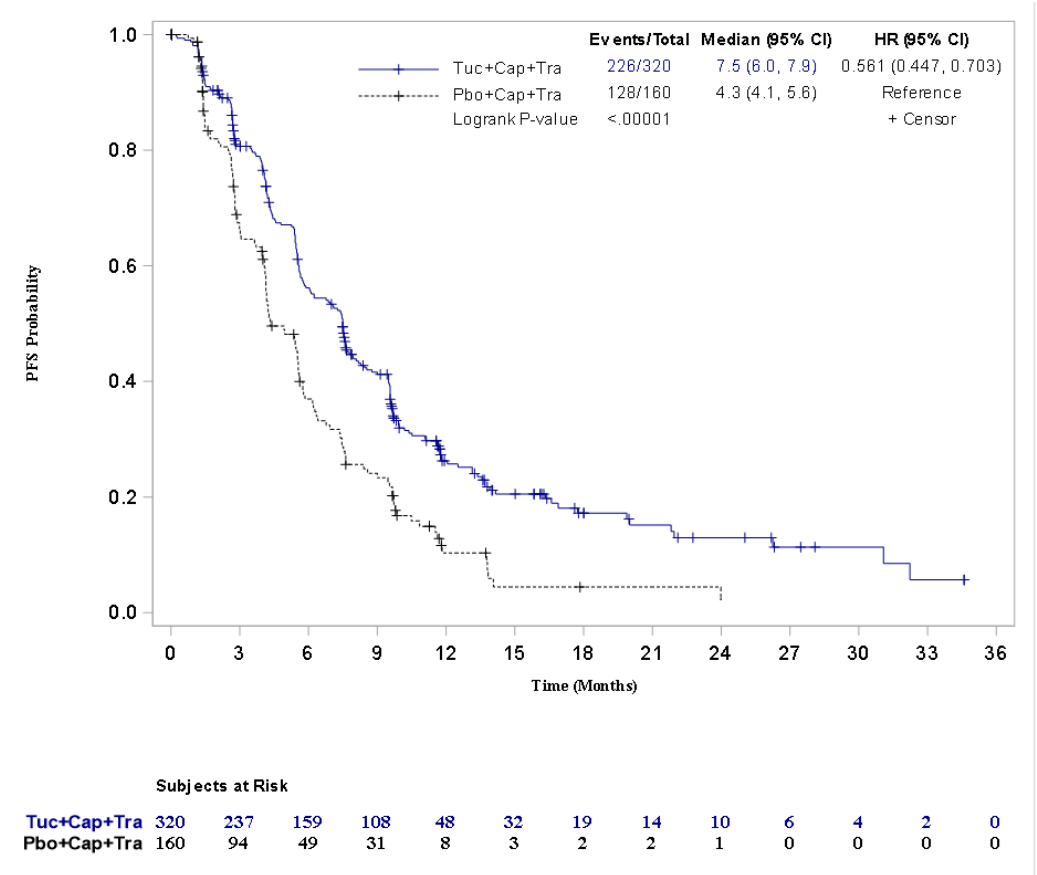
	Tuc+Cap+Tra (N=340)	Pbo+Cap+Tra (N=171)
Best Overall Response[a]		
CR	3 (0.9)	2 (1.2)
PR	135 (39.7)	37 (21.6)
SD	155 (45.6)	100 (58.5)
PD	27 (7.9)	24 (14.0)
Not evaluable (NE)	0	1 (0.6)
Not available[b]	20 (5.9)	7 (4.1)

	Tuc+Cap+Tra (N=340)	Pbo+Cap+Tra (N=171)
Subjects with Objective Response of confirmed CR or PR, n	138	39
ORR, %	40.6	22.8
95% CI[c] for ORR	(35.3, 46.0)	(16.7, 29.8)
Stratified CMH p-value for ORR[d]	0.00008	

Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
a. Confirmed best overall response assessed per RECIST 1.1.
b. Subjects with no postbaseline response assessments
c. Two-sided 95% exact confidence interval computed using the Clopper-Pearson method (1934).
d. CMH test controlling for stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: North America/Rest of World) at randomization.
Source: ONT-380-206 CSR, Table 19

Other Secondary Endpoints - PFS per Investigator Assessment: PFS per investigator was improved in the tucatinib arm versus the control arm with a 44% reduction in the risk of disease progression or death (Figure 20).The median PFS per investigator was 7.5 months in the tucatinib arm versus 4.3 months in the control arm.

Figure 20: PFS per Investigator by Treatment Arm, HER2CLIMB (ITT-PFS)



Hazard ratio was computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG PS: 0/1, and Region of world: US/Canada/Rest of World) at randomization.
Two-sided nominal P-value was calculated from stratified log-rank test (Rosenberger and Lachin, 2002).
Source: ONT-380-206 CSR

Other Secondary Endpoint - ORR per investigator: ORR per investigator in the ITT-OS population in the tucatinib arm was 40.9% (95% CI: 35.8, 46.2) versus 21.4% (95% CI: 15.5, 28.3) in the control arm (nominal P=0.00001).

Other Secondary Endpoint - Duration of Response: DOR was analyzed in patients with measurable disease at baseline in the ITT-OS population. The median DOR per BICR was 8.3 months (95% CI: 6.2, 9.7) in the tucatinib arm and 6.3 months (95% CI: 5.8, 8.9) in the control arm. The median DOR per investigator was 6.9 months (95% CI: 6.2, 8.3) in the tucatinib arm and 6.9 months (95% CI: 4.2, 8.9) in the control arm.

Other Secondary Endpoint - Clinical Benefit Rate: The CBR was analyzed in the entire ITT-OS population. The CBR per BICR was 59.8% (95% CI: 54.8, 64.5) for subjects in the tucatinib arm compared with 38.1% (95% CI: 31.4, 45.2) for subjects in the control arm (nominal P<0.00001). Similar results were obtained by investigator assessment.

The Applicant's Position:
The study met all primary and key secondary endpoints and the addition of tucatinib to the combination of trastuzumab and capecitabine resulted in superior PFS and OS for subjects with metastatic HER2+ BC, and superior PFS in subjects with brain metastases.

The interim analyses for the key secondary endpoints OS and $PFS_{BrainMets}$ were conducted as a result of the statistically significant PFS primary analysis. Both key secondary endpoints were statistically significant; therefore, OS and $PFS_{BrainMets}$ were considered to be final analyses and no additional formal statistical testing will be conducted. Additionally, ORR by BICR was formally tested between the two treatment arms and was also found to be significant in favor of the tucatinib arm.

The addition of tucatinib to trastuzumab and capecitabine reduced the risk of disease progression or death by 46% in heavily pretreated subjects with HER2+ locally advanced unresectable or MBC and by 52% in subjects with brain metastases. Most importantly, tucatinib also reduced the risk of death by approximately one-third in the overall population.

Regulatory Authorities Assessment:
The regulatory authorities generally agree with the results and conclusions presented in this section. Given the statistically significant primary analysis, the secondary endpoints with alpha-control were OS (with a two-sided alpha-level of 0.0074 allocated to the interim analysis), $PFS_{BrainMets}$ by BICR (with a two-sided alpha-level of 0.0080 allocated to the interim analysis), and ORR by BICR (with a two-sided alpha-level of 0.05 if both OS and $PFS_{BrainMets}$

were statistically significant). The analyses of all three endpoints were statistically significant in favor of the tucatinib arm. The FDA has the following additional notes:

1. **The stratified OS hazard ratio was 0.66 (95% CI: 0.50, 0.87), the stratified OS hazard ratio based on actual stratification values collected by EDC at baseline was 0.68 (0.52, 0.90), and the unstratified OS hazard ratio was 0.69 (95% CI: 0.52, 0.90). The applicant also presented the 1-year and 2-year OS rates by arm, which are exploratory. The estimate does not represent the entire effect size of the treatment and the chosen landmark time is arbitrary. We note that 35.0% of patients (36.6% on the tucatinib arm and 31.7% on the placebo arm) were censored prior to 1-year and 58.7% of patients (60.7% on the tucatinib arm and 54.5% on the placebo arm) were censored prior to 2-years, so these estimates may not be robust.**
2. **The stratified $PFS_{BrainMets}$ hazard ratio was 0.48 (95% CI: 0.34, 0.69), the stratified hazard ratio based on actual stratification values collected by EDC at baseline was 0.48 (95% CI: 0.34, 0.68), and the unstratified hazard ratio was 0.47 (0.33, 0.67). The 6-month and 1-year $PFS_{BrainMets}$ rates presented are exploratory because the estimate does not represent the entire effect size of the treatment and the chosen landmark time is arbitrary. Additionally, the estimate may not be robust as 32.3% of patients (27.3% on the tucatinib arm and 43.0% on the placebo arm) were censored prior to 6-months and 43.3% of patients (42.4% on the tucatinib arm and 45.2% on the placebo arm) were censored prior to 1-year.**
3. **Results for $PFS_{BrainMets}$ by investigator were consistent showing a stratified hazard ratio of 0.45 (95% CI: 0.33, 0.62), with a median PFS of 7.5 months (95% CI: 5.9, 8.8) on the tucatinib arm and 4.1 months (95% CI: 3.6, 5.4) on the placebo arm. The concordance between investigator and BICR in the ITT- $PFS_{BrainMets}$ population was 80.8% on the tucatinib arm and 72.0% on the placebo arm. The OS hazard ratio in the subgroup of patients with brain metastases at baseline was 0.58 (95% CI: 0.40, 0.85), but this result is considered exploratory. Similarly, all subgroup analyses of OS and $PFS_{BrainMets}$, while appearing consistent, are considered exploratory only.**
4. **For the key secondary endpoint of ORR by BICR, the analysis was conducted in the subset of subjects with measurable disease among the ITT-OS population. We note that there were no clear imbalances in baseline characteristics between arms within this subset (Table 26).**

Table 26: Demographics and Baseline Characteristics in the Measurable Disease Set (ITT-OS), HER2CLIMB

	Tuc+Cap+Tra (N=340) n (%)	Pbo+Cap+Tra (N=171) n (%)
Age (years)		
Mean (STD)	**54.2 (11.3)**	**54.4 (10.4)**
Median	**55**	**54**
Min, Max	**27, 80**	**25, 78**
Age Category		
<65 years	**268 (78.8)**	**140 (81.9)**
≥65 years	**72 (21.2)**	**31 (18.1)**
Sex		
Male	**3 (0.9)**	**2 (1.2)**
Female	**337 (99.1)**	**169 (98.8)**
Race		
Asian	**15 (4.4)**	**5 (2.9)**
Black or African American	**36 (10.6)**	**13 (7.6)**
White	**237 (69.7)**	**133 (77.8)**
Other*	**3 (0.9)**	**2 (1.2)**
Unknown	**49 (14.4)**	**18 (10.5)**
Ethnicity		
Hispanic or Latino	**32 (9.4)**	**14 (8.2)**
Not Hispanic or Latino	**301 (88.5)**	**154 (90.1)**
Not Available	**7 (2.1)**	**3 (1.8)**
ECOG PS		
0	**163 (47.9)**	**83 (48.5)**
1	**177 (52.1)**	**88 (51.5)**

* **Other includes "Multiple" and "Native Hawaiian or Other Pacific Islander"**
Source: ADaM dataset ADSL

Dose/Dose Response

Data:
Data are presented in Clinical Pharmacology Section 6.3.2.3 of the assessment aid.

The Applicant's Position:
The applicant's position is presented in Section 6.3.2.3 of the assessment aid.

Regulatory Authorities Assessment:
The regulatory authorities also refer to Section 6.3.2.3 of the assessment aid.

Durability of Response

Data:
Please see data on PFS and OS presented in Section 8.1.2.

The Applicant's Position:
Durability of response to tucatinib in combination with trastuzumab and capecitabine is reflected by the clinically meaningful PFS and OS results demonstrated in the HER2CLIMB study and is discussed above under Efficacy Results – Primary Endpoint and Efficacy Results – Secondary endpoints.

Regulatory Authorities Assessment:
There are no data on durability of response beyond what is presented in the preceding portion of the assessment aid.

Persistence of Effect

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
There are no long-term efficacy data beyond what is presented in the preceding portion of the assessment aid.

Efficacy Results – Secondary or exploratory PRO endpoints

Data:
HRU was assessed in the safety analysis set from healthcare data collected from randomization through the 30-day follow-up post-end of treatment (EOT) visit of the HE2CLIMB study. The mean cumulative incidence of hospitalizations per subject-year was 0.9 (range, 0.0–37.5) in the tucatinib arm versus 1.1 (range, 0.0–23.1) in the control arm. In subjects who were hospitalized, the median total length of stay per subject-year was 12.3 days (range, 1.4-178.7) in the tucatinib arm and 16.1 days (range, 0.9-263.5) in the control arm. The reasons for

hospitalization visits were predominantly due to AEs (86.7% in the tucatinib arm vs. 85.3% in the control arm). The mean number of emergency room visits was 3.1 (range 0.3-10) in the tucatinib arm versus 3.3 (range 0.9-11.6) in the control arm.

The EQ-5D-5L, which consists of the European Quality of Life 5-Dimensional (EQ-5D) descriptive system and the EQ visual analogue scale (VAS), was added in protocol version 7 (30-Aug-2017) to assess HRQoL. Only those subjects who consented to protocol version 7 were included in these analyses (N=217 in the tucatinib arm and N=113 in the control arm). (b) (4)

[redacted]

The Applicant's Position:

(b) (4)

[redacted]

Regulatory Authorities Assessment:

FDA verified the data presented regarding HRU.

Since there is no pre-specified statistical testing procedure to control for Type I error, all patient reported outcome (PRO) analyses are considered to be exploratory. (b) (4)

[redacted]

The applicant collected PRO data using the EQ-5D-5L, but this was only implemented starting with protocol version 7. A total of 217 patients on the tucatinib arm and 113 on the placebo arm consented to protocol version 7 or later, representing 53.9% of the ITT-OS population, so PRO data are limited and no conclusions can be drawn. Additionally, we note that the EQ-5D-5L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument is a generic preference based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit (b) (4) [redacted]**, though we acknowledge that this instrument is often used by other regulatory authorities and/or payers.**

Additional Analyses Conducted on the Individual Trial

Data:

PFS in the ITT-OS Population: Consistent with the primary analysis in the ITT-PFS population, exploratory analysis of PFS per BICR in the ITT-OS population was improved in the tucatinib arm versus the control arm (stratified HR=0.54 [95% CI: 0.42, 0.68], nominal P<0.00001), with a 46% reduction in the risk of progression or death for the tucatinib arm versus control arm.

$PFS_{BrainMets}$ per Investigator in the Brain Metastases Population: Consistent with the BICR assessment, $PFS_{BrainMets}$ per investigator was improved in the tucatinib arm versus the control arm (stratified HR=0.45 [95% CI: 0.33, 0.62], nominal P<0.00001), with a 55% reduction in the risk of a $PFS_{BrainMets}$ event for the tucatinib arm versus control arm.

PFS per BICR in the Non-Brain Metastasis Population: PFS per BICR in subjects without known brain metastases at study entry in the ITT-OS population was improved in the tucatinib arm versus the control arm (stratified HR=0.57 [95% CI: 0.41, 0.80], nominal P=0.00085), with a 43% reduction in the risk of progression or death for the tucatinib arm versus control arm.

PFS per Investigator in the Non-Brain Metastasis Population: In the ITT-OS population, PFS per investigator in subjects without known brain metastases at study entry was improved in the tucatinib arm versus the control arm (stratified HR=0.64 [95% CI: 0.48, 0.85], nominal P=0.00195), with a 36% reduction in the risk of progression or death for the tucatinib arm versus control arm.

ORR in the ITT-PFS Population: Among subjects in the ITT-PFS population with measurable disease at baseline, the ORR per BICR of 40.7% (95% CI: 34.8, 46.7) and 23.4% (95% CI: 16.6, 31.3) for subjects in the tucatinib arm and the control arm, respectively (nominal P=0.00059) was similar to that of the ITT-OS population. Similar results were obtained by investigator assessment.

PFS per Investigator in the ITT-PFS Population: An exploratory analysis of PFS per investigator conducted in the ITT-OS population, showed improvement in the tucatinib arm versus the control arm (stratified HR=0.56 [95% CI: 0.45, 0.70], nominal P<0.00001), with a 44% reduction in the risk of progression or death. These results are consistent with the primary analysis in the ITT-PFS population.

CBR in the ITT-PFS Population: The CBR per BICR in the ITT-PFS population was 61.9% (95% CI: 56.3, 67.2) for subjects in the tucatinib arm compared with 40.0% (95% CI: 32.3, 48.0) for subjects in the control arm (nominal P<0.00001).

DOR in the ITT-PFS Population: The median DOR per BICR in the ITT-PFS population with measurable disease at baseline was 8.0 months (95% CI: 6.2, 9.7) in the tucatinib arm and 6.3 months (95% CI: 5.3, 8.9) in the control arm.

The Applicant's Position:
The results of all exploratory efficacy analyses were consistent with and supportive of the primary and secondary endpoint analyses. Additional support is provided by the exposure-efficacy analyses, described in Section 6.3.2.1.

Analysis of PFS in the ITT-OS population (all randomized subjects) demonstrated outcomes similar to the primary analysis population (first 480 subjects enrolled). In addition, analysis of PFS in subjects without brain metastases demonstrated tucatinib benefits all subjects, regardless of presence or absence of brain metastases.

Regulatory Authorities Assessment:

The regulatory authorities generally agree with the results and conclusions presented in this section, except for the presentation of the p-values. Since these are exploratory analyses, these p-values should be considered nominal only as noted above. We note that the analysis of PFS in subjects without brain metastases specifically mentioned in the applicant's position is considered an exploratory analysis. The regulatory authorities generally agree with the results and conclusions presented in this section but reiterates that they should be interpreted as exploratory only. We note that the analysis of PFS in subjects without brain metastases specifically mentioned in the applicant's position is considered an exploratory analysis.

Additional Analyses:

The applicant also conducted a post-hoc exploratory analysis to examine the site of first progression in patients with brain metastases and submitted this in response to an Information Request. Patients with untreated brain metastases (n=66) and treated and progressing brain metastases (n=108) at baseline were grouped together in an active brain metastases category. The site of first progression in this group by treatment arm is shown in the Table 27below.

Table 27: Site of first progression in patients with active brain metastases, ITT-PFS$_{brainmets}$, HER2CLIMB

Site of progression	Tuc+Cap+Tra (N=118) n (%)	Pbo+Cap+Tra (N=56) n (%)
Overall progression of disease	62 (53)	33 (59)
Brain only	32 (27)	16 (29)
Body only	22 (19)	11 (20)

Brain and body	**4 (3.4)**	**1 (1.8)**
Neither brain nor body	**4 (3.4)**	**5 (9)**

Source: Information amendment from applicant dated February 6, 2020.

In patients with active metastases, the two treatment arms were generally equivalent in terms of the brain, body, or both as the site of first progression. In the overall active brain metastases population, progression in the brain first occurred only slightly more frequently than progression in the body first. However, this entire analysis should be interpreted with caution. It is post-hoc, exploratory, and includes a relatively small number of patients. Additionally, active brain lesions may have been small, so even a meaningful change in diameter may not be enough on its own to count as a progression event.

8.1.3. Integrated Review of Effectiveness

Regulatory Authorities Assessment:

The HER2CLIMB trial was a well-designed, well-conducted, randomized (2:1), double-blinded, placebo-controlled clinical trial in patients with advanced unresectable or metastatic HER2-positive breast cancer, including those with brain metastases, which met its primary and all key secondary endpoints. All patients had previously received trastuzumab, pertuzumab, and T-DM1 in the (neo)adjuvant and/or metastatic setting, and all patients had been exposed to at least one line of therapy in the metastatic setting. Notably, the trial showed a statistically significant and clinically meaningful improvement in the primary endpoint of PFS by BICR and key secondary endpoint of OS in patients who received tucatinib, trastuzumab, and capecitabine compared to placebo, trastuzumab, and capecitabine. HER2CLIMB enrolled a heavily pretreated patient population that had received a median of 3 prior lines of therapy in the metastatic setting (range: 1 to 14).

Additionally, though patients with active brain metastases are typically excluded from breast cancer clinical trials, HER2CLIMB permitted enrollment of patients with treated and stable brain lesions, as well as patients with treated and progressing brain lesions and untreated brain lesions. These patients with brain metastases made up 48% of the overall study population. The key secondary endpoint of $PFS_{brainmets}$ examined PFS specifically in this subgroup and also showed a statistically significant and clinically meaningful improvement of PFS in favor of the treatment arm. The remaining key secondary endpoint was ORR by BICR, which was also statistically significant and clinically meaningful in favor of the treatment arm.

Beyond the primary and key secondary endpoints, the regulatory authorities consider all other analyses exploratory and these should not form the basis for any efficacy claims. In particular, the landmark estimates included for PFS, OS, and $PFS_{brainmets}$ include arbitrary

landmark times and do not represent the entire effect size of the treatment. Additionally, p-values should not be presented for exploratory analyses.

The FDA reviewed the healthcare utilization and PRO data submitted by the applicant which cannot support any efficacy claims. These analyses are also exploratory, and in addition, were not adequately powered (b) (4)

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

The data presented herein compares efficacy results from the randomized, double-blind HER2CLIMB trial with the tucatinib triplet combination cohort from Study ONT-380-005, a single arm, open-label trial. Both studies enrolled subjects with progressive HER2+ BC, including subjects with progressing brain metastases, who received prior treatments with both trastuzumab and T-DM1 for metastatic disease. In HER2CLIMB, PFS was analyzed for the first 480 subjects as assessed per BICR. In ONT-380-005, PFS was analyzed for the 27 subjects enrolled in the tucatinib triplet combination cohort, 11 of whom had a baseline history of brain metastases, as assessed per investigator using unconfirmed responses (Table 28).

Table 28: PFS per BICR in HER2CLIMB (ITT-PFS) and per Investigator in the ONT-380-005 Triplet Combination Cohort

	HER2CLIMB Tuc+Cap+Tra (N=320)	ONT-380-005 Tuc+Cap+Tra (N=27)
Median (95% CI)	7.8 (7.5, 9.6)	7.8 (4.1, 12.5)
25th, 75th Percentile	4.3, 17.8	4.1, 19.1
Observed Min, Max	0.0+, 34.6+	1.3, 28.9

Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
'+' means the observed time is from censored subjects
Source(s): CSR ONT-380-206 Table 16; CSR ONT-380-005, Table 16

The Applicant's Position:

A pooled analysis was not conducted due to substantial differences in trial design and sample size between these studies. (b) (4)

Regulatory Authorities Assessment:

The regulatory authorities consider HER2CLIMB to be the main trial for the assessment of benefit-risk for tucatinib. ONT-380-005 is a small single-arm trial from which limited

conclusions can be drawn. Additionally, time-to-event endpoints such as PFS are uninterpretable in single-arm trials. While we agree with the results presented by trial, we do not agree with (b) (4) **We note also that PFS in HER2CLIMB was per BICR while PFS in ONT-380-005 was per investigator.**

Secondary and Other Endpoints

Data:

In the HER2CLIMB study, ORR and DOR were analyzed for subjects with measurable disease in the ITT-OS population (all randomized subjects) based on confirmed responses per BICR. In Study ONT-380-005, ORR and DOR were assessed in the measurable disease set – all subjects who had at least 1 measurable target lesion at baseline and (1) had at least 1 post-baseline disease assessment or (2) if they had no post-baseline disease assessment, discontinued study treatment due to death, clinical or radiologic PD, or an AE (Table 29). Responses in ONT-380-005 were not required to be confirmed.

Table 29: Responses per BICR in HER2CLIMB (ITT-OS) and per Investigator in the ONT-380-005 Triplet Combination Cohort

	HER2CLIMB Tuc+Cap+Tra (N=340)	ONT-380-005 Tuc+Cap+Tra (N=23)
Best overall response[a], n (%)		
CR	3 (0.9)	1 (4.3)
PR	135 (39.7)	13 (56.5)
SD	155 (45.6)	6 (26.1)
PD	27 (7.9)	3 (13.0)
Not evaluable	0 (0)	0 (0)
Not available[b]	20 (5.9)	-
ORR		
n (%)	138 (40.6)	14 (60.9)
95% CI[c]	35.3, 46.0	38.5, 80.3
DOR (months)		
Median[d] (95% CI)	8.3 (6.2, 9.7)	11.1 (2.9, 18.7)
25th, 75th Percentile[e]	4.3, 12.5	3.5, 18.7

Cap=capecitabine; Tra=trastuzumab; Tuc=tucatinib
Confirmed best overall response assessed per RECIST 1.1 in HER2CLIMB. Responses are unconfirmed in ONT-380-005
HER2CLIMB: Subjects with no post-baseline response assessments
HER2CLIMB: Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). ONT-380-005: Exact binomial confidence interval
As estimated using Kaplan-Meier methods
Calculated using the complementary log-log transformation method (Collett, 1994)
Source(s): CSR ONT-380-206 Table 14.2.5.3b, Table 14.2.7.3; m5.3.3.2, CSR ONT-380-005, Table 14.2.1.2.1, Table 14.2.1.1.1.

The Applicant's Position:
In both studies, the ORR was >40% in subjects that received tucatinib in combination with trastuzumab and capecitabine, and the median DOR was >8.0 months. (b) (4) [redacted] Any variability in the data between the 2 studies is likely due to the small sample size in the ONT-380-005 triplet combination. The findings of these 2 studies compare favorably to other studies using systemic therapy in a late-line setting and support the proposed indication in patients with locally advanced unresectable or metastatic HER2+ BC.

Regulatory Authorities Assessment:
The regulatory authorities consider HER2CLIMB to be the pivotal trial for the assessment of benefit risk for tucatinib. ONT-380-005 is a small single-arm trial from which limited conclusions can be drawn. While we agree with the results presented by trial, (b) (4) [redacted] Additionally, we note that ORR and DOR in HER2CLIMB was per BICR while ORR and DOR in ONT-380-005 was per investigator.

Subpopulations

Data:
NA

The Applicant's Position:
All subgroups analyzed in the HER2CLIMB study demonstrated a PFS and OS benefit consistent with the overall outcomes for these endpoints. Sample size in ONT-380-005 is too small (27 subjects) for a meaningful evaluation of subpopulations.

Regulatory Authorities Assessment:
The regulatory authorities again reiterate that ONT-380-005 is a small single-arm trial from which limited conclusions can be drawn. The regulatory authorities agree that subgroup analyses of this study population would not be meaningful.

Additional Efficacy Considerations

Regulatory Authorities Assessment:
NA

8.1.5. Integrated Assessment of Effectiveness

Data:
HER2CLIMB enrolled subjects with locally advanced unresectable or metastatic HER2+ BC, approximately half of whom had history of brain metastases or baseline brain metastases, who had previously received trastuzumab, pertuzumab, and T-DM1 in any setting. All primary and alpha-controlled secondary endpoints were met. The activity of the control regimen was consistent with other contemporary trials using chemotherapy with trastuzumab or lapatinib (Rugo 2019; Saura 2019).

Results from the HER2CLIMB study indicate an unequivocal benefit from the addition of tucatinib to the combination of trastuzumab and capecitabine. The study demonstrated a statistically significant and clinically meaningful 46% reduction in the risk of disease progression or death in the tucatinib arm relative to the control arm, with a 52% reduction in the risk of progression or death in subjects with brain metastases. Most importantly, there was a 34% reduction in the risk of death relative to the control arm in a setting where no agents have previously shown a survival benefit.

Efficacy observed in the pivotal HER2CLIMB study is supported by data from the ONT 380-005 study. Tucatinib in combination with trastuzumab and capecitabine in HER2+ metastatic BC had an ORR of 60.9% (95% CI: 38.5, 80.3) and median PFS per investigator of 7.8 months (95% CI: 4.1, 12.5), and supported the initiation of the HER2CLIMB study. In both studies, clinically meaningful activity was observed in subjects with and without brain metastases.

The Applicant's Position:
HER2CLIMB demonstrated a statistically significant and clinically meaningful improvement in efficacy in subjects randomized to treatment with tucatinib, trastuzumab and capecitabine versus those randomized to the control arm of placebo, trastuzumab and capecitabine, including an overall survival benefit. The observed reduction in the risk of PFS per BICR was robust and consistent across pre-specified subgroups. The risk of death associated with the tucatinib arm was reduced by 34% compared to the control arm. The activity of the control regimen was consistent with other contemporary trials using chemotherapy with trastuzumab or lapatinib (Rugo 2019; Saura 2019).

Regulatory Authorities Assessment:

Overall, the regulatory authorities agree that tucatinib with trastuzumab and capecitabine showed statistically significant and clinically meaningful improvements in efficacy for the indicated population. The FDA's evaluation of benefit-risk is primarily based on the pivotal HER2CLIMB study. HER2CLIMB met its primary endpoint: PFS by BICR, and all alpha-controlled key secondary endpoints: OS, $PFS_{BrainMets}$ by BICR, and ORR by BICR.

Subgroup analyses were prespecified and generally consistent with overall findings. However, subgroup analyses were not alpha-controlled other than the evaluation of $PFS_{BrainMets}$ in the ITT-$PFS_{BrainMets}$ population (which is a subset of the ITT-OS population). The applicant states that there was clinically meaningful activity in patients with and without brain metastases. We note that while efficacy results in HER2CLIMB appear consistent in patients with and without of brain metastases, analyses in the subgroup of patients without brain metastases are exploratory.

ONT-380-005 is a small single-arm trial from which limited conclusions can be drawn.

(b) (4)

8.2. Review of Safety

Data:

The safety data in this application support the use of tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2+ BC, including patients with brain metastases, who have received at least three prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting.

The safety of tucatinib, administered as monotherapy or in combination, was evaluated in 861 subjects across 12 clinical trials; 4 trials including 571 subjects with cancer and 8 trials including 290 subjects without cancer.

The primary focus is on data from the pivotal trial, HER2CLIMB (ONT-380-206), a randomized, double-blind, placebo-controlled, active-comparator trial evaluating tucatinib in combination with trastuzumab and capecitabine in subjects with previously treated, locally advanced unresectable or metastatic HER2+ BC with and without brain metastases. The HER2CLIMB safety analysis set includes 404 subjects randomized to the tucatinib arm and 197 to the control arm. To provide a comprehensive evaluation of safety, an integrated analysis was conducted with results from HER2CLIMB and two preceding phase 1 studies: (1) ARRAY-380-101, a dose escalation study that evaluated tucatinib as monotherapy in subjects with HER2+ solid tumors and (2) ONT-380-005, a dose optimization study that evaluated tucatinib with trastuzumab and/or capecitabine in subjects with metastatic HER2+ BC. Another phase 1 study, ONT-380-

004, evaluated tucatinib in combination with T-DM1 in subjects with metastatic HER2+ BC. Safety results from ONT-380-004 are presented separately due to differences in indication and combination regimen.

Of the 8 studies supporting the safety of tucatinib in subjects without cancer, only clinical pharmacology results pertinent to the evaluation of tucatinib safety in patients with HER2+ BC are discussed as part of the review.

The Applicant's Position:
The cumulative safety data collected across the 12 studies and 861 subjects who received at least 1 dose of tucatinib adequately characterizes the safety profile of tucatinib. Tucatinib in combination with trastuzumab and capecitabine was well tolerated with a manageable safety profile in subjects with previously treated, locally advanced unresectable or metastatic HER2+ BC, including subjects with brain metastases.

Regulatory Authorities Assessment:
The FDA's safety analysis is based primarily on data from HER2CLIMB, a phase 2, randomized (2:1), double-blind, placebo-controlled trial in patients with advanced unresectable or metastatic HER2-positive breast cancer. The FDA also examined data from two dose-finding studies: ONT-380-005 (tucatinib with trastuzumab and/or capecitabine) and ARRAY-380-101 (tucatinib monotherapy). The FDA agrees with the applicant that the combination regimen in ONT-380-004 (tucatinib with T-DM1) would have a different safety profile than the combination regimen in HER2CLIMB. The applicant did not include data from ONT-380-004 in the assessment aid and the FDA did not review data from this study.

The results in this section are based on data submitted with an initial cutoff date of September 4, 2019. The FDA also reviewed the 90-day safety update with a data cutoff of November 8, 2019 and did not identify any new safety signals.

8.2.1. Safety Review Approach

Data:
To provide a comprehensive safety evaluation of tucatinib in combination with trastuzumab and capecitabine in subjects with HER2+ BC, an integrated safety analysis was conducted. Safety was evaluated from 3 of the 4 studies conducted in subjects with cancer, with the primary safety data for the proposed indication provided by the pivotal trial, HER2CLIMB. The following analysis populations comprise the tucatinib integrated safety population:

- HER2CLIMB safety analysis population: All randomized subjects who received at least 1 dose of study treatment (tucatinib 300 mg PO BID or placebo, capecitabine, or trastuzumab), with subjects allocated to the treatment group associated with the regimen received (N=601; 404 on the tucatinib arm and 197 on the control arm)

- Pooled safety analysis population 1 (Pool 1): Subjects who received tucatinib ≥300 mg PO BID tablet in combination with capecitabine and trastuzumab on Studies HER2CLIMB and ONT-380-005 (N=431)
- Pooled safety analysis population 2 (Pool 2): Subjects who received tucatinib ≥300 mg PO BID tablet in combination with capecitabine alone, trastuzumab alone, or capecitabine and trastuzumab on Studies HER2CLIMB and ONT-380-005 (N=464)
- Monotherapy analysis population: Subjects who received tucatinib ≥600 mg PO BID powder-in-capsule (PIC) on Study ARRAY-380-101 (N=31)

These analysis populations are displayed in a side-by-side tabular format, with HER2CLIMB results presented by treatment arm: tucatinib arm (tucatinib + capecitabine + trastuzumab) and control arm (placebo + capecitabine + trastuzumab).

The two key events that emerged during the tucatinib development program were diarrhea and elevated liver function tests (LFTs; AST, ALT, and bilirubin); therefore, additional safety analyses were conducted to comprehensively evaluate events of gastrointestinal toxicity and hepatotoxicity in the tucatinib integrated safety population.

Cardiac toxicity was evaluated for the tucatinib integrated safety population with a focus on (1) QT prolongation and (2) left ventricular ejection fraction (LVEF) measurements/ treatment-emergent adverse events (TEAEs) of LVEF decreased.

Palmar-plantar erythrodysesthesia (PPE), a well-characterized side effect of capecitabine, was also evaluated as part of the integrated safety review.

Elevated creatinine levels have been observed in subjects treated with tucatinib. Study SGNTUC-020 was conducted in healthy subjects to evaluate the effect of tucatinib inhibition of transporters responsible for the renal secretion of creatinine (organic cation transporter 2 [OCT2]/multidrug and toxin extrusion [MATE1]). TEAEs of creatinine increase were evaluated for subjects treated on the tucatinib and control arms of HER2CLIMB.

The Applicant's Position:

A comprehensive review of safety data pertinent to tucatinib was conducted across 12 clinical studies. Events of interest were well-characterized based on a thorough analysis of all available safety data in subjects with and without cancer who received tucatinib either alone or in combination with other agents, including T-DM1 or trastuzumab and capecitabine. The safety data were consistent across studies and demonstrate an acceptable safety profile for the addition of tucatinib to trastuzumab and capecitabine in subjects with locally advanced unresectable or metastatic HER2+ BC.

Regulatory Authorities Assessment:

The FDA's primary analysis of safety is based on the 601 patients who received at least one dose of study treatment on HER2CLIMB, including 404 patients on the tucatinib arm and 197 patients on the control arm. Data from ONT-380-005 and the Pool 1 and Pool 2 safety

populations defined by the applicant, as well as data from ARRAY-380-101, provided supportive evidence of safety. The FDA did not review all submitted data from ONT-380-005 and ARRAY-380-101 but used it to support certain safety analyses and conclusions as noted throughout the assessment aid below.

The FDA's safety analysis focused on deaths, and treatment-emergent adverse events (TEAEs) including serious TEAEs, TEAEs leading to study drug discontinuation, reduction, or interruption, and AEs of special interest (AESIs). The applicant-identified AESIs for HE2CLIMB were: hepatoxicity, diarrhea, cardiac toxicity/left ventricular dysfunction, cerebral edema, and increased serum creatinine. The applicant selected these based on toxicity concerns throughout the tucatinib development program, and the FDA agrees that these warrant additional attention.

8.2.2. Review of the Safety Database

A comprehensive review of the safety database was conducted with the analysis populations described in Section 8.2.1.

Overall Exposure

Data:
A total of 861 subjects have received at least 1 dose of tucatinib; 571 subjects with cancer and 290 subjects without cancer (Table 30).

Table 30: Overall Number of Subjects Exposed to Tucatinib

Study ID	Tucatinib Dose	Diagnosis	Subjects Exposed	Planned Duration	Range of Exposure
Subjects with cancer					
ARRAY-380-101	25 to 800 mg PO BID	Solid tumors	50	Until progression or unacceptable toxicity	<1 to 21.8 months
ONT-380-004	300 or 350 mg PO BID	MBC	57	Until progression	<1 to 40.0 months
ONT-380-005	300 or 350 mg PO BID	MBC	60	Until progression	<1 to 32.9 months
HER2CLIMB	300 mg PO BID	MBC	404	Until progression	<0.1 to 35.1 months
Subjects without cancer					
ARRAY-380-102	300 mg	Healthy	14	Total 4 doses	
ARRAY-380-103	300 mg	Healthy	12	Total 4 doses	
ONT-380-008	300 mg	Healthy	8	Single Dose	
ONT-380-009	300 mg	Healthy/hepatic impaired	37	Single Dose	
ONT-380-011[a]	300 mg	Healthy	51	Total 9 doses	
ONT-380-012	300 mg	Healthy	28	Total 2 doses	
			28	Total 2 doses	
			28	Total 2 doses	
			17	Total 20 doses (10 days BID)	

Study ID	Tucatinib Dose	Diagnosis	Subjects Exposed	Planned Duration	Range of Exposure
			13	Total 28 doses (14 days BID)	
SGNTUC-015	300 mg	Healthy	36	Total 27 doses (13 days BID, 1 day QD)	
SGNTUC-020	300 mg	Healthy	18	Total 14 doses (7 days BID)	

Abbreviations: BID=twice daily; QD=once a day; PIC=powder-in-capsule; PO=oral

The HER2CLIMB population included 601 subjects: 404 on the tucatinib arm and 197 on the control arm. All subjects received at least 1 dose of tucatinib/placebo. On the tucatinib arm, 3 subjects did not receive ≥1 dose of capecitabine, and 1 subject did not receive ≥1 dose of trastuzumab. As of the 04-Sep-2019 data cutoff, 118 subjects (29.2%) on the tucatinib arm and 27 subjects (13.7%) on the control arm remained on study treatment.

Subjects on the tucatinib arm of HER2CLIMB had longer duration of treatment compared with the control arm (median duration of exposure 5.8 and 4.4 months in the tucatinib and control arms, respectively (Table 31).

The median duration of exposure to capecitabine was 5.7 versus 4.4 months in the tucatinib and control arms, respectively. The median duration of exposure to trastuzumab was 6.0 versus 4.6 months. As treatment was given for longer periods of time on the tucatinib arm, median cumulative doses of capecitabine and trastuzumab were higher on the tucatinib arm than on the control arm (CSR ONT-380-206 Section 10.2.5.1).

The integrated safety population included all subjects who received tucatinib doses at or above the maximum tolerated dose (MTD)/RP2D (600 mg PO BID PIC or 300 mg PO BID tablet). The median duration of tucatinib exposure in Pool 1 and Pool 2 were consistent with HER2CLIMB, with subjects remaining on treatment a median of 5.8 months (range, <0.1 to 35.1). Tucatinib exposure duration was longer in HER2CLIMB compared to the tucatinib monotherapy study.

Table 31: Summary of Treatment Duration

	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Duration of tucatinib or placebo exposure (months)					
n	197	404	431	464	31
Mean (STD)	5.6 (4.3)	7.6 (6.3)	7.9 (6.7)	7.8 (6.7)	3.9 (4.2)
Median	4.4	5.8	5.8	5.8	2.7
Min, Max	<0.1, 24.0	<0.1, 35.1	<0.1, 35.1	<0.1, 35.1	<0.1, 21.8
Duration of capecitabine exposure (months)					
n	197	401	428	439	
Mean (STD)	5.4 (4.1)	7.3 (6.0)	7.6 (6.4)	7.6 (6.4)	
Median	4.4	5.7	5.8	5.8	
Min, Max	0.3, 24.1	0.3, 35.4	0.3, 35.4	0.3, 35.4	
Duration of trastuzumab exposure (months)					
n	197	403	430	452	
Mean (STD)	5.7 (4.3)	7.9 (6.4)	8.1 (6.7)	8.0 (6.7)	
Median	4.6	6.0	6.2	6.0	
Min, Max	0.7, 24.3	0.7, 35.4	0.7, 35.4	0.7, 35.4	

Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from studies HER2CLIMB and ONT-380-005. Data cutoff: ONT-380-206, 04-Sep-2019; ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013.

a. Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) ≥600 mg PO BID.

Source: ISS Table 10.1.4

The Applicant's Position:

(b) (4)

Regulatory Authorities Assessment:

The FDA agrees with the applicant's data on duration of exposure to tucatinib, placebo, trastuzumab, and capecitabine on HER2CLIMB. The FDA did not independently verify the duration of exposure information for Pool 1, Pool 2, and ARRAY-380-101. The FDA disagrees

(b) (4)

Relevant characteristics of the safety population:

Data:

Demographics and characteristics of the safety populations are summarized in Table 32.

Table 32: Demographic and Baseline Characteristics

	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Age (yr)					
n	197	404	431	464	31
Mean (STD)	54.1 (10.4)	53.8 (11.3)	53.6 (11.3)	53.3 (11.2)	55.4 (9.4)
Median	54.0	55.0	54.0	54.0	55.0
Min, Max	25, 78	22, 80	22, 80	22, 80	31, 69
Age Category, n (%)					
<65 years	164 (83.2)	322 (79.7)	346 (80.3)	374 (80.6)	25 (80.6)
≥65 years	33 (16.8)	82 (20.3)	85 (19.7)	90 (19.4)	6 (19.4)
≥75 years	4 (2.0)	8 (2.0)	8 (1.9)	8 (1.7)	0
Gender, n (%)					
Male	2 (1.0)	3 (0.7)	3 (0.7)	3 (0.6)	0
Female	195 (99.0)	401 (99.3)	428 (99.3)	461 (99.4)	31 (100)
Geographic Region, n (%)					
North America[b]	119 (60.4)	241 (59.7)	268 (62.2)	301 (64.9)	31 (100)
Rest of World	78 (39.6)	163 (40.3)	163 (37.8)	163 (35.1)	0
Race, n (%)					
Asian	5 (2.5)	18 (4.5)	19 (4.4)	19 (4.1)	2 (6.5)
Black or African American	14 (7.1)	39 (9.7)	42 (9.7)	43 (9.3)	2 (6.5)
White	153 (77.7)	283 (70.0)	306 (71.0)	335 (72.2)	25 (80.6)
Not available	0	0	0	3 (0.6)	0
Other	2 (1.0)	3 (0.7)	3 (0.7)	3 (0.6)	2 (6.5)
Unknown	23 (11.7)	61 (15.1)	61 (14.2)	61 (13.1)	0

Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from studies HER2CLIMB and ONT-380-005. Data cutoff: ONT-380-206, 04-Sep-2019; ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013.

a. Includes subjects from ARRAY-380-101 study who received PIC (powder-in-capsule) ≥600 mg PO BID.

b. 'North America' includes US and Canada.

Source: m2.7.4, Table 5

Baseline disease characteristics are summarized for the tucatinib integrated safety population in Table 33.

Table 33: Summary of Baseline Disease Characteristics

	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
History or presence of brain metastases at baseline, n (%)					
Yes	91 (46.2)	194 (48.0)	205 (47.6)	227 (48.9)	4 (12.9)
No	105 (53.3)	209 (51.7)	225 (52.2)	236 (50.9)	27 (87.1)
Unknown	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0

	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Time from initial diagnosis of breast cancer to enrollment (months)					
n	191	385	412	444	31
Mean (STD)	68.1 (60.7)	59.7 (42.5)	59.7 (42.8)	60.1 (42.9)	90.0 (61.3)
Median	48.9	47.9	47.7	47.7	70.7
Min, Max	8.7, 447.5	7.0, 234.8	7.0, 234.8	7.0, 234.8	15.6, 251.9
Time from initial diagnosis of locally advanced/metastatic breast cancer to enrollment (months)					
n	83	180	207	239	31
Mean (STD)	34.6 (27.9)	33.3 (31.1)	32.8 (30.0)	33.9 (30.6)	69.6 (45.3)
Median	29.9	25.9	25.6	26.6	66.0
Min, Max	1.6, 150.9	0.8, 183.3	0.8, 183.3	0.8, 183.3	7.5, 157.3
Number of prior regimens for breast cancer					
n	197	404	431	464	31
Mean (STD)	4.0 (1.9)	4.0 (1.8)	4.1 (1.8)	4.2 (2.0)	6.2 (2.9)
Median	4.0	4.0	4.0	4.0	6.0
Min, Max	2, 17	2, 14	2, 14	2, 14	2, 15
ECOG Performance Status, n (%)					
0	91 (46.2)	203 (50.2)	220 (51.0)	235 (50.6)	10 (32.3)
1	106 (53.8)	201 (49.8)	211 (49.0)	229 (49.4)	20 (64.5)
2	0	0	0	0	1 (3.2)

Incomplete initial diagnosis dates were imputed when calculating time to enrollment. Missing day was imputed with Day 15. Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from studies HER2CLIMB and ONT-380-005. Data cutoff: ONT-380-206, 04-Sep-2019; ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013.

a. Includes subjects from ARRAY-380-101 who received PIC (powder-in-capsule) ≥600 mg PO BID.

Source: ISS Table 10.1.3

The Applicant's Position:

Subject demographics and characteristics were balanced across the tucatinib integrated safety population. On both the tucatinib and control arms, most subjects were female, white, from North America, and had similar median ages.

Baseline disease characteristics were also balanced across the tucatinib integrated safety population. In HER2CLIMB, the proportion of subjects with a history or presence of brain metastases at baseline, the median time from initial diagnosis of BC to enrollment, and the median time from first diagnosis of metastatic disease to enrollment were similar across the tucatinib and control arms. Baseline characteristics among subjects in Pool 1 and Pool 2 were also similar to those on the tucatinib arm of HER2CLIMB.

In the tucatinib monotherapy study, most subjects did not have a history or presence of brain metastases. These subjects also had a longer median time from initial BC diagnosis, longer

median time from initial diagnosis of metastatic disease to enrollment, and were more heavily pretreated than those in HER2CLIMB and the pooled populations.

Overall, the safety population across the tucatinib development program was representative of the population expected for the indication under study. Across treatment arms in the pivotal HER2CLIMB study, the population was well balanced with regard to demographics and baseline disease characteristics. Subjects were mainly female and under 65 years of age. Although the majority of subjects from HER2CLIMB were from North America, the population from the EU and Rest of World were adequately represented and results were consistent across regions.

Regulatory Authorities Assessment:

The FDA agrees with the applicant's assessment that demographics and baseline disease characteristics were balanced between the two treatment arms in HER2CLIMB, and generally consistent among the HER2CLIMB, Pool 1, and Pool 2 populations.

The median age in the HER2CLIMB safety population (n=601 patients) was 54, 19.1% of patients were older than 65 years, and 2% of patients were older than 75 years. The safety population contained almost all women (99.2%) although men were eligible for this study and 5 men were included in the safety population. There were not expected to be differences in the safety profile of tucatinib between women and men. There were 72.5% White patients and 8.8% Black patients. Almost half (47.4%) of patients in the HER2CLIMB safety population had brain metastases at baseline.

Over half (53.6%) of patients were from the U.S. Generally, the safety population was representative of a U.S. population with advanced or metastatic HER2-positive breast cancer.

Adequacy of the safety database:

Data:
The sponsor is providing safety data for a total of 861 subjects who received at least 1 dose of tucatinib; 571 subjects with cancer and 290 subjects without cancer. The HER2CLIMB study evaluated tucatinib in combination with trastuzumab and capecitabine at the recommended clinical dose for subjects with HER2+ BC. Of the 601 subjects in the HER2CLIMB safety analysis set, 404 subjects received tucatinib.

The Applicant's Position:
The safety database is adequate for an informed assessment of the safety profile of tucatinib in combination with trastuzumab and capecitabine, as well as for evaluation of the overall benefit-risk in subjects with previously treated, locally advanced unresectable or metastatic HER2+ BC, including subjects with brain metastases. The double-blind, placebo-controlled, active comparator trial, HER2CLIMB, randomized 600 subjects in a 2:1 ratio to either the experimental arm or control arm. This safety database is also considered adequate for the

detection and characterization of common AEs and to provide guidance on toxicity management.

Regulatory Authorities Assessment:
The regulatory authorities generally agree that the safety database is adequate to evaluate the safety profile of tucatinib.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
Clinical sites across studies evaluating the safety of tucatinib were monitored following study-specific monitoring plans for consistency. Data were queried per study-specific data management plans. Additionally, an IDMC reviewed safety data for HER2CLIMB on an ongoing basis.

The Applicant's Position:
No issues were identified regarding data integrity or submission quality that affected the safety review.

Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's assessment of data integrity and submission quality based on our own review and clinical inspections from the FDA Office of Scientific Investigations (OSI). Please see Section 4.1 for additional information.

Categorization of Adverse Events

Data:
NA

The Applicant's Position:
HER2CLIMB: AEs reported in HER2CLIMB were classified according to the MedDRA version 22.0 and their severity graded according to NCI CTCAE, version 4.03. Unless otherwise noted, AEs were treatment-emergent. TEAEs were defined as events that were new or worsened after receiving the first dose of study treatment (tucatinib/placebo, trastuzumab, or capecitabine) and up through 30 days after the last dose of study treatment. The following TEAEs of special interest were to have been reported to the sponsor irrespective of seriousness or causality within 24 hours.

Potential drug-induced liver injury: To ensure reporting of any potential drug-induced liver injury, the following protocol-defined laboratory criteria were used to define this AESI for reporting purposes, regardless of etiology: AST or ALT elevations >3x upper limit of normal

(ULN) with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2xULN, except in subjects with documented Gilbert's syndrome. Additional clinical data were then considered in these cases to assist in determination of its etiology, such as concomitant medications, conjugated/unconjugated bilirubin, ALP, presence of liver metastases, and other clinical evaluations.

Left ventricular systolic dysfunction: HER2-directed therapies have the potential to cause cardiotoxicity. Given the mechanism of action of tucatinib on inhibition of HER2, as well as the increased risk for cardiac dysfunction in this subject population due to previous treatment with known cardiotoxic therapies, left ventricular systolic dysfunction leading to dose modification or discontinuation was considered an AESI in HER2CLIMB.

Cerebral edema: Cerebral edema: An index case of cerebral edema occurred in a subject on Study ONT-380-005 with known brain metastases who was found to have cerebral edema in an area surrounding a known metastasis in the thalamus. Imaging findings were consistent with cytotoxic edema in myelinated fibers identified as associated with capecitabine in published literature. Given that this event of cerebral edema was evaluated as a possible treatment-emergent effect rather than actual tumor progression, the HER2CLIMB protocol was amended to collect events of cerebral edema not clearly attributable to progression of disease as AEs of interest.

ONT-380-005: The primary endpoint of this study was the incidence of AEs by toxicity grade. Safety was monitored throughout the study, and assessments included all AEs, dose-limiting toxicities (DLTs), clinical laboratory parameters, electrocardiogram (ECG), ECOG PS, vital signs, physical examination findings, and LVEF as determined by either echocardiogram (ECHO) or multigated acquisition (MUGA) scans. For subjects that participated in the long-term extension phase of the study, only SAEs and events of interest were collected.

ARRAY-380-101: Safety was assessed throughout the study and included the monitoring of AEs, DLTs, clinical laboratory parameters, ECG and ECHO/MUGA scan results and physical examination findings.

Regulatory Authorities Assessment:

THE regulatory authorities agree with the applicant's categorization of adverse events (AEs) on the HER2CLIMB study. Treatment-emergent AEs were defined as AEs occurring after the first dose of study drug to within 30 days after the last dose of study drug.

The FDA's safety assessment focused on the frequency and severity of all TEAEs on HER2CLIMB, with additional focus on TEAEs leading to death; SAEs, TEAEs leading to study drug discontinuation, dose reduction, or dose interruption; and AESIs.

Routine Clinical Tests

Data:
NA

The Applicant's Position:
HER2CLIMB: Serum chemistry and hematology samples were collected per protocol specified schedules. All laboratory results were converted into Système International (SI) units for analysis and graded using the laboratory reference ranges and the criteria from NCI CTCAE version 4.03 by the Sponsor. For lab parameters ALT, AST, bilirubin, ALP, activated partial thromboplastin time (aPTT) and international normalized ratio (INR), the reference ranges from individual laboratories were used if available; for other lab parameters, the Sponsor's standard normal ranges were used to perform toxicity grading.

Incidence of Laboratory Toxicities: The incidence of laboratory toxicities by grade are summarized by treatment arm. For each test, only the worst (i.e., highest) toxicity grade is counted for subjects with multiple toxicities within a time period (including scheduled and unscheduled assessments). The change of toxicity grade from baseline to worst baseline grade (shift table) is also summarized. In addition to summary tables, listings of laboratory test results are provided.

Incidence of Liver Abnormalities: The incidence of liver abnormalities are summarized by treatment arm. A liver abnormality is defined as AST or ALT elevations that are >3 x ULN with concurrent elevation (same day or within 21 days following AST and/or ALT elevations) of total bilirubin >2 x ULN.

Ejection Fraction: The minimal post baseline ejection fraction and the maximum decrease from baseline are summarized for each treatment group. Time to minimal post baseline ejection fraction was also tabulated.

Vital Signs: Vital signs (weight, body temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure) are listed. The frequency and percentage of subjects with post baseline clinically significant vital signs are summarized. For weight, the maximum decrease from baseline is also summarized.

Clinically significant laboratory abnormalities or vital signs (e.g., requiring intervention, meeting serious criteria, resulting in study termination or interruption of study treatment, or associated with signs and symptoms) were to be recorded as AEs.

There were minor differences in laboratory parameter collection between studies in the tucatinib integrated safety population (e.g., blood and urine samples were collected at the time points specified per protocol for analysis of the standard clinical chemistry, hematology, and urinalysis parameters).

Regulatory Authorities Assessment:

The FDA performed an independent analysis of clinical data collected on HER2CLIMB including laboratory tests (Section 8.2.4) and left ventricular ejection fraction (Section 8.2.5.4). The FDA's analysis of laboratory abnormalities focused on patients with worsening lab values from baseline and tabulated the worst post-baseline grade (shift table). The FDA's analysis of liver abnormalities included frequency and severity of abnormalities in individual liver tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin (Tbili). The FDA's analysis also included patients who met initial screening criteria for Hy's law (AST and/or ALT > 3 x upper limit of normal (ULN) with concurrent Tbili > 2x ULN). The FDA's analysis of left ventricular ejection fraction included the worst post-baseline ejection fraction and the maximum change in ejection fraction from baseline.

8.2.4. Safety Results

Deaths

Data:

In HER2CLIMB, a total of 14 subjects experienced TEAEs leading to death, 8 (2%) on the tucatinib arm and 6 (3%) on the control arm (Table 34). For 1 subject on the control arm, the cause of death was reported as both Grade 5 respiratory failure and progressive disease. For the 2 subjects on the tucatinib arm with Grade 5 sudden death, the cause of death was reported as unknown.

Table 34: Treatment-Emergent Adverse Events Leading to Death

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a,b] N=31
Subjects with any event	6 (3.0)	8 (2.0)	8 (1.9)	8 (1.7)	1 (3.2)
Sudden death	0	2 (0.5)	2 (0.5)	2 (0.4)	0
Cardiac arrest	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0
Cardiac failure	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Dehydration	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0
Sepsis	1 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0
Septic shock	0	1 (0.2)	1 (0.2)	1 (0.2)	0
Malignant neoplasm progression	0	0	0	0	1 (3.2)
Myocardial infarction	1 (0.5)	0	0	0	0
Respiratory failure	1 (0.5)	0	0	0	0

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a,b] N=31
Systemic inflammatory response syndrome	1 (0.5)	0	0	0	0

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column. Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from studies HER2CLIMB and ONT-380-005. Data cutoff: ONT-380-206, 04-Sep-2019; ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013.

a. Includes subjects from ARRAY-380-101 who received PIC (powder-in-capsule) ≥600 mg PO BID.

b. In ARRAY-380-101, 1 death due to malignant neoplasm progression was reported as an adverse event.

Source: ISS Table 10.2.7

The Applicant's Position:

The number and incidence of deaths due to TEAEs were balanced between the tucatinib and control arms of HER2CLIMB, with the majority on both treatment arms due either to infection or a cardiovascular event. Events leading to deaths were similar between the tucatinib arm of HER2CLIMB and Pools 1 and 2. No signal was identified.

Regulatory Authorities Assessment:

The FDA performed an independent analysis of deaths in the HER2CLIMB study. There were 28 deaths in the safety population which occurred within 30 days of the last dose of study treatment. Half of these deaths (n=14) were due to disease progression, with 7 (1.7%) occurring on the tucatinib arm and 7 (3.6%) occurring on the placebo arm. The other 14 deaths were due to TEAEs, with 8 (2.0%) on the tucatinib arm and 6 (3.0%) on the placebo arm.

The FDA reviewed all death narratives provided by the applicant. The FDA considers grade 4 diarrhea from the combination of tucatinib and capecitabine as contributing to two deaths on the tucatinib arm. A summary of all 14 deaths due to TEAEs are included below, listed by treatment arm. Tucatinib arm:

Patient ID (b) (6): This 68 year old female patient presented with new onset atrial fibrilliaton and rapid ventricular response on study day 942. An echocardiogram showed a left ventricular ejection fraction (LVEF) of 20%; previous LVEF was 50% on study day 928. During admission, she had a cardiac arrest. Although she had return of spontaneous circulation (ROSC) following CPR, repeat echocardiogram showed LVEF 5% and she died on study day 945 due to cardiogenic shock. Her last dose of tucatinib was on study day 940 and trastuzumab was on study day 932. Capecitabine was discontinued earlier due to palmar-plantar erythrodysestehesia (PPE) syndrome. The FDA agrees that the events leading to death are unlikely to be related to the study treatment but cannot completely exclude this possibility that tucatinib and trastuzumab contributed.

Patient ID (b) (6): This 70 year old female patient presented with nausea, vomiting, and abdominal pain and a partial small bowel obstruction on study day 57. She subsequently developed respiratory failure and sepsis. Her family switched care to comfort measures only and she died on study day 62 due to sepsis. Her last dose of tucatinib was on study day 49, capecitabine was on study day 56, and trastuzumab was on study day 43. The FDA agrees that nausea, vomiting, abdominal pain were related to tucatinib and capecitabine. However, this patient's partial small bowel obstruction was a major contributor to death and it is not clear how this developed or that it was related to study treatment.

Patient ID (b) (6): This 68 yo female patient presented with grade 4 diarrhea and hypotension on study day 18. She had a history of atrial fibrillation and was having a rapid ventricular response. She tested negative for *Clostridium difficile* infection. She developed an acute kidney injury with oliguria, had continued hypotension requiring pressors, and had presumed sepsis and was receiving antibiotics without a source isolated. She ultimately died. She tested negative for the IVS14+1G>A mutation in the dihydropyrimidine dehydrogenase (DPD) gene. Her last dose of tucatinib was on study day 18, last dose of capecitabine on study day 14, and last dose of trastuzumab on study day 1. The FDA disagrees with the applicant's assessment and considers grade 4 diarrhea which contributed to this patient's death as related to both tucatinib and capecitabine.

Patient ID (b) (6) This 68 yo female patient presented with nausea, vomiting, and large volume diarrhea on study day 36. She tested negative for *Clostridium difficile* infection but tested positive for influenza A on nasal swab, had Mycoplasma pneumoniae IgM antibody in blood, and a positive Streptococcus pneumoniae antigen in urine. Her diarrhea worsened to grade 4, she started treatment with steroids and octreotide and switched goals to comfort care. She died on study day 49. Her last dose of tucatinib and capecitabine were on study day 35, and last dose of trastuzumab was on study day 22. The FDA disagrees with the applicant's assessment and considers both the grade 4 diarrhea and dehydration which led to this patient's death as related to tucatinib and capecitabine.

Patient ID (b) (6) This 53 year old female patient with malignant bilateral pleural effusions at baseline developed fever, chills, and worsening shortness of breath at home on study day 106 and started treatment with doxycycline. She had a cardiac arrest at home on study day 107, experienced CPR with ROSC, but was neurologically unresponsive and died shortly thereafter. Her last day of tucatinib was on study day 105, capecitabine was on study day 98, and trastuzumab was on study day 85. The FDA considers the cause of death sudden death and agrees that tucatinib, as well as the other study treatments, are unlikely to be related. However, there is not enough information to completely exclude this possibility.

Patient ID (b) (6): This 51 year old female patient developed *Clostridium difficile* colitis requiring hospitalization on study day 9. She became neutropenic (absolute neutrophil count nadir 0), developed septic shock, and died on study day 18. Her last dose of tucatinib was on study day 12, capecitabine was on study day 12, and trastuzumab was on study day 1. The

FDA disagrees with the applicant and attributes this patient's death from septic shock in the setting of neutropenia to the study treatment combination, not only capecitabine.

Patient ID (b) (6): This 60 year old female patient with baseline liver and brain metastatses died suddenly at home on study day 6. She had a history of diabetes mellitus type II but no cardiac history and LVEF was 69% on baseline echocardiogram. The FDA considers the cause of death as sudden death and disagrees with the applicant that it is unrelated to tucatinib. There is not enough information to determine if it was related to study treatments.

Patient ID (b) (6): This 51 yo female patient died suddenly in her sleep on study day 38. She developed grade 3 peripheral edema of her bilateral arms on study day 22. The suspected cause was thrombosis and she started anticoagualation. Peripheral edema improved. Her last doses of tucatinib and capecitabine were on studay day 37, and last dose of trastuzumab was on study day 29. The FDA considers sudden death the cause of death and disagrees with the applicant that it is unrelated to tucatinib. There is insufficient information to determine if it was related to study treatments.

Placebo arm:

Patient ID (b) (6): This 49 yo female patient had metastatic disease involving her lungs. She stopped study treatment on day 43 due to disease progression. On study day 59, she died fron respiratory failure secondary to disease progression. The FDA agrees with the applicant that this patient's death is not related to study treatments and attributes it to disease progression.

Patient ID (b) (6) This 42 year-old female patient with metastatic disease to her lungs and brain stopped study treatment on day 124 due to disease progression. On study day 138 she had a cardiac arrest and died. She also had a history of diabetes and deep vein thrombosis. The FDA agrees with the applicant that the cause of death is unknown but it is unlikely to be related to the study treatments.

Patient ID (b) (6): This 53 year-old female patient with metastatic disease involving her lungs discontinued study treatment on day 55 due to disease progression. She began treatment with doxorubicin and cyclophosphamide on day 64, developed fever and shortness of breath, and died on day 69. During admission, a CT scan showed innumerable pulmonary nodules and masses. The FDA agrees with the applicant that these events were unrelated to study treatment and attributes this patient's death to disease progression.

Patient ID (b) (6) This 65 year-old patient had metastatic disease involving the lungs, liver, and brain and malignant pleural effusions. She had a myocardial infarction on study day 75, and died on study day 76. Her last dose of placebo was on study day 62, capecitabine was on study day 56, and trastuzumab was on study day 43. The FDA disagrees that this patient's death from myocardial infarction is unrelated to study treatment. There is not enough information to make this determination .

Patient ID (b) (6): This 70 year-old female patient developed grade 3 diarrhea and a urinary tract infection with a *Klebsiella* spp. on study day 81. She developed shock, neutropenia (ANC nadir 350), and acute renal failure. She was negative for Clostridium difficile, and no additional pathogens were identified, but CT-scan was consistent with acalculous cholecystitis. She died on study day 93. Her last dose of placebo was on study day 78, capecitabine was on study day 77, and trastuzumab was on study day 64. The FDA agrees with the applicant and attributes this patient's death from neutropenic sepsis as related to study treatments.

Patient ID (b) (6) This 67 year-old female patient with metastatic disease involving the brain developed mental status changes on study day 13. MRI brain showed lesions atypical for metastases, but the patient started dexamethasone. She developed *Clostridium difficile* colitis on study day 36. She developed left hemiplegia with evidence of a recent stroke on brain MRI on study day 42; it was unclear if small brain lesions were a contributor. She continued to be encephalopathic. She had a cardiac arrest during a blood transfusion for anemia on study day 52. The FDA agrees that this patient's death is not related to the study treatments.

Serious Adverse Events

Data:
In HER2CLIMB, SAEs were reported for 104 subjects (25.7%) and 53 subjects (26.9%) on the tucatinib and control arms, respectively. The most frequently reported SAE on the tucatinib arm was diarrhea (4%), followed by vomiting (2.5%) and nausea (2.0%), which occurred with similar incidence on the control arm (3.6%, 2.5%, and 1.5%, respectively)

The overall incidence of SAEs was similar across the tucatinib integrated safety population. Although the highest incidence observed was in the tucatinib monotherapy study (35.5%), subjects were more heavily pretreated compared to those in Pool 1 and Pool 2 (median prior therapies 6 vs. 4), with a higher percentage of subjects having an ECOG of 1 or greater. The most frequently reported SAEs on the tucatinib arm of HER2CLIMB occurred with similar incidence in Pool 1; diarrhea (3.7%), vomiting (2.3%), and nausea (1.9%). The overall incidence was similar in Pool 2. Among subjects in the tucatinib monotherapy study, the incidence of diarrhea and vomiting (3.2% each) were similar to the pooled populations.

The Applicant's Position:
Across the tucatinib development program, tucatinib SAE incidence rates were low and no new safety signals were identified. Treatment-emergent SAEs were similar between the tucatinib and control arms of HER2CLIMB, and Pools 1 and 2. The most common SAEs in the tucatinib integrated safety population, diarrhea and vomiting, were representative of the overall safety profile of tucatinib.

Regulatory Authorities Assessment:

The FDA conducted an independent analysis of SAEs and generally agrees with the applicant's assessment. The percentages of patients with SAEs were similar between the two treatment arms of HER2CLIMB. The frequencies of overall SAEs were similar across the tucatinib safety population, except in the tucatinib monotherapy study, ARRAY-380-101, in which a greater percentage of patients had SAEs. The FDA agrees with the applicant's assessment that this is likely because patients were more heavily pretreated disease and had worse performance status. The FDA also notes that in ARRAY-380-101, disease progression was an AE.

The most frequent SAEs (≥2%) on the tucatinib arm of HER2CLIMB were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%) [grouped preferred terms: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness], and seizure (2%) [grouped preferred terms: seizure, generalised tonic-clonic seizure, epilepsy]. The placebo arm of HER2CLIMB had similar incidences of diarrhea, vomiting, nausea, and seizure, but 0 patients with an SAE of abdominal pain. Diarrhea and vomiting were the most frequent SAEs across the tucatinib integrated safety population, occurring at similar incidences as on HER2CLIMB.

The incidence of fracture was higher in patients on the tucatinib arm of HER2CLIMB compared to the placebo arm, 1.7% versus 0%, when pooling all "fracture"-related preferred terms [spinal fracture, fracture nonunion, ankle fracture, foot fracture, patella fracture,radius fracture, spinal compression fracture, and sternal fracture]. The causes of fracture included car accident (n=2 patients), hardware failure from prior pathologic fracture (n=1), spinal compression fracture following a fall, not clearly pathologic (n=2 patients), patellar fracture following a fall, not pathologic (n=1 patient), and pathologic fracture (n=1 patient). There were two additional patients with fracture SAEs following falls in the overall tucatinib safety population. It is unclear if either was pathologic. The FDA does not consider these fractures related to tucatinib.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Discontinuation of tucatinib or placebo due to TEAEs was infrequent in both tucatinib and control arms of HER2CLIMB (5.7% vs. 3.0%). The most common events were diarrhea (1.0% vs. 0.5%), elevated LFTs (ALT increased [1.0% vs. 0.5%], AST increased [0.7% vs. 0.5%], and blood bilirubin increased [0.7% vs. 0.5%]), and vomiting (0.7% vs. 0%).

The incidence rates of treatment discontinuation due to TEAEs in Pool 1 and Pool 2 were similar to the tucatinib arm of HER2CLIMB (5.8% and 5.4%); the most common events in Pool 1 were diarrhea (1.2%), elevated LFTs (ALT increased [0.9%], AST increased [0.7%], and blood bilirubin increased [0.7%]), and vomiting (0.7%). In the tucatinib monotherapy study, the incidence of treatment discontinuation was 12.9%, the higher rate was due to 2 of 31 subjects (6.5%) who

had malignant neoplasm progression reported as an AE. Progression of disease was not considered an AE in tucatinib studies other than the monotherapy study.

A total of 41 subjects (10.1%) on the tucatinib arm and 18 subjects (9.1%) on the control arm of HER2CLIMB discontinued capecitabine due to a TEAE. The most common TEAE leading to capecitabine discontinuation on the tucatinib and control arms was PPE syndrome (2.2% vs. 2.0%). Other TEAEs leading to capecitabine discontinuation on the tucatinib and control arms included diarrhea (1.7% vs. 1.0%), ALT increased (1.0% vs. 0), and dehydration (0.7% vs. 0).

A total of 18 subjects (4.5%) on the tucatinib arm and 5 subjects (2.5%) on the control arm of HER2CLIMB discontinued trastuzumab due to a TEAE. The most common TEAEs leading to trastuzumab discontinuation on the tucatinib and control arms included; ALT increased (0.7% vs. 0), diarrhea (0.7% vs. 0.5%), AST increased (0.5% vs. 0), blood bilirubin increased (0.5% vs. 0.5%), respiratory failure (0.5% vs. 0), and sepsis (0.5% vs. 0.5%).

The Applicant's Position:
The overall incidence of TEAEs leading to tucatinib discontinuation was low in the tucatinib and control arms of HER2CLIMB and Pools 1 and 2. The most common events that led to tucatinib treatment discontinuation, diarrhea and elevated LFTs, were consistent with the overall safety profile of tucatinib. On the tucatinib and control arms of HER2CLIMB, similar proportions of subjects discontinued capecitabine due a TEAE, most commonly PPE syndrome, a well characterized side effect of capecitabine.

Regulatory Authorities Assessment:
The FDA conducted an independent assessment of TEAEs associated with study drug discontinuation. The FDA agrees with the applicant's assessment that study drug discontinuations were low on HER2CLIMB, although they were more discontinuations of tucatinib than placebo (5.7% versus 3.0%).

The most common reasons for tucatinib discontinuation (≥1.0%) were hepatotoxicity (1.5%) [grouped preferred terms: hyperbilirubinaemia, blood bilirubin increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, hepatocellular injury, bilirubin conjugated increased], diarrhea (1%), increased bilirubin (1%) [grouped preferred terms: hyperbilirubinaemia, blood bilirubin increased, bilirubin conjugated increased], and increased ALT (1%) [grouped preferred terms: alanine aminotransferase increased, transaminases increased]. The corresponding incidences of these TEAEs leading to discontinuation of placebo were: hepatoxicity 1%, diarrhea 0.5%, increased bilirubin 0.5%, and increased ALT 0.5%.

The FDA agrees with the applicant that the overall incidence of TEAEs leading to capecitabine discontinuation and the incidence of palmar-plantar erythrodysesthesia syndrome leading to capecitabine discontinuation were similar on the tucatinib arm compared to the placebo arm

of HER2CLIMB. The FDA notes that capecitabine discontinuations due to diarrhea and dehydration were both more common on the tucatinib arm.

The FDA agrees with the applicant's assessment that the incidence of TEAEs leading to trastuzumab discontinuation was low in HER2CLIMB, although slightly higher in the tucatinib arm compared to the placebo arm. The most common reason for trastuzumab discontinuation was hepatotoxicity, occurring in 1% of patients on the tucatinib arm versus 0.5% on the placebo arm. Discontinuation due to decreased ejection fraction was rare, only occurring in one patient on the tucatinib arm.

Dose Interruption/Reduction Due to Adverse Effects

Data:
A total of 216 subjects (53.5%) on the tucatinib arm and 80 subjects (40.6%) on the control arm of HER2CLIMB had a tucatinib or placebo dose hold due to a TEAE; the most common events were diarrhea (13.9% and 8.6%), blood bilirubin increased (8.2% and 7.1%), ALT increased (6.4% and 0.5%), and PPE syndrome (6.4% and 2.0%). Dosing resumed at the same dose following the dose hold in 220 of 382 total events (57.6%) on the tucatinib arm and 67 of 115 total events (58.3%) on the control arm. The median duration of dose holds due to TEAEs (calculated for subjects who resumed dosing at the same dose or at a reduced dose) was 7.0 days (range, 1 to 42) on the tucatinib arm and 8.0 days (range, 1 to 50) on the control arm.

The proportion of subjects with tucatinib dose holds was consistent between HER2CLIMB and Pool 1 (53.5% and 53.1%). The most common reasons for dose withheld in Pool 1 were diarrhea (13.7%), blood bilirubin increased (7.9%), PPE syndrome (6.5%), and ALT increased (6.3%); incidence rates were similar in Pool 2. TEAEs reported in the tucatinib monotherapy study that were consistent with those in Pool 1 and Pool 2 included diarrhea (3.2%), ALT increased (9.7%), AST increased (3.2%), and vomiting (3.2%).

In HER2CLIMB, TEAEs led to tucatinib or placebo dose reductions in 84 subjects (20.8%) on the tucatinib arm and 21 subjects (10.7%) on the control arm. On the tucatinib arm, 60 subjects (14.9%) were dose reduced to 250 mg BID, 15 subjects (3.7%) were dose reduced to 200 mg BID, and 9 subjects (2.2%) were dose reduced to 150 mg BID. The most common TEAEs leading to tucatinib or placebo dose reductions were diarrhea (5.7% and 4.6%), ALT increased (4.7% and 0.5%), AST increased (4.2% and 1.0%), and blood bilirubin increased (2.2% and 1.0%) on the tucatinib and control arms, respectively.

The proportion of subjects with tucatinib dose reductions was consistent between HER2CLIMB and Pool 1 (20.8% and 20.9%). The most common reasons for reduction in Pool 1 were diarrhea (5.3%), ALT increased (4.9%), and AST increased (4.4%). The overall incidence was similar in Pool 2. Fewer subjects in the tucatinib monotherapy study had dose reductions (12.9%), which were due to ALT and AST increased (6.5% each).

In HER2CLIMB, TEAEs led to capecitabine dose reductions in 243 subjects (60.1%) on the tucatinib arm and 78 subjects (39.6%) on the control arm. The most common reasons for capecitabine dose reductions were PPE syndrome (32.9% and 24.4%), diarrhea (16.8% and 6.6%), fatigue (4.5% and 2.0%), and stomatitis (4.0% and 1.5%) on the tucatinib arm and control arm, respectively. Dose reductions for trastuzumab were not allowed per protocol.

The Applicant's Position:
Tucatinib/placebo dose modifications occurred with greater frequency on the tucatinib arm compared to the control arm (dose holds: 53.3% vs. 40.6% and dose reductions: 20.8% vs. 10.7%); however, the median relative dose intensities were comparable between treatment arms (93.6% and 97.0%), indicating most subjects were able to receive the intended dose of tucatinib over their treatment duration.

The overall incidence of TEAEs leading to tucatinib dose hold or reduction were consistent between the tucatinib arm of HER2CLIMB and Pools 1 and 2. Fewer dose modifications occurred with tucatinib monotherapy. The most common events leading to tucatinib dose modifications, diarrhea and elevated LFTs, were representative of the overall safety profile of tucatinib.

(b) (4)

Regulatory Authorities Assessment:
The FDA performed an independent analysis of TEAEs leading to dose interruptions and reductions on HER2CLIMB. Compared to the applicant's analysis, there were overall slightly fewer patients with dose interruptions and reductions. The applicant's analysis is based on two datasets: the adverse event analysis dataset (ADAE) and the exposure summary analysis dataset (ADEX). When the FDA compared the two datasets, we found several discrepancies in the dose interruption data in ADEX. For example, a patient was recorded as having a dose interruption in ADEX on the same date as disease progression and treatment discontinuation, or a patient was recorded as having a dose interruption in ADEX on the same date as dose discontinuation due to an TEAE. The FDA only used the ADAE dataset to examine dose interruptions and reductions.

Dose interruptions in HER2CLIMB were more common with tucatinib than placebo, occurring in 52% versus 39% of patients on each arm. The most common reasons for tucatinib interruption were diarrhea: 13% versus 8%, and hepatotoxicity: 18% versus 9%, which included increased bilirubin: 12% versus 9%, increased ALT: 7% versus 0.5%, and increased AST: 6% versus 1%.

Dose reductions were also more common with tucatinib versus placebo in HER2CLIMB, occurring in 18% versus 9% of patients. The most common reason was hepatotoxicity which

occurred in 8% of patients on the tucatinib arm versus 2.5% on the placebo arm and included increased ALT: 4.7% versus 0.5%, increased AST: 4% versus 1%, and increased total bilirubin: 2.7% versus 1.5%. The incidence of dose reductions for diarrhea was similar between the two arms: 4.2% with tucatinib and 3.6% with placebo. Overall, the FDA agrees with the applicant's assessment that the predominance of GI and liver-associated TEAEs as reasons for dose interruptions and reduction is consistent with the overall safety profile of tucatinib.

Capecitabine dose interruptions and reductions in HER2CLIMB were more common on the tucatinib arm compared to the placebo arm, occurring in 67% versus 56% of patients and 55% versus 38% of patients respectively. The most common reasons for capecitabine dose reductions on the tucatinib arm were palmar-plantar erythrodysesthesia syndrome occurring in 32% versus 22% of patients and diarrhea occurring in 15% versus 9% of patients. The FDA disagrees with the applicant's conclusion (b) (4)

Trastuzumab dose interruptions in HER2CLIMB were slightly more common on the tucatinib arm compared to the placebo arm, occurring in 24% of patients versus 19% of patients. Notably, interruptions for decreased ejection fraction were rare and balanced between the two arms, occurring in 1% of patients on the tucatinib arm versus 1.5% of patients on the placebo arm.

Significant Adverse Events

Data:

For the purposes of this section, Grade ≥3 TEAEs are considered to be significant. At least one Grade ≥3 TEAE was reported for 55.2% of subjects on the tucatinib arm and 48.7% on the control arm of HER2CLIMB. See Table 35 for a summary of Grade ≥3 TEAEs occurring in ≥2% of subjects in Pool 1.

Table 35: Treatment-Emergent Grade ≥3 AE Occurring in ≥2% of Pool 1 Subjects

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Subjects with any event	96 (48.7)	223 (55.2)	241 (55.9)	252 (54.3)	18 (58.1)
Palmar-plantar erythrodysaesthesia syndrome	18 (9.1)	53 (13.1)	56 (13.0)	57 (12.3)	0
Diarrhoea	17 (8.6)	52 (12.9)	55 (12.8)	56 (12.1)	1 (3.2)
Alanine aminotransferase increased	1 (0.5)	22 (5.4)	24 (5.6)	25 (5.4)	2 (6.5)
Fatigue	8 (4.1)	19 (4.7)	23 (5.3)	24 (5.2)	0
Aspartate aminotransferase increased	1 (0.5)	18 (4.5)	20 (4.6)	21 (4.5)	2 (6.5)

n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Anaemia	5 (2.5)	15 (3.7)	17 (3.9)	17 (3.7)	2 (6.5)
Nausea	6 (3.0)	15 (3.7)	15 (3.5)	16 (3.4)	1 (3.2)
Hypokalaemia	10 (5.1)	13 (3.2)	14 (3.2)	14 (3.0)	2 (6.5)
Pulmonary embolism	4 (2.0)	13 (3.2)	13 (3.0)	13 (2.8)	0
Hypophosphataemia	4 (2.0)	11 (2.7)	12 (2.8)	13 (2.8)	0
Vomiting	7 (3.6)	12 (3.0)	12 (2.8)	14 (3.0)	0
Stomatitis	1 (0.5)	10 (2.5)	10 (2.3)	10 (2.2)	0
Neutropenia	9 (4.6)	9 (2.2)	9 (2.1)	10 (2.2)	0

Data are sorted by descending order of frequency and then by ascending alphabetic order of preferred term in Pool 1 column. Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from studies HER2CLIMB and ONT-380-005. Data cutoff: ONT-380-206, 04-Sep-2019; ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013.

a. Includes subjects from ARRAY-380-101 study who received PIC (powder-in-capsule) ≥600 mg PO BID.

Source: ISS Table 10.2.6

The Applicant's Position:

The incidence of Grade ≥3 TEAEs was higher on the tucatinib arm than the control arm of HER2CLIMB, with incidence rates consistent between the tucatinib arm, and Pools 1 and 2. The most common Grade ≥3 event, PPE syndrome, was not reported in the tucatinib monotherapy study, which supports the association of PPE syndrome with capecitabine treatment.

Regulatory Authorities Assessment:

The FDA performed an independent analysis of severe (Grade ≥3) TEAEs and this is included in Table 37below. The Applicant's Table 35includes deaths (Grade 5 TEAEs) as part of Grade ≥3 AEs whereas the FDA's Table 37does not, leading to slight differences in the number of all Grade ≥3 AEs.

There were slight discrepancies between the applicant's analysis and the FDA's analysis due to differences in pooling preferred terms. The incidence of Grade ≥3 fatigue [grouped terms: fatigue, asthenia] on HER2CLIMB was 5% in the tucatinib arm versus 4.6% in the placebo arm. The incidence of Grade≥3 increases in ALT [grouped terms: alanine aminotransferase increased, transaminases increased] was 6% on the tucatinib arm versus 0.5% on the placebo arm. The incidence of Grade ≥3 increases in AST [grouped terms: aspartate aminotransferase increased; transaminases increased] was 4.7% on the tucatinib arm versus 0.5% on the placebo arm.

Grade≥3 TEAEs occurred in approximately half of patients on HER2CLIMB and were more common on the tucatinib arm versus the placebo arm. The most common Grade ≥3 TEAEs associated with tucatinib were palmar-plantar erythrdysthesia (PPE) syndrome, diarrhea, and

increased ALT and AST. Although, there were no Grade≥3 TEAEs of PPE syndrome on the tucatinib monotherapy study, this was a relatively small study (n=33 patients).

Treatment Emergent Adverse Events and Adverse Reactions

Data:
Despite subjects on the tucatinib arm of HER2CLIMB having longer median treatment duration than subjects on the control arm (5.8 vs. 4.4 months), incidence rates of TEAEs, Grade ≥3 TEAEs, SAEs, and treatment discontinuations due to TEAEs were similar between treatment arms.

In general, the total incidence and severity of TEAEs in Pool 1, Pool 2, and the tucatinib monotherapy study were similar to the tucatinib arm of HER2CLIMB. An overall summary of TEAEs is presented for the tucatinib integrated safety population in Table 36.

Table 36: Summary of Treatment-Emergent Adverse Events

Subjects n (%)	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Any TEAE	191 (97.0)	401 (99.3)	428 (99.3)	461 (99.4)	30 (96.8)
Grade ≥3 TEAE	96 (48.7)	223 (55.2)	241 (55.9)	252 (54.3)	18 (58.1)
TE SAE	53 (26.9)	104 (25.7)	115 (26.7)	124 (26.7)	11 (35.5)
TEAEs leading to death	6 (3.0)	8 (2.0)	8 (1.9)	8 (1.7)	1 (3.2)
Discontinued any study treatment due to TEAE	19 (9.6)	45 (11.1)	48 (11.1)	48 (10.3)	4 (12.9)
Discontinued tucatinib/placebo due to TEAE	6 (3.0)	23 (5.7)	25 (5.8)	25 (5.4)	4 (12.9)
Discontinued capecitabine due to TEAE	18 (9.1)	41 (10.1)	44 (10.2)	44 (9.5)	NA
Discontinued trastuzumab due to TEAE	5 (2.5)	18 (4.5)	20 (4.6)	20 (4.3)	NA

Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from studies HER2CLIMB and ONT-380-005. Data cutoff: ONT-380-206, 04-Sep-2019; ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013.

a. Includes subjects from ARRAY-380-101 who received PIC (powder-in-capsule) ≥600 mg PO BID.

Source: ISS Table 10.2.1

The most commonly reported TEAEs on the tucatinib and control arms of HER2CLIMB were diarrhea (80.9% vs. 53.3%), PPE syndrome (63.4% vs. 52.8%), nausea (58.4% vs. 43.7%), fatigue (45.0% vs. 43.1%), and vomiting (35.9% vs. 25.4%). When adjusted for exposure using at-risk time, the incidence rate per 100 person-years of PPE syndrome was 21 and 19 on the tucatinib and control arms, respectively.

The most common TEAEs of any grade on the tucatinib arm of HER2CLIMB occurred with similar incidence in Pool 1: diarrhea (80.5%), PPE syndrome (63.6%), nausea (59.6%), fatigue (45.0%),

and vomiting (36.9%); the incidence rates were similar in Pool 2. Among subjects treated with tucatinib monotherapy, the most common TEAEs were similar to those reported in the other groups with the exception of PPE syndrome, which was not reported. For a discussion of PPE syndrome in the tucatinib integrated safety population, see Section 8.2.5.3.

TEAEs that have been determined by the sponsor to be associated with tucatinib based on the totality of the safety data include diarrhea, elevated LFTs, nausea and vomiting, and stomatitis. All events of interest from the tucatinib development program, including events for which any association with tucatinib has been refuted, are described in Section 8.2.5.

The Applicant's Position:
Treatment with tucatinib has been well tolerated with a manageable safety profile in subjects with HER2+ BC. In the pivotal trial HER2CLIMB, locally advanced unresectable or metastatic HER2+ BC subjects whose disease had progressed after multiple HER2-targeted agents, including those with brain metastases, were treated with tucatinib in combination with trastuzumab and capecitabine. (b) (4) No new safety signals were identified.

Regulatory Authorities Assessment:
The regulatory authorities agree with the summary of TEAEs presented by the applicant in Table 36.

The FDA conducted an independent analysis of all TEAEs on HER2CLIMB. Table 37 shows all grade TEAEs occurring in ≥10% of patients on the tucatinib arm. Table 37 also includes grade ≥3 TEAEs.

Table 37: TEAEs occurring in ≥10% of patients receiving tucatinib in HER2CLIMB

TEAE by preferred term	Tucatinib+Trastuzumab +Capecitabine n= 404		Placebo+Trastuzumab +Capecitabine n= 197	
	All grades %	Grade 3-4 %	All grades %	Grade 3-4 %
All	99	53	97	46
Diarrhoea	81	13	53	9
Palmar-plantar erythrodysaesthesia syndrome	63	13	53	9
Nausea	58	3.7	44	3

Fatigue[1]	**51**	**5**	**50**	**4.6**
Hepatotoxicity[2]	**42**	**9**	**24**	**3.6**
Vomiting	**36**	**3**	**25**	**3.6**
Stomatitis[3]	**32**	**2.5**	**21**	**0.5**
Decreased appetite	**25**	**0.5**	**20**	**0**
Blood bilirubin increased[4]	**25**	**1.2**	**14**	**3**
Aspartate aminotransferase increased[5]	**22**	**4.7**	**12**	**0.5**
Abdominal pain[6]	**22**	**1.2**	**23**	**1.5**
Headache	**22**	**0.5**	**20**	**1.5**
Alanine aminotransferase increased[7]	**21**	**6**	**7**	**0.5**
Anemia[9]	**21**	**3.7**	**13**	**2.5**
Rash[8]	**20**	**0.7**	**15**	**0.5**
Blood potassium decreased[10]	**17**	**3.2**	**13**	**5**
Arthralgia	**15**	**0.5**	**4.6**	**0.5**
Constipation	**15**	**0.7**	**20**	**0.5**
Cough	**14**	**0**	**12**	**0.5**
Blood creatinine increased	**14**	**0**	**1.5**	**0**
Weight decreased	**13**	**1**	**6**	**0.5**
Neuropathy peripheral[11]	**13**	**0.5**	**7**	**1**
Neutrophil count decreased[12]	**12**	**2.5**	**11**	**4.6**
Dyspnoea	**12**	**1.7**	**12**	**5**
Epistaxis	**12**	**0**	**5**	**0**
Dizziness	**11**	**0.5**	**14**	**0**
Back pain	**11**	**0.7**	**12**	**3**
Platelet count decreased[13]	**11**	**0.7**	**8**	**1**

Urinary tract infection[14]	11	0.5	8	1
Dyspepsia	11	0	10	0
Oedema peripheral	10	0	10	0.5
Pain in extremity	10	0.2	9	0.5

1. Fatigue includes fatigue and asthenia
2. Hepatotoxicity includes hyperbilirubinaemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury
3. Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysaesthesia, tongue ulceration, and aphthous ulcer
4. Bilirubin increased includes blood bilirubin increased, bilirubin conjugated increased, and hyperbilirubinaemia
5. AST increased includes aspartate aminotransferase increased and transaminases increased
6. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness
7. ALT increased includes alanine aminotransferase increased and transaminases increased
8. Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis
9. Anemia includes anaemia, haemoglobin decreased, and normocytic anaemia
10. Blood potassium decreased includes hypokalaemia and blood potassium decreased
11. Neuropathy peripheral includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy
12. Neutrophil count decreased includes neutrophil count decreased and neutropenia
13. Platelet count decreased includes platelet count decreased and thrombocytopenia
14. Urinary tract infection includes urinary tract infection and escherichia urinary tract infection

Source: ADaM dataset ADAE

The regulatory authorities disagree that (b) (4) **The incidence of diarrhea was markedly higher with tucatinib compared to placebo. The incidences of palmar-plantar erythrodysesthesia syndrome, nausea, hepatotoxicity, vomiting, stomatitis, blood bilirubin increase, AST increase, ALT increase, and blood creatinine increase were also ≥10% higher on the tucatinib arm. A more detailed examination of GI toxicitiy, hepatotoxicity, palmar-plantar erythrodysesthesia syndrome, and increased creatinine is included in section 8.2.5.**

Laboratory Findings

Data:

Transient elevations of transaminases were the dose-limiting toxicity of single agent tucatinib in the monotherapy study. See Section 8.2.5.2 for an analysis of hepatotoxicity by LFTs for the tucatinib integrated safety population. Increases in serum creatinine were observed in subjects

treated with tucatinib. See Section **Error! Reference source not found.** for an analysis of creatinine and blood urea nitrogen (BUN) values over time in subjects on both treatment arms of HER2CLIMB.

The Applicant's Position:
See Section 8.2.5.2 and Section **Error! Reference source not found.** of the assessment aid.

Regulatory Authorities Assessment:

The FDA conducted an independent analysis of laboratory values in HER2CLIMB. Table 38below shows laboratory values worsening from baseline in ≥20% of patients receiving tucatinib, and ≥5% higher than in the placebo arm of HER2CLIMB.

Table 38: Laboratory abnormalities (≥20%) worsening from baseline in patients who received tucatinib and with a difference of ≥5% compared to placebo in HER2CLIMB

	Tucatinib + Trastuzumab + Capecitabine[1] N = 404		Placebo + Trastuzumab + Capecitabine[1] N = 197	
	All Grades %	Grades ≥3 %	All Grades %	Grades ≥3 %
Hematology				
Hemoglobin Decreased	59	3.3	51	1.5
Platelets Decreased	29	0.3	25	1
Activated Partial Thromboplastin Time Prolonged	16	0.6	14	3.5
Chemistry				
Phosphate Decreased	57	8	45	7
Bilirubin increased	47	1.5	30	3.1
ALT Increased	46	8	27	0.5
AST Increased	43	6	25	1
Magnesium Decreased	40	0.8	25	0.5
Potassium Decreased[2]	36	6	31	5
Creatinine Increased[3]	33	0	6	0
Sodium Decreased	28	2.5	23	2

Alkaline Phosphatase Increased	**26**	**0.5**	**17**	**0**

[1] The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).
[2] Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
[3] There is no definition for Grade 2 in CTCAE v.4.03.
Source: ADaM dataset ADLB. This is a duplicate of the laboratory table provided in Section 6 of the TUKYSA USPI.

This analysis confirms that the incidences of all grade and grade ≥3 increases in ALT and AST were higher among patients on the tucatinib arm of HER2CLIMB compared to the control arm. All grade increases in total bilirubin and alkaline phosphatase were also more common on the tucatinib arm compared to the control arm, but grade ≥3 increases were equivalent or less frequent. There is a more detailed assessment of hepatotoxicity in Section 8.2.5.2.

Increased serum creatinine was also much more common on the tucatinib arm compared to the control arm in HER2CLIMB, although there were no grade ≥3 increases on either arm. This is consistent with the Pool 1 and Pool 2 safety populations and the tucatinib monotherapy safety populations which had all grade creatinine increases of 34%, 33%, and 48%, respectively. There were no grade ≥3 creatinine increases across the entire tucatinib safety population. A more detailed assessment of increased serum creatinine is in 8.2.5.6.

Vital Signs

Data:
Routine vital signs data, including weight, blood pressure, heart rate, temperature, and respiration rate were collected and presented by subject. Any clinically significant changes were captured as AEs.

The Applicant's Position:
Clinically significant post-baseline vital signs were similar between the treatment arms of the HER2CLIMB study and consistent across the study populations.

Regulatory Authorities Assessment:
The FDA did not review vital sign data and agrees that any clinically significant changes would be captured as AEs.

Electrocardiograms (ECGs)

Data:
NA

The Applicant's Position:
See QT Section below.

Regulatory Authorities Assessment:
NA

QT

Data:
A dedicated thorough QT/QTc (TQT) study, ONT-380-011, demonstrated no effect of tucatinib on QT prolongation. For a discussion of QT prolongation TEAEs in the tucatinib integrated safety population, see Section 8.2.5.4.

The Applicant's Position:
See ECG section above.

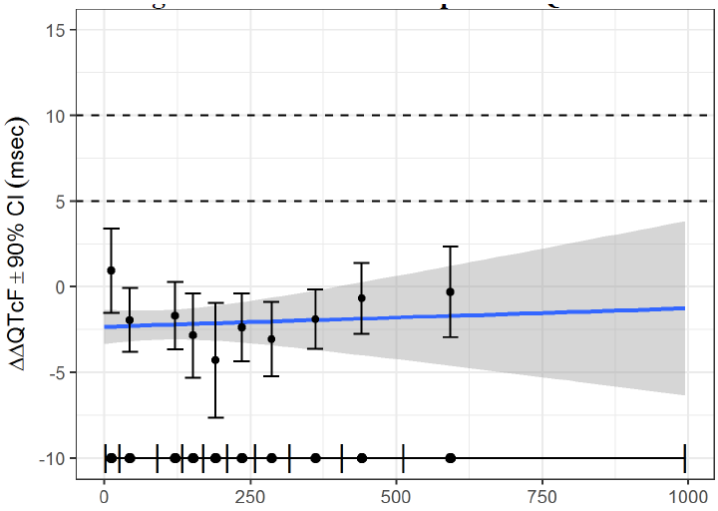
Regulatory Authorities Assessment:
FDA agrees with the Applicant's position on the assessment of effect of tucatinib on QT prolongation. ONT-380-011 is a randomized, partially double-blind, 3-period-6-arm cross-over, single dose, positive and placebo-controlled thorough QT study. The highest dose that 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 (Table 39).

Table 39: 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)

The findings of this analysis are further supported by exposure response analysis (Figure 21) and categorical analysis. Refer to QT-IRT for more details (Reference ID: 4554391).

Figure 21: Predictions from tucatinib concentration-QTc model



Immunogenicity

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
NA

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Gastrointestinal toxicity

Data:
Diarrhea: Treatment-emergent events of diarrhea are summarized in the Table 40. The incidence of diarrhea in HER2CLIMB was higher on the tucatinib arm compared to the control arm. In both treatment arms, most events were Grade 1 and Grade 2, with Grade ≥3 events in 12.9% and 8.6% of subjects in the tucatinib and control arm, respectively.

The proportion of subjects who permanently discontinued due to diarrhea was similar between treatment arms). The median time to diarrhea onset was 12 days on the tucatinib arm and 22 days on the control arm; the extent of resolution and median time to resolution of diarrhea events were similar across treatment arms. There were two subjects, both on the tucatinib arm, who reported Grade 4 events of diarrhea. One of the 2 subjects died from dehydration, the other from multiple organ dysfunction syndrome. In both subjects, diarrhea was ongoing at the time of death. Both subjects had suspected infection concurrent with the diarrhea event.

Among subjects on the tucatinib and control arms of HER2CLIMB who reported diarrhea TEAEs, 77.1% of subjects on the tucatinib arm and 58.1% of subjects on the control arm took antidiarrheal medication and reported diarrhea in any treatment cycle during study. Antidiarrheal medication was reported in 49.7% and 39.8% of the total number of cycles in which diarrhea was reported on the tucatinib and the control arms, respectively. When used, the median duration was 3 days per cycle in both arms.

The incidence of diarrhea TEAEs, time to onset of first TEAE, time to resolution, and percent of events resolved were similar between the tucatinib arm of HER2CLIMB, Pool 1, and Pool 2. The incidence of diarrhea TEAEs was lower, time to onset was longer and time to resolution was shorter in the tucatinib monotherapy study (Table 40).

Table 40: Summary of Treatment-Emergent Adverse Events of Diarrhea

	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[a] N=31
Subject with any TEAE of Diarrhoea, n (%)	105 (53.3)	327 (80.9)	347 (80.5)	365 (78.7)	19 (61.3)
Number of Diarrhoea events	182	721	753	782	23
Number of Diarrhoea events resolved, n (%)	153 (84.1)	574 (79.6)	593 (78.8)	612 (78.3)	19 (82.6)
Time to onset of first TEAE of Diarrhoea (days)					
n	105	327	347	365	19
Mean (STD)	42.6 (46.0)	24.0 (41.0)	23.7 (40.2)	23.4 (40.2)	42.8 (42.9)
Median	22.0	12.0	12.0	12.0	29.0
Min, Max	1, 205	1, 420	1, 420	1, 420	1, 171
Time to resolution (days)					
n	153	574	593	612	19
Mean (STD)	19.3 (34.2)	37.0 (67.6)	38.0 (70.5)	37.2 (69.7)	32.2 (62.9)
Median	6.0	8.0	8.0	8.0	4.0
Min, Max	1, 284	1, 548	1, 548	1, 548	1, 229
Number of Diarrhoea events recovering/resolving, n (%)	3 (1.6)	15 (2.1)	15 (2.0)	16 (2.0)	0

Resolution is defined as event outcome of recovered/resolved or recovered/resolved with sequelae. Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from studies HER2CLIMB and ONT-380-005. Data cutoff: ONT-380-206, 04Sep-2019; ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013.
[a] Includes subjects from ARRAY-380-101 study who received PIC (powder-in-capsule) ≥600 mg PO BID
Source: ISS Table 10.4.1

Nausea and Vomiting: Nausea occurred in 58.4% of subjects on the tucatinib arm of HER2CLIMB, and vomiting occurred in 35.9% of subjects. Incidence rates for both nausea and vomiting were higher compared to the control arm (43.7% for nausea and 25.4% for vomiting). Most events on the tucatinib and control arms were Grade 1 (32.7% vs. 25.4% for nausea, and 21.8% vs. 15.2% for vomiting) or Grade 2 (22% vs. 15.2% for nausea, and 11.1% vs. 6.6% for

vomiting). The incidence of Grade 3 events of nausea and vomiting was similar between the tucatinib and control arms (3.7% vs. 3% for nausea, and 3% vs. 3.6% for vomiting, respectively). On the tucatinib arm, tucatinib dose discontinuations due to nausea or vomiting were infrequent and were observed in 0.5% and 0.7% of subjects, respectively.

The incidence of nausea and vomiting TEAEs, time to onset of first TEAE, time to resolution, and percent of events resolved were similar between the tucatinib arm of HER2CLIMB and Pools 1 and 2. In tucatinib monotherapy, the incidence rates were similar, time to onset was longer for both nausea and vomiting, while time to resolution was shorter for nausea only. Prophylactic use of anti-emetics was not required per protocol in any tucatinib study.

Stomatitis: TEAEs of stomatitis based on a special search query (SSQ) occurred in 32.4% of subjects on the tucatinib arm of HER2CLIMB. The incidence was higher on the tucatinib arm compared to the control arm (21.3%). On both treatment arms, TEAEs of stomatitis were primarily Grades 1 and 2 and were manageable with dose modifications. Grade ≥3 events were reported in 2.5% and 0.5% of subjects on the tucatinib and control arms, respectively. No subjects discontinued treatment due to TEAEs of stomatitis.

The incidence rates of stomatitis TEAEs were consistent between the tucatinib arm of HER2CLIMB, Pool 1, and Pool 2. The lowest incidence occurred in the tucatinib monotherapy study (16%), with higher incidence in studies of tucatinib in combination with capecitabine.

The Applicant's Position:
In HER2CLIMB, diarrhea was the most common event observed on both treatment arms, with higher rates reported on the tucatinib arm compared to the control arm. Events were primarily Grades 1 and 2 and were manageable with dose modifications and treatment with antidiarrheal medication. Antidiarrheal medication was reported in approximately 50% of tucatinib treatment cycles in which diarrhea was reported, and when used, the median duration was 3 days per cycle. Diarrhea has been well described with capecitabine as a single agent, and studies combining tucatinib with capecitabine have demonstrated an increase in the rates of diarrhea compared to tucatinib monotherapy.

TEAEs of nausea and vomiting, and stomatitis were observed across tucatinib studies, with incidence rates higher on the tucatinib arm compared to the control arm. Events were mainly Grades 1 and 2 and were manageable with dose modifications.

Regulatory Authorities Assessment:
The FDA conducted an independent review of GI-related TEAEs in HER2CLIMB.

Diarrhea: Given the incidence and severity of diarrhea on the tucatinib arm of HER2CLIMB, the FDA included diarrhea in the Warnings and Precautions section of the TUKYSA USPI.

Diarrhea is an area of overlapping toxicity between tucatinib and capecitabine. On HER2CLIMB, 81% of patients on the tucatinib arm experienced diarrhea compared to 53% on

the control arm. The incidence of Grade ≥3 diarrhea on HER2CLIMB was also higher in the tucatinib arm versus control arm: 13% versus 9%. Dose interruptions due to diarrhea were more common on the tucatinib arm: 18% versus 9%, dose reductions were balanced: 4.2% versus 3.6%, and discontinuations were rare but more frequent with tucatinib: 1% versus 0.5%. Two patients on HER2CLIMB experienced Grade 4 diarrhea with sequelae including dehydration, hypotension, and acute kidney injury. Both patients were on the tucatinib arm, and both died, with diarrhea contributing to death.

Diarrhea occurred relatively early in treatment, with a median time to first onset of 12 days in the tucatinib arm, and 75% of first events starting within 21 days. The median time to resolution of any episode of diarrhea was 8 days. On the tucatinib arm, 66% of patients reported antidiarrheal use at any point during the study compared to 36% of patients on the control arm. Loperamide was the most common antidiarrheal on study, used by 96% of patients who reported antidiarrheal use on the tucatinib arm and 97% of patients on the control arm. The HER2CLIMB datasets did not include detailed information about how many patients used antidiarrheal prophylaxis either initially or after a first episode of diarrhea. (Prophylaxis was not mandated in the protocol.)

The regulatory authorities agree with the applicant's description of nausea, vomiting, and stomatitis in HER2CLIMB. The FDA did not verify the incidences or the durations of diarrhea, vomiting, and nausea on studies other than HER2CLIMB.

8.2.5.2. Hepatotoxicity

Data:

Hepatotoxicity TEAEs: The following PTs were grouped for this analysis: AST increased, ALT increased, blood bilirubin increased, and hyperbilirubinemia. The individual PTs blood bilirubin increased and hyperbilirubinemia are discussed in aggregate as bilirubin increased.

TEAEs of AST/ALT/bilirubin increase occurred in 39.4% of subjects treated with tucatinib on HER2CLIMB. The incidence was higher on the tucatinib arm than the control arm (22.8%). TEAEs on both treatment arms were primarily Grades 1 and 2, with Grade ≥3 events reported in 8.2% and 3.6% of subjects on the tucatinib and control arms, respectively. The incidence of all-grade TEAEs was similar between the tucatinib arm in HER2CLIMB, Pool 1, and Pool 2, and lower in the tucatinib monotherapy study. The incidence of Grade ≥3 TEAEs was similar between the tucatinib arm in HER2CLIMB, Pool 1, Pool 2, and the tucatinib monotherapy study.

Of the total all-grade AST/ALT/bilirubin events reported, 83.7% and 68.8% resolved on the tucatinib and control arms in HER2CLIMB, respectively. Time to onset was similar between treatment arms, with a median 36.0 days on the tucatinib arm and 32.0 days on the control arm; median time to resolution was 22.0 days and 26.5 days. The time to onset, percent of events resolved and time to resolution were consistent between the tucatinib arm in HER2CLIMB, Pool 1, and Pool 2. The time to onset was shorter and time to resolution was longer in the tucatinib monotherapy study.

Potential Drug-Induced Liver Injury: The HER2CLIMB protocol specified a set of broadly defined laboratory criteria as an AESI to ensure reporting of any potential drug-induced liver injury. Any subjects meeting these laboratory criteria were reported as having an AESI, regardless of etiology, and regardless of the presence of underlying hepatobiliary metastases: AST or ALT elevations >3xULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2xULN, except in subjects with documented Gilbert's syndrome. Once a subject met this initial screen of elevated laboratory values (AST/ALT and bilirubin), additional clinical data were then considered in these cases to assist in determination of its etiology, including ALP, presence of liver metastases, concomitant medications (e.g., for capecitabine-associated isolated bilirubin increase), conjugated/unconjugated bilirubin, and other clinical evaluations.

Hy's Law criteria of AST or ALT elevations >3xULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2xULN and ALP <1.5xULN with no alternative etiology was used for this analysis. A total of 11 subjects in the tucatinib integrated safety population met the initial broader laboratory criteria of AST/ALT>3xULN and concurrent bilirubin>2xULN. Of these, a total of 5 subjects met Hy's Law laboratory criteria (AST/ALT>3xULN, and concurrent bilirubin>2xULN and ALP<1.5xULN). The remaining 6 subjects did not meet Hy's Law laboratory criteria because ALP concentrations were greater than 1.5xULN (Table 41). No subjects treated with tucatinib had AST/ALT elevations greater than 20xULN.

Of the 5 subjects who met Hy's Law laboratory criteria, 4 subjects did not qualify as Hy's Law cases due to plausible alternative etiologies, including, presence of liver and/or bone metastases or other indicators of cholestatic liver disease. Of note, 1 of these subjects who had both liver and bone metastases, subsequently received an additional 20 treatment cycles after the laboratory event with dose reduction of both tucatinib (250 mg) and capecitabine, experienced only transient low-grade fluctuations in LFTs upon rechallenge.

A single subject met Hy's law criteria. A narrative is provided for this subject below.

Table 41: Subject Incidence of Post-Baseline Hepatotoxicity by Liver Function Tests

	HER2CLIMB Pbo+Cap+Tra N=197	HER2CLIMB Tuc+Cap+Tra N=404	Pool 1 Tuc+Cap+Tra N=431	Pool 2 Tuc and (Cap and/or Tra) N=464	ARRAY-380-101 Tuc Mono[c] N=31
(AST and/or ALT) >3xULN + total bilirubin>2xULN[a]	2 (1.0)	9 (2.2)	11 (2.6)	11 (2.4)	0
AST/ALT>3xULN + total bilirubin >2xULN + alkaline phosphatase <1.5xULN[b]	0	3 (0.7)	5 (1.2)	5 (1.1)	0
(AST and/or ALT)>10xULN	1 (0.5)	8 (2.0)	9 (2.1)	9 (1.9)	1 (3.2)
(AST and/or ALT)>20xULN	0	0	0	0	0

Pool 1 analysis set includes subjects who received tucatinib in combination with capecitabine and trastuzumab from studies HER2CLIMB and ONT-380-005; Pool 2 analysis includes subjects who received tucatinib in combination with capecitabine and/or trastuzumab from Studies HER2CLIMB and ONT-380-005. Post-baseline laboratory values include collections up through 30 days after the last dose of study treatment (i.e., last dose of tucatinib/placebo). Data cutoff: ONT-380-206, 04-Sep-2019;

ONT-380-005, 06-Mar-2018; ARRAY-380-101, 26-Nov-2013. AST/ALT elevation of >3xULN and a concurrent or subsequent elevation of total bilirubin >2xULN within 21 days (including the same laboratory draw). AST/ALT elevation of >3xULN and a concurrent or subsequent elevation of total bilirubin >2xULN plus ALP <1.5xULN within 21 days (including the same laboratory draw). Includes subjects from ARRAY 380-101 study who received PIC (powder-in-capsule) ≥600 mg PO BID.
Source: Table ISS 10.3.14

HER2CLIMB Hy's Law Case: One subject described below on the tucatinib arm met Hy's law criteria but demonstrated an adaptive response with recovery; laboratory values returned to baseline levels following dose modification of both tucatinib and capecitabine. This subject continued treatment for 6 more cycles until stopping due to disease progression. The continuation of treatment was a protocol deviation.

Subject (b) (6) was a 57-year-old female with a diagnosis of Stage IV MBC randomized to the tucatinib arm. Baseline ALT, AST, and bilirubin values for the subject were normal. On Study Day 73, the subject experienced Grade 2 events of hepatic cytolysis and bilirubin increased. ALT was 5.9xULN, AST was 4.7xULN, ALP was 1.3xULN, and total bilirubin was 2.0xULN. On Study Day 80, tucatinib dosing was interrupted. On Study Day 83, the events of Grade 2 hepatic cytolysis and Grade 2 bilirubin increased were reported as resolved with no intervention. Tucatinib was restarted at the same dose (300 mg BID). Capecitabine was dose-reduced to 750 mg/m^2 BID. On Study Day 93, the subject experienced a Grade 2 event of hepatic cytolysis. ALT was 4.8xULN, AST was 3.6xULN, and total bilirubin was 2.2xULN. Tucatinib dosing was interrupted. Dosing with trastuzumab and capecitabine was not changed. On Study Day 106, events of Grade 2 hepatocellular injury were resolved. Tucatinib dosing was restarted at a reduced dose (250 mg BID). On Study Day 113, the subject experienced a Grade 2 event of bilirubin increased. ALT was 1.7xULN, AST was 1.8xULN, and total bilirubin was 2.1xULN. On Study Day 116, tucatinib dosing was interrupted. On Study Day 127, the Grade 1 bilirubin increased was resolved. Tucatinib was restarted at a reduced dose (200 mg BID). On Study Day 148, the subject experienced a Grade 1 event of AST increased. On Study Day 156, the subject experienced a Grade 1 event of bilirubin increased. Dosing of all 3 study drugs was not changed. On Study Day 168, the Grade 1 bilirubin increased was resolved. The subject completed a total of 12 cycles of study treatment and achieved the best response of stable disease. The study treatment was discontinued due to progressive disease.

The Applicant's Position:
Transient elevations of transaminases were the dose-limiting toxicity of single agent tucatinib in ARRAY-380-101. Events of hepatotoxicity were seen in other tucatinib studies, but these events and laboratory abnormalities were primarily Grades 1 and 2, transient, asymptomatic, reversible, and manageable with dose modification.

In further analyses for any potential drug-induced liver injury, all subjects except one with combined elevations of transaminases and bilirubin had confounding possible alternative etiologies for these abnormalities, and absolute elevations of transaminases and bilirubin were modest. In the single Hy's law case where no confounding etiologies were present, the subject demonstrated an adaptive response, received an additional 6 treatment cycles after dose

reductions of tucatinib and capecitabine, and resolution of laboratory abnormalities to ≤Grade 1.

Regulatory Authorities Assessment:

The FDA conducted an independent assessment of hepatotoxicity, reviewed the independent expert hepatology review submitted by the applicant on December 28, 2019, and solicited an internal review from FDA colleagues in the Division of Gastroenterology and Inborn Errors Products (DGIEP) to review all 9 cases that met initial screening criteria for Hy's law. Based on the incidence and severity of hepatotoxicity on the tucatinib arm of HER2CLIMB, the FDA included it under the Warnings and Precautions section of the TUKYSA USPI.

The FDA used the adverse events analysis dataset (ADAE) ADaM dataset and grouped the following preferred terms to analyze hepatotoxicity: hyperbilirubinaemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury. The incidence of any Grade hepatotoxicity was 42% on the tucatinib arm versus 24% on the control arm, and the incidence of Grade ≥3 hepatotoxicity was 9% on the tucatinib arm compared to 3.6% on the control arm. The most common hepatotoxicity-associated AEs of any Grade on the tucatinib arm compared to the control arm were: increased total bilirubin 25% versus 14%, AST increase in 22% versus 12%, and ALT increase in 21% versus 7%. The Grade ≥3 incidences of these toxicities on the tucatinib arm compared to the control arm were: increased total bilirubin 1.2% versus 3%, AST increase 4.7% versus 0.5%, and ALT increase 6% versus 0.5%.

Hepatotoxicity led to dose interruptions in 18% of patients on the tucatinib arm compared to 9% on the control arm; dose reductions in 8% on the tucatinib arm compared to 2.5% on the control arm; and discontinuations in 1.5% on the tucatinib arm versus 1% on the control arm.

The FDA used the laboratory analysis dataset (ADLB) to perform a comprehensive search for potential signals of severe drug-induced liver injury. We examined patients with ALT and/or AST increase >3 x ULN, ALT and/or AST increase >5 x ULN, ALT and/or AST increase > 10 x ULN, ALT and/or AST > 20x ULN, and patients who met initial laboratory criteria of Hy's law with ALT and/or AST increase > 3 x ULN with concurrent total bilirubin increase > 2 x ULN.

A table of our findings is shown in Table 42:

Table 42: Increases in AST, ALT, and/or total bilirubin in the tucatinib safety database

	HER2CLIMB Pbo+Cap+Tra N=197 N (%)	HER2CLIMB Tuc+Cap+Tra N=404 N (%)	Pool 1 Tuc+Cap+Tra N=431 N (%)	Pool 2 Tuc + Cap and/or Tra N=464 N (%)	ARRAY-380-101 Tuc Mono N=31 N (%)

AST and/or ALT > 3 x ULN	**15 (8)**	**75 (19)**	**83 (19)**	**88 (19)**	**7 (23)**
AST and/or ALT > 5 x ULN	**4 (2.0)**	**36 (9)**	**38 (9)**	**39 (8)**	**4 (13)**
AST and/or ALT > 10 x ULN	**1 (0.5)**	**8 (2.0)**	**9 (2.1)**	**9 (1.9)**	**1 (3.2)**
AST and/or ALT > 20 x ULN	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
AST and/or ALT > 3 x ULN and Tbili > 2 x ULN	**2 (1.0)**	**9 (2.2)**	**11 (2.6)**	**11 (2.4)**	**0 (0)**

Source: ADaM dataset ISS ADLB

FDA DO1 and DGIEP reviewed each case of potential's Hy's law on the tucatinib arm of HER2CLIMB which are summarized here:

Patient ID (b) (6): This 57 yo female patient had metastatic disease to the lung and bone at study entry. Her liver tests at baseline were: AST 1.6xULN, ALT 1.0xULN, AP 2.3x ULN, and total bilirubin 1.0xULN. On study day 32, her liver tests were: AST 5.5xULN, ALT 3.0xULN, and total bilirubin 2.8xULN. There was no AP on that date. All three study treatments were discontinued due to increases in AST, ALT, and total bilirubin. Her AST and ALT were within normal limits on day 66, and total bilirubin was resolving. The FDA considers this case as possible DILI from either tucatinib and/or capecitabine.

Patient (b) (6) This 38 yo female patient had metastatic disease to liver at study entry. Her liver tests at baseline were: AST 3.6xULN, ALT 3.1xULN, AP 6.8xULN, and Tbili 1.0xULN. On study day 12, her liver tests were: AST 3.0xULN, ALT 1.7xULN, AP 5.0xULN< and Tbili2.1xULN. Study treatments were interrupted, CT scan showed progression of disease in the liver, and study treatments were permanently discontinued. The FDA considers this case as unlikely DILI, and more likely due to metastatic disease.

Patient (b) (6): This 55 yo female patient had metastatic disease to liver and bones at study entry. Her liver tests at baseline were AST 1.2xULN, ALT normal, AP 2.6xULN, and bilirubin normal. All three study treatments were discontinued on study day 230 due to progression of disease, shortly after was admitted with pancreatitis, and CT scan showed metastatic disease in liver and possibly pancreas. On study day 259, her liver tests were AST 3.4 xULN, ALT 1.6xULN, AP 3.2xULN, and Tbili10.4xULN. The FDA considers this case as unlikely DILI and related to metastatic disease.

Patient (b) (6): This 45 yo patient had metastatic disease to brain and bone at study entry. At study baseline, her AST, ALT, AP, and Tbili were all normal. On study day 43, her liver tests were: AST 4.6 x ULN, ALT 3.8 x ULN, AP 1.2 x ULN, and Tbili 1.3 x ULN. Tucatinib and capecitabine were interrupted. On study day 49, with drugs interrupted, her AST improved to 2.7 x ULN and ALT Improved to 2.5 x ULN, but Tbili rose further to 2.1 xULN. On study day 53, tucatinib was restarted at a reduced dose of 250 mg BID, and capecitabine at a reduced dose of 1500 mg/m2/day. On study day 62, AST, ALT, AP, and Tbili were all normal. On study day 85, AST was 2.3 x ULN, ALT was 2.4 x ULN, AP was 1.3 x ULN, and Tbili was normal. No actions were taken with any study drugs. Study treatments were permanently discontinued on study day 483 after second disease progression, following isolated progression in the brain. The FDA considers this case as possible DILI associated with tucatinib and/or capecitabine.

Patient (b) (6) This 67 yo female patient had metastatic disease to the liver at study entry. Her liver tests at baseline were AST 1.1 x ULN, ALT 1.0xULN, AP 4.1xULN, and Tbili 1.1 x ULN. On study day 49, the patient's liver tests were: AST 5.5 x ULN, ALT 7.5 x ULN, AP 2.1 x ULN, and Tbili 2.5 x ULN. All study drugs were discontinued. A CT scan showed peritoneal carcinomatosis. On study day 79, AST and ALT were normal, AP was 2.4 x ULN and Tbili was 1.2 x ULN. The FDA considers this case as probable DILI from tucatinib and/or capecitabine based on the marked increases in AST and ALT along with the increase in Tbili, and improvement after study drug discontinuation. The concurrent decrease in AP suggests that liver tumor burden was not responsible for the transaminase and Tbili rise.

Patient (b) (6): This 28 yo female patient had metastatic disease to the liver and bone at study entry. Her liver tests at baseline were AST normal, ALT normal, AP 1.4 x ULN< and Tbili normal. On study day 22, her liver tests were AST 2.9 x ULN, ALT 4.7 x ULN, AP 3.4 x ULN, and Tbili 2.1 x ULN, and all three study drugs were discontinued. A CT-scan showed increased liver metastatic disease and intrahepatic/extrahepatic ductal dilatation. The patient received a common bile duct stent. The FDA considers this case as not DILI and due to liver tumor burden.

Patient (b) (6): This 57 yo female patient had metastatic disease to lung at study entry. Her liver tests at baseline were AST normal, ALT normal, AP normal, and Tbili normal. By study day 35, her transaminases had started to rise. On study day 73, her AST was 4.7 x ULN, ALT was 5.9 x ULN, AAP was 1.3 x ULN, and Tbili was 2.0 x ULN. Tucatinib was interrupted. On study day 85, AST was 1.8 x ULN, ALT was 2.3 x ULN, AP was 1.3 x ULN, and Tbili was normal, and tucatinib was restarted at the starting dose of 300 BID. On study day 93, the patient's liver tests increased again with AST 3.5 x ULN, ALT 2.9 x ULN, and Tbili 2.1 x ULN. Tucatinib was interrupted and was restarted at a reduced dose of 250 mg BID on study day 106 when AST, ALT, and Tbili were all normal. On study day 113, the patient's liver tests were: AST 1.8 x ULN, ALT 1.7 x ULN, and Tbili 2.1 x ULN. Tucatinib was interrupted for elevated bilirubin and resumed on study day 127 at a reduced dose of 200 mg BID. On study day 251, the patients

stopped all three study drugs due to progression from disease. No changes to capecitabine or trastuzumab were made throughout the study. The FDA considers this a case of probable DILI from tucatinib and/or capecitabine and that this patient was able to accommodate DILI from tucatinib based on reduced increases in transaminases following tucatinib dose reduction.

Patient (b) (6): This 52 yo female patient had metastatic disease to the liver at study entry. Her liver tests at baseline were AST normal, ALT normal, AP normal, and Tbili normal. On study day 34, her liver tests were: AST 4.2 x ULN, ALT 4.9 x ULN, AP 1.0 x ULN and Tbili 2.3 x ULN. Tucatinib was interrupted but not capecitabine or trastuzumab. On study day 43, her liver tests were: AST not reported, ALT 1.3 x ULN, AP normal, and Tbili 1.5 x ULN. The patient resumed tucatinib at the starting dose of 300 mg BID. On study day 61, her liver tests were AST 1.0 x ULN, ALT normal, AP 1.0 x ULN, and Tbili 1.3 x ULN. However, all three study drugs were discontinued due to progression of disease. The FDA considers this as a case of probable DILI due to tucatinib. However, at the time of the "event" but study day unspecified, the patient was taking amoxicillin/clavulanate and methimazole which can also cause liver injury.

Patient (b) (6): This 38 yo female patient had metastatic disease to the brain, lung, liver, kidney, and bone at study entry. Her liver tests at baseline were AST 1.2 x ULN, ALT normal, AP 2.0 x ULN, and Tbili 1.0 x ULN. On study day 64, her AST, ALT, and AP remained close to baseline, however Tbili increased to 2.0 x ULN and capecitabine was dose reduced. On study day 106, her liver tests were: AST 3.2 x ULN, ALT 1.4 x ULN, AP 1.9 x ULN, and Tbili 2.6 x ULN. Tucatinib and capecitabine were interrupted. On study day 108, her transaminases and AP rose further to: AST 6.6 x ULN, ALT 4.7 x ULN, AP 3.9 x ULN, and Tbili 2.2 x ULN. By study day 111, liver tests were improving, and patient restarted tucatinib at the starting dose: 300 mg BID, and capecitabine at her previous dose: 1500 mg/m2/day. By study day 127, her liver tests improved with AST, ALT, and AP at or below baseline values and Tbili 1.3 x ULN. On study day 231, all three study drugs were discontinued due to progression of disease. The FDA does not think there is enough information to make an assessment about DILI.

In addition to these patients, there were three patients who discontinued tucatinib due to hepatotoxicity. These patients are summarized here:

(b) (6): The patient is a 33 yo female patient with metastatic disease to the brain and lung at study entry. Her liver tests at baseline were: AST 1.2 x ULN, ALT normal, AP 1.1 x ULN, and Tbili normal. On study day 14, capecitabine was interrupted due to vomiting, and on study day 16, tucatinib was interrupted due to diarrhea. On study day 22, her liver tests were: AST 10.8 x ULN, ALT 16.3 x ULN, AP 1.4 xULN, and Tbili 1.4 x ULN. Tucatinib and capecitabine were still interrupted and trastuzumab was also held. On study day 29, AST was 9.3 x ULN, ALT was 10.5 x ULN, AP was 1.6 x ULN, and Tbili was 1.1 x ULN and capecitabine was restarted at a reduced dose: 1500 mg/m2/day. On day 37, AST was 1.9 x ULN, ALT was 2.3 xULN, AP was 1.2 x ULN, and Tbili was normal, and tucatinib was restarted at a reduced dose of 250 mg BID. On

study day 38, the patient had grade 2 pyrexia, grade 2 diarrhea, grade 2 nausea, and grade 2 vomiting, and all three study drugs were discontinued. On study day 71, AST, ALT, AP, and Tbili were normal.

(b) (6): The patient is a 50 yo woman with metastatic disease to the brain and liver at study entry. Her liver tests at baseline were: AST 1.8 x ULN, ALT 1.4 x ULN, AP normal, and Tbili normal. On study day 106, her liver tests were AST 3.2 x ULN, ALT 4.5 x ULN, AP 1.2 x ULN, and Tbili 1.9 x ULN. Tucatinib and capecitabine were interrupted until study day 113 and then restarted at the same doses. On study day 127, the patient's liver tests were: AST normal, ALT 1.8 x ULN, AP normal, and Tbili 1.5 x ULN. On study day 148, the patient's liver tests were: AST 3.7 x ULN, ALT 4.2 x ULN, AP 1.3 x ULN, and Tbili 2.0 x ULN. All study drugs were discontinued. On study day 179, the patient's liver tests were AST: 1.3 x ULN, ALT nl, AP 1.1 x ULN, and Tbili normal.

(b) (6): The patient is a 56 yo female patient with metastatic disease to the bone at study baseline. Her liver tests at baseline were: AST 1.7 x ULN, ALT 1.8 x ULN, AP normal, and Tbili normal. On study day 22, her liver tests were: AST 5 x ULN, ALT 8.8 x ULN, AP normal, and Tbili normal. All three study drugs were interrupted. On study day 28, her transaminases rose further to AST 13.6 x ULN and ALT 19.5 x ULN, with continued normal AP and Tbili. She had a liver biopsy on the same day which showed acute hepatitis and was discussed with a hepatologist by the investigator who recommended stopping the study drug due to potential drug-related toxicity. All three study treatments were permanently discontinued. By study day 73, AST was improved to 1.8 x ULN, ALT improved to 2.0 x ULN, and AP and Tbili remained normal.

In the FDA's assessment with input from DGIEP colleagues, evaluation of tucatinib- associated DILI in HER2CLIMB is challenging for several reasons. All patients who received tucatinib were also receiving capecitabine which is associated with an increase in total bilirubin and can also be associated with transaminase elevation. In many of the cases reviewed, tucatinib and capecitabine were held at the same time, so attribution of hepatotoxicity to one drug or the other is difficult. Additionally, many patients had metastatic disease to the liver, elsewhere in the abdominal cavity, and/or bone which further complicated adjudication of hepatotoxicity.

Tucatinib is a possible cause of DILI, and based on the data available, is associated with a mild to modest rise in transaminases. This rise decreases with drug withdrawal, and patients were able to tolerate a reduced dose. The information available, including the case summary detailed by the applicant, does not point to a Hy's law signal associated with tucatinib, but based on the confounders listed and the relatively small tucatinib safety database, the possibility cannot be entirely excluded.

There were no cases of hepatotoxicity leading to liver failure or death in HER2CLIMB.

8.2.5.3. Cutaneous Reactions

Data:

Palmar-Plantar Erythrodysesthesia Syndrome: The incidence of PPE syndrome was higher on the tucatinib arm compared to the control arm (63.4% vs. 52.8%). The events on both treatment arms were primarily Grades 1 and 2, with Grade ≥3 events reported in 13.1% and 9.1% of subjects, respectively. When adjusted for the longer duration of exposure to capecitabine on the tucatinib arm compared to the control arm, the difference in incidence of Grade ≥3 PPE syndrome between the treatment arms was decreased to 21 per 100 person-years in the tucatinib arm and 19 per 100 person-years in control arm. Among all subjects with reported PPE syndrome, 54.2% and 58.3% resolved on the tucatinib and control arms of HER2CLIMB, respectively. Time to onset was similar between treatment arms, with a median 33.0 days on the tucatinib arm and 34.5 days on the control arm; median time to resolution was 51.0 days and 62.5 days, respectively. TEAEs of PPE syndrome did not lead to tucatinib treatment discontinuation in any subjects in HER2CLIMB.

The incidence, time to onset, time to resolution, and percent of events resolved were similar between the tucatinib arm of HER2CLIMB, Pool 1, and Pool 2. PPE syndrome was not reported in the tucatinib monotherapy study ARRAY-380-101.

Rash: TEAEs of rash based on an SSQ occurred in 20.3% of subjects treated with tucatinib in HER2CLIMB. The incidence was higher on the tucatinib arm compared to the control arm (14.7%). The TEAEs were primarily Grade 1 on both treatment arms, with Grade ≥3 events reported in 0.7% and 0.5% of subjects, respectively.

Of the total all-grade TEAEs of rash reported, 72.8% and 69.2% resolved on the tucatinib and control arms, respectively. Time to onset was longer on the tucatinib arm, with a median 34.0 days compared to 27.0 days on the control arm; median time to resolution was 25.0 days and 12.0 days. TEAEs of rash resulting in tucatinib discontinuation occurred in 0.5% of subjects on the tucatinib arm; rash maculo-papular (0.2%) and urticaria (0.2%). No subjects discontinued placebo on the control arm due to a TEAE of rash.

The incidence of rash TEAEs, time to onset of first TEAE, time to resolution, and percent of events resolved were similar between the HER2CLIMB tucatinib arm, Pool 1, and Pool 2. The incidence of rash TEAEs was higher in the tucatinib monotherapy study compared to subjects on the tucatinib arm of HER2CLIMB (29.0% vs. 20.3%); however, the sample size was small in the monotherapy study (N=31). Most events in the monotherapy study were Grade 1. The most common all-grade events included erythema (16.1%) and rash (6.5%), with 1 Grade 3 event of rash reported for a single subject. The median time to onset of first TEAE was 28.0 days. The median time to resolution of all-grade TEAEs was 15.0 days, and 75.0% of all-grade TEAEs resolved.

The Applicant's Position:
PPE syndrome is a well-characterized side effect of capecitabine. Across studies in the tucatinib integrated safety population, PPE syndrome was reported with tucatinib when administered in combination with capecitabine. PPE syndrome was not reported with the tucatinib + trastuzumab combination in the ONT-380-005 study or in the tucatinib monotherapy study.

Rash was commonly reported across tucatinib studies; however, most events were Grade 1 or Grade 2 and were manageable with dose modifications and supportive care.

Regulatory Authorities Assessment:

PPE

The incidence of all Grade PPE and Grade ≥3 PPE were both higher on the tucatinib arm than on the control arm. PPE led to interruptions of tucatinib versus placebo in 6% versus 2% of patients and dose reductions in 1.2% versus 0.5% of patients. There were no discontinuations of tucatinib or placebo due to PPE. The FDA confirmed that incidence of PPE was similar in the Pool 1 and Pool 2 populations and no PPE was reported on ARRAY-380-101, the tucatinib monotherapy study.

When adjusted for exposure, the incidence of all grade PPE was higher on the tucatinib arm compared to the control arm: 248 per 100 person-years versus 206 per 100 person-years. Grade ≥3 PPE was slightly higher on the tucatinib arm compared to the control arm: 21 per 100 person-years versus 19 per 100 person-years. The regulatory authorities cannot conclude that PPE observed on HER2CLIMB is solely due capecitabine. It is possible that PPE could also be potentiated by tucatinib.

Rash

The regulatory authorities agree with the applicant's description of rash on the HER2CLIMB study and did not independently verify the incidence, onset, and duration of rash across the tucatinib safety database. Although the incidence of all Grade rash on HER2CLIMB was slightly higher on the tucatinib arm compared to the control arm, the incidence of Grade ≥3 rash was low (<1%) on both arms. Rash was an infrequent reason for dose interruption (1.7% on the tucatinib arm versus 1.5% on the control arm), and a rare reason for dose reduction or discontinuation.

8.2.5.4. Cardiac Toxicity

Data:

QT Prolongation: A dedicated TQT study (ONT-380-11) demonstrated no effect of tucatinib on QT prolongation. The study was conducted to evaluate the effects of tucatinib on the QT interval corrected for HR using Fridericia's method in healthy adult subjects.

Results from the tucatinib integrated safety analysis are consistent with the outcome of this dedicated TQT study. TEAEs of QT prolongation were searched using the Torsade de pointes/QT prolongation standard MedDRA query (SMQ) (broad scope) for the tucatinib integrated safety population. The incidence of all-grade TEAEs was similar between the tucatinib and control arms of HER2CLIMB (4.2% vs. 4.6%); Grade ≥3 events occurred in 2.5% and 2.0% of subjects, respectively. Overall, QT prolongation events occurred in <5% of subjects across all populations in the integrated analysis. In HER2CLIMB, 2 subjects discontinued treatment; 1 subject (0.2%) on the tucatinib arm due to cardiac arrest and 1 subject (0.5%) on the control arm due to multiple organ dysfunction syndrome. There were no subjects with dose modifications or discontinuations due to TEAEs of QT prolongation in the tucatinib monotherapy study.

Decreased Left Ventricular Ejection Fraction: Although other HER2-directed therapies, including trastuzumab, have previously demonstrated the potential to cause cardiotoxicity, in HER2CLIMB the incidence of LVEF decreased TEAEs was similar between the tucatinib and control arms. Overall, rates of ejection fraction changes were consistent across tucatinib studies, with the lowest incidence in the tucatinib monotherapy study.

Events of LVEF decreased were searched using the Cardiac failure SMQ (narrow) and Cardiomyopathy SMQ (narrow) for the tucatinib integrated safety population. A total of 14 subjects experienced TEAEs of decreased LVEF in HER2CLIMB; 9 subjects (2.2%) on the tucatinib arm and 5 subjects (2.5%) on the control arm. The incidence of Grade ≥3 events was comparable between treatment arms; 0.7% vs. 0.5% of subjects, respectively. TEAEs resulting in dose modification or treatment discontinuation occurred in 1.5% and 2.0% of subjects on the tucatinib and control arms, respectively. The incidence of LVEF decreased TEAEs on the tucatinib arm of HER2CLIMB was consistent with Pool 1 and Pool 2; no events were reported among subjects in the tucatinib monotherapy study.

The Applicant's Position:
Events of QT prolongation and LVEF decreased are not considered to be associated with tucatinib. A dedicated TQT study demonstrated no effect of tucatinib on QT prolongation. Based on data across the tucatinib development program, a causal association between tucatinib and decreased LVEF is excluded.

Regulatory Authorities Assessment:
QT Prolongation

The regulatory authorities agree with the applicant's assessment. The FDA conducted an independent analysis of the effect by tucatinib on QT prolongation. Refer to 8.2.4. section QT and QT-IRT review (Reference ID: 4554391) for more details.

LVEF

The FDA conducted an independent analysis of decreased LVEF on HER2CLIMB using the left ventricular ejection fraction dataset (ADCV) which recorded worst post-baseline LVEF.

There were 2 patients (0.5%) on the tucatinib arm versus 1 patient (0.5%) on the control arm with a worst post-baseline LVEF of <40%. There were an additional 21 patients (5.2%) on the tucatinib arm versus 14 patients (7.1%) on the control arm with an LVEF <55% and a ≥10% decrease from pretreatment baseline, or an absolute decrease of LVEF of ≥16% from pretreatment baseline. The incidence of decreased LVEF on the tucatinib arm of HER2CLIMB was similar to the incidences in the Pool 1 and Pool 2 populations. There was only one patient on the tucatinib monotherapy study with a post-baseline LVEF <55% and a ≥10% decrease from pre-treatment baseline. This patient's worst post-baseline LVEF was 45% from a baseline of 55%.

The regulatory authorities agree with the applicant's assessment that based on available data, tucatinib does not appear to decrease LVEF more than trastuzumab alone. The FDA will continue to review tucatinib safety reports in the post-marketing setting.

8.2.5.5. Cerebral Edema

Data:
An index case of suspected cerebral edema not attributed to disease progression was reported in Study ONT-380-005; the MRI findings in the index case were consistent with findings associated with capecitabine use in published literature.

Based on the index report, the HER2CLIMB study defined cerebral edema not clearly attributable to progression of disease as an AE of special interest that mandated reporting to the sponsor irrespective of regulatory seriousness criteria or causality. There were no subjects on the tucatinib arm of HER2CLIMB who reported cerebral edema-related TEAEs. Two subjects (1.0%) reported events on the control arm. No additional similar events have occurred across tucatinib studies.

The Applicant's Position:
Aside from the index case of cerebral edema in Study ONT-380-005, no additional events of cerebral edema not attributed to disease progression were observed in the tucatinib clinical development program. Therefore, a causal association between tucatinib and cerebral edema is excluded.

Regulatory Authorities Assessment:
There were 2 cases of cerebral edema which occurred on the HER2CLIMB study, and both were in the placebo arm. The regulatory authorities agree with the applicant that there is no signal from the HER2CLIMB study that tucatinib is associated with cerebral edema. The FDA will continue to review tucatinib safety reports in the post-marketing setting.

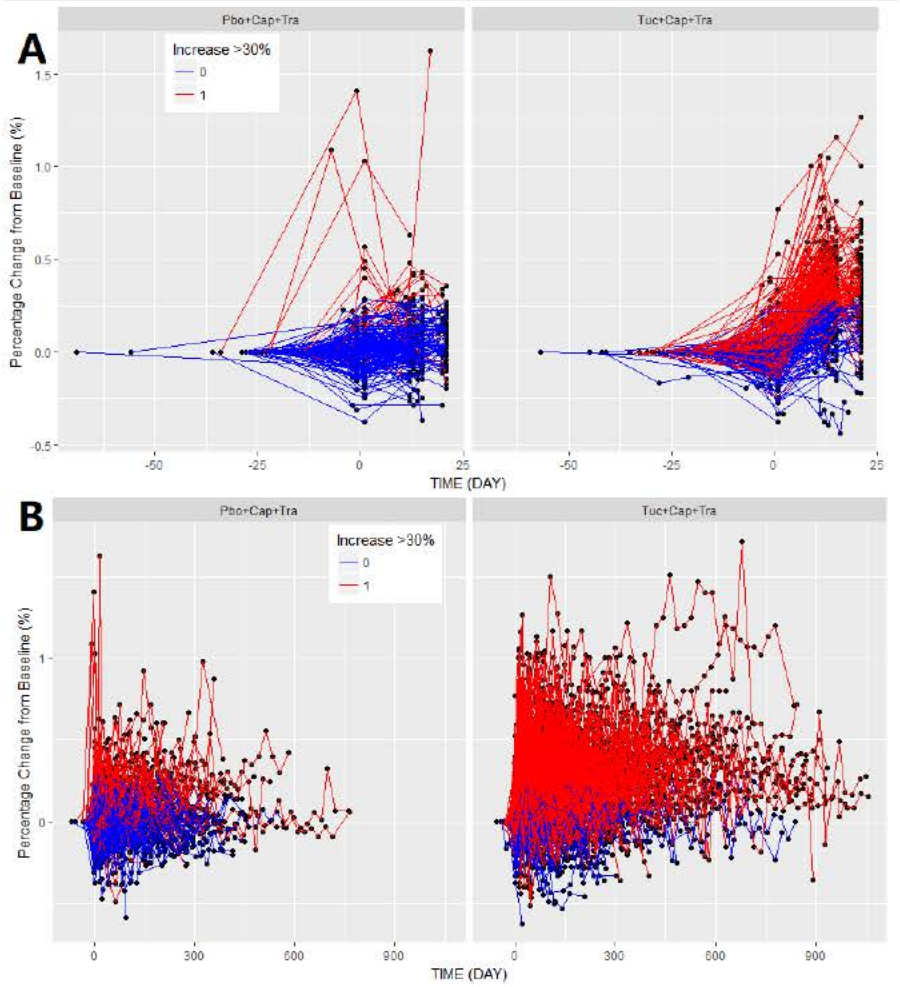
8.2.5.6. Creatinine Increase

Data:
TEAEs of blood creatinine increased were observed in 13.9% of subjects on the tucatinib arm of HER2CLIMB, among these the majority were Grade 1. Acute kidney injury and renal failure TEAEs were infrequent with similar incidence between treatment arms. A mean increase in creatinine levels of approximately 30% was observed within the first cycle of tucatinib treatment, remained elevated but stable throughout treatment and were reversible upon treatment discontinuation. No subjects discontinued treatment due to events of creatinine increase. Most post-baseline values were within the ULN. BUN values remained stable throughout tucatinib treatment, further demonstrating no impact of tucatinib on renal function.

The Applicant's Position:
Results from a separate dedicated study (SGNTUC-020) demonstrated that tucatinib has no effects on renal function, and elevations of serum creatinine in subjects treated with tucatinib are a result of tucatinib inhibition of the kidney transporters, OCT2/MATE1. Other dedicated markers of renal function (e.g., iohexol clearance) were unaffected during treatment. Consistent with these findings, increases in serum creatinine in subjects treated with tucatinib in HER2CLIMB were reversible upon treatment discontinuation.

Regulatory Authorities Assessment:
FDA conducted independent analysis to evaluate the effect by tucatinib on creatinine increase. FDA in general agrees with the Applicant's assessment. The profile of creatinine over time from Study HER2CLIMB was plotted and compared between the tucatinib arm and Placebo arm (A. creatinine profile in the 21 days; B. over the study period. Figure 22). The mean percentage increase over the first 21 days are 31.5% vs 13.9%, for the tucatinib arm and placebo arm, respectively; and are 47.8% vs 25.4% over the treatment period, for the tucatinib arm and placebo arm, respectively. The percentage of patients with maximum level of creatinine level increase >30% are 52.3% (214/409) vs 9% (19/201) over the first 21 days; and are 77.3% (316/409) vs 30.3% (61/201) over the whole treatment period, for TUC and PBO arm, respectively.

Figure 22: Creatinine Profile



Source: Reviewer's Independent Analysis.

FDA agrees with the Applicant's position that serum creatinine increase appears to be attributed to the inhibition of tubular secretion of creatinine via OCT2 and MATE1 by tucatinib, instead of due to the impaired renal function. This conclusion is supported by results from Study SGNTUC-020, in which tucatinib is demonstrated to be a weak inhibitor of MATE1/MATE2-K renal extrusion transporters by using metformin as probe (Table 43).

Table 43: Effect of Tucatinib On Metformin Pharmacokinetic Parameters

	Geometric Least Squares (LS) Mean				Geometric LS Mean Ratio (Test/Reference)	
	Metformin with Tucatinib (Test)		Metformin Alone (Reference)			
Parameter	n	Result	n	Result	Estimate	90% CI
$AUC_{0\text{-last}}$ (h* µg/mL)	17	11.054	17	8.147	1.357	(1.220, 1.509)
$AUC_{0\text{-inf}}$ (h* µg/mL)	17	11.558	17	8.333	1.387	(1.251, 1.539)
C_{max} (µg/mL)	17	1.418	17	1.314	1.079	(0.951, 1.225)

Source: Study SGNTUC-020 CSR, Table 9

Iohexol clearance was evaluated to determine whether multiple dosing of tucatinib also impacted actual GFR (aGFR) in Study SGNTUC-020. Iohexol exposure was unaffected by the presence and absence of tucatinib, indicating that aGFR is not impacted by multiple dose administration of tucatinib (Table 44).

Table 44: Iohexol Pharmacokinetic Parameters

	Arithmetic Mean (CV%)	
Pharmacokinetic Parameters	**Metformin Alone**	**Metformin + Tucatinib**
$AUC_{0\text{-last}}$ (h*ug/mL)	345.5 (21.2)	346.4 (21.7)
$AUC_{0\text{-inf}}$ (h*ug/mL)	440.5 (27.9)	441.9 (27.2)
CL_{syst} (mL/min)	129.8 (22.7)	129.0 (22.0)
$t_{1/2}$ (h)	1.762 (18.9)	1.784 (17.5)
C_0 (ug/mL)	175.6 (18.0)	178.5 (21.5)
aGFR (mL/min/1.73 m^2)	94.99 (17.4)	94.56 (16.9)

Source: Study SGNTUC-020 CSR, Table 6

8.2.5.7. Pneumonitis

Regulatory Authorities Assessment:

The applicant did not include pneumonitis as an AESI in HER2CLIMB because they did not observe this TEAE in the tucatinib development program. Lapatinib, another tyrosine kinase inhibitor of HER2 which also inhibits epidermal growth factor receptor (EGFR) is associated with pneumonitis/interstitial lung disease. The lapatinib USPI lists Pneumonitis/Interstitial Lung Disease under Warnings and Precautions. Trastuzumab is also associated with pneumonitis and its USPI includes Pulmonary Toxicity in a Black Box Warning.

The FDA did an analysis of pneumonitis in the HER2CLIMB safety database using the following preferred terms: acute interstitial pneumonitis, interstitial lung disease, organising pneumonia, and pneumonitis. There was one patient on the tucatinib arm who experienced Grade 1 pneumonitis. A brief narrative is below:

Patient ID (b) (6): This 70 year-old female patient had metastatic breast cancer involving her lungs, mediastinal and axillary lymph nodes, brain, and bones. She also had a history of immune thrombocytopenic purpura and a dry cough. On study day 38, she developed grade 1 pneumonitis. It is unclear if this diagnosis was made clinically and/or radiographically. On study day 44, she received azithromycin(Z-pak) for a possible lung infection. There were no dose modifications of tucatinib, trastuzumab, or capecitabine. The patient continued to have grade 1 pneumonitis until cycle 13 when she discontinued study treatment. The investigator and the applicant thought pneumonitis was unrelated to tucatinib or the other study treatments.

The regulatory authorities agree with applicant's assessment that based on the safety information available, tucatinib does not appear to be associated with pneumonitis. The FDA will continue to monitor for this in the post-marketing setting.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Data:
NA

The Applicant's Position:
None of the studies supporting this application collected clinical outcome assessment data.

Regulatory Authorities Assessment:
Refer to the FDA's assessment of COA/PRO data in 8.1.2.

8.2.7. Safety Analyses by Demographic Subgroups

Data:
Age: On the tucatinib arm of HER2CLIMB, the safety profile of subjects <65 years was comparable to that of subjects ≥65 years. The most frequent events included diarrhea (79.5% vs. 86.6%), PPE syndrome (63.4% vs. 63.4%), nausea (57.5% vs. 62.2%), fatigue (43.5% vs. 51.2%), and vomiting (34.5% vs. 41.5%) in the <65 and ≥65 years of age subgroups, respectively. A total of 12 subjects ≥75 years of age were enrolled and randomized in the HER2CLIMB study, including 8 subjects on the tucatinib arm and 4 subjects on the control arm. Due to the limitation of this small sample size, no conclusions can be drawn from this subgroup analysis.

Gender: A total of 5 male subjects were enrolled and randomized in the HER2CLIMB study, including 3 subjects on the tucatinib arm and 2 subjects on the control arm. (b) (4) No other male subjects were included in the tucatinib integrated safety population.

Hepatic and Renal Insufficiency: In Study ONT-380-009, a single 300 mg dose of tucatinib was well tolerated in subjects with mild, moderate, or severe hepatic function. In subjects with moderate and severe hepatic impairment, increases in tucatinib exposure were <2-fold compared to subjects with normal hepatic function, and did not meaningfully impact tucatinib exposure. Renal elimination is a minor contributor to tucatinib elimination (4% of radiolabeled dose was recovered in urine in Study ONT-380-008. Renal impairment is predicted to have no impact on tucatinib PK.

The Applicant's Position:

(b) (4)

Regulatory Authorities Assessment:

The FDA conducted an independent safety analysis of key demographic subgroups:

Age: The most frequent all Grade AEs (≥30%) on the tucatinib arm of HER2CLIMB in those < 65 years compared to those ≥65 years were: diarrhea 79.5% versus 86.6%, PPE 63.4% versus 63.4%, nausea 57.5% versus 62.2%, fatigue 49.7% versus 56.1%, hepatotoxicity 40.4% versus 47.6%, vomiting 34.5% versus 41.5%, and stomatitis 32.3% versus 32.9%. Differences between the FDA analysis and applicant analysis are due to differences in grouping PTs. The FDA strategy is detailed in Section 8.2.4.

SAEs on the tucatinib arm of HER2CLIMB occurred in 24% of patients < 65 years versus 34% of patients ≥65 years. Tucatinib discontinuations on HER2CLIMB occurred in 4.7% of patients < 65 years versus 10% of patients ≥65 years.

The FDA disagrees with the applicant's assessmen (b) (4) **Patients ≥65 years on the tucatinib arm were more likely to experience most common AEs, more likely to experience an SAE, and more likely to discontinue tucatinib compared to patients <65 years on the tucatinib arm. The FDA agrees that there were too few patients ≥75 years to assess for differences in safety in this age group.**

Sex: The FDA disagrees (b) (4) **There were too few male patients in the tucatinib safety database to assess for differences in safety.**

Hepatic and Renal Insufficiency

The FDA in general agrees with the Applicant's position on the assessment of hepatic impairment and renal impairment. However, the FDA recommends to reduce the starting dose to 200 mg BID in patients with severe hepatic impairment. This recommendation is made based on the increased median exposure and increased between subject variability observed in the severe hepatic impairment group, as well as an increased TEAE of AST/ALT observed in HER2CLIMB. The FDA recommends to remove the proposed (b) (4) **due to a lack of clinical data to support this conclusion. Since tucatinib is used in combination therapy with capecitabine, which is contraindicated in patients with severe renal impairment, a statement will be added to Section 8 of the tucatinib label to warn against the use of the tucatinib and capecitabine combination therapy in this patient population. Refer to section 6.3.2.3 for more details.**

8.2.8. Specific Safety Studies/Clinical Trials

Data:
Study SGNTUC-020 a DDI study conducted in healthy subjects treated with tucatinib to evaluate increased serum creatinine, demonstrated that the elevations were due to tucatinib inhibition of transporters responsible for renal secretion of creatinine (OCT2/MATE1). The elevations were transient, not recorded as TEAEs, resolved after cessation of dosing, and were not associated with decreased renal function as measured by sensitive markers of glomerular filtration (e.g., iohexol clearance).

The Applicant's Position:
Although not an adverse reaction, increased serum creatinine was observed in subjects treated with tucatinib due to inhibition of renal tubular transport of creatinine without affecting glomerular function. In clinical studies, increases in serum creatinine (30% mean increase) occurred within the first 21 days of treatment with tucatinib, remained elevated but stable throughout treatment and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

Regulatory Authorities Assessment:
FDA agrees with the Applicant's assessment. Refer to section 8.2.5.6 for detailed FDA's independent analysis on creatinine increase.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
NA. There were no human carcinogenicity studies of tucatinib and limited long-term data on tucatinib use.

Human Reproduction and Pregnancy

Data:
NA

The Applicant's Position:
There are no available human data on tucatinib use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Tucatinib can cause fetal harm based upon findings from an embryo-fetal toxicity study in rabbits that demonstrated embryo-fetal teratogenicity at a maternal exposure approximating exposure in humans at the recommended therapeutic dose. Female subjects of childbearing potential treated with tucatinib should be advised of the potential risk to the fetus.

Regulatory Authorities Assessment:
See Section 5.4.5.4 for more information. In the USPI, the FDA advises that all females of reproductive potential should have pregnancy status verified prior to initiating tucatinib. Females of reproductive potential and male patients with female partners of reproductive potential should use effective contraception during treatment with tucatinib and for at least 1 week after the last dose of tucatinib. Embryo-fetal toxicity is included under Warnings and Precautions.

The FDA agrees that there were no pregnancies in the tucatinib development program.

Pediatrics and Assessment of Effects on Growth

Data:
NA

The Applicant's Position:
NA

Regulatory Authorities Assessment:
Not Applicable

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:
A single subject in HER2CLIMB took tucatinib 600 mg BID for 14 days of each 21-day cycle for 14 cycles. For the last 6 cycles, the subject took capecitabine for 7 days on, 7 days off as a dose reduction for PPE syndrome. Reported events included 2 treatment-related AEs of Grade 1 nausea and stomatitis and a single Grade 3 AE of PPE syndrome. No significant lab abnormalities were reported. The subject, who continued to receive treatment on study, was re-educated on accurate dosing and the site initiated weekly outreach to ensure compliance.

The Applicant's Position:
The effects of overdose of tucatinib are unknown. The potential for tucatinib drug abuse and dependency is unknown.

Regulatory Authorities Assessment:
The regulatory authorities agree with the applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:
NA

The Applicant's Position:
Tucatinib is not currently approved or marketed in any country.

Regulatory Authorities Assessment:
Not applicable

Expectations on Safety in the Postmarket Setting

Data:
NA

The Applicant's Position:
Toxicities are adequately represented in the HER2CLIMB study. Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected AEs.

Regulatory Authorities Assessment:
The regulatory authorities generally agree that the safety of tucatinib has been adequately characterized in HER2CLIMB and the other tucatinib studies reviewed as part of this application. The FDA will continue to monitor post-marketing reports and safety reports submitted after approval.

8.2.11. Integrated Assessment of Safety

Data:
Treatment with tucatinib as both monotherapy and in combination with trastuzumab and capecitabine was well tolerated in subjects across all tucatinib clinical studies. The addition of tucatinib to the well-established combination of trastuzumab and capecitabine resulted in a comparable safety profile to trastuzumab and capecitabine alone. No new safety signals were identified. Overall, clinical studies evaluating tucatinib demonstrated a manageable safety profile and a low rate of TEAEs leading to discontinuation of treatment.

On HER2CLIMB, TEAEs of diarrhea and elevation in liver function tests (AST, ALT, bilirubin), which were previously reported in phase 1 trials (ARRAY-380-101 and ONT 380 005), were observed at a higher incidence on the tucatinib arm compared with the control arm. Diarrhea events were primarily Grade 1 and were manageable with antidiarrheal medication and dose modification. Elevated LFTs generally occurred early in treatment, were primarily Grades 1 and 2, and were transient and manageable with dose modification.

Applicant's Position:
(b) (4)

Regulatory Authorities Assessment:
Overall, tucatinib demonstrated an acceptable tolerability for the indicated population which has a serious and life-threatening disease.

The regulatory authorities consider the HER2CLIMB trial and the reviewed portions of the tucatinib safety database as adequate to characterize the safety profile of tucatinib in combination with trastuzumab and capecitabine.

Almost all patients enrolled to HER2CLIMB experienced a TEAE, and the overall incidence of TEAEs was similar between the tucatinib arm and the control arm. The most common TEAEs on the tucatinib arm of HER2CLIMB (≥20%) were diarrhea, PPE syndrome, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, increased blood bilirubin, AST increased, increased ALT, anemia, and rash. Grade ≥3 AEs occurred in approximately half of patients enrolled to HER2CLIMB and were slightly higher on the tucatinib arm versus control arm. The most common severe (grade 3-4) AEs on the tucatinib arm of HER2CLIMB (≥5%) were PPE syndrome, diarrhea, hepatoxicity, increased ALT, and fatigue.

SAEs were balanced between the two treatment arms and the most common serious adverse reactions (≥2%) in patients on the tucatinib arm were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%).

TEAEs leading to dose interruption, reduction, and discontinuation were all more common on the tucatinib arm compared to the control arm. However, dose discontinuation was relatively infrequent, occurring in only 6% of patients on the tucatinib arm.

Important safety signals for tucatinib include diarrhea and severe hepatotoxicity. Diarrhea led to dose reductions of tucatinib in 4.2% of patients and discontinuation of tucatinib in 1% of patients. Two patients on the tucatinib arm of HER2CLIMB experienced a TEAE of grade 4 diarrhea, and both patients died, with diarrhea as a contributor to death. Hepatotoxicity led to dose reduction of tucatinib in 8% of patients and discontinuation of tucatinib in 1.5% of patients. The FDA labeled diarrhea and hepatotoxicity under Warnings and Precautions in the USPI.

The regulatory authorities disagree with the applicant (b) (4)

Although the overall incidences of TEAEs and SAEs were similar between the two treatment arms of HER2CLIMB, dose interruptions, reductions, and discontinuations were all more common with tucatinib. Importantly, all grade and grade ≥3 diarrhea and hepatotoxicity were both higher on the tucatinib arm compared to the control arm. Grade 4 diarrhea leading to death only occurred on the tucatinib arm.

The FDA believes that the safety profile of tucatinib is manageable with labeling.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Regulatory Authorities Assessment:

There were no major statistical issues with this application. HER2CLIMB showed a statistically significant improvement in favor of the tucatinib arm with respect to the primary endpoint PFS by BICR and secondary endpoints OS, $PFS_{BrainMets}$, and ORR by BICR.

8.4. Conclusions and Recommendations

Regulatory Authorities Assessment:

The HER2CLIMB trial, a randomized, double-blind, placebo-controlled clinical trial in 612 patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior trastuzumab, pertuzumab, and T-DM1 demonstrated that additional treatment with tucatinib resulted in a significant and clinically meaningful improvements in the primary efficacy outcome (PFS by BICR) and all the key secondary outcomes (OS, $PFS_{brainmets}$, and ORR by BICR). The safety profile of tucatinib is acceptable for the intended population, and is manageable with product labeling.

Based on a favorable risk-benefit assessment of tucatinib, the FDA clinical and statistical reviewers recommend regular approval with the following indication:

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.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

Regulatory Authorities Assessment:

FDA did not refer this new drug application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10 Pediatrics

The Applicant's Position:
Tucatinib has not been studied in the pediatric population.

Regulatory Authorities Assessment:
The FDA agreed with the applicant's Initial Pediatric Study Plan (iPSP) under IND 119421 on March 3, 2017. The applicant submitted a full Pediatric Research Equity Act (PREA) waiver request on January 6, 2020 which was granted by the FDA on January 13, 2020.

The regulatory authorities agree with the applicant's assessment that tucatinib has not been studied in the pediatric population.

11 Labeling Recommendations

Data:
This is an original application. Please see the draft labeling label in Module 1.14.1.1 for proposed labeling.

The Applicant's Position:
NA

Regulatory Authorities Assessment:
The FDA's labeling revisions to the applicant's proposed labeling are included in the table below. The other regulatory authorities are still reviewing the applicant's proposed labeling including the indication statement. Their indication statements may differ from the FDA's and vary from authority to authority.

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's Labeling Revisions**
Highlights	**Included the phrase "who have received at least 3 prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting" to describe prior therapies under Indications and Usage** **Females of Reproductive Potential included under Use in Specific Populations**	***FDA revised the proposed labeling as follows:*** ***- Added the established pharmacologic class (EPC) "kinase inhibitor" to Indications and Usage*** ***- Revised the indication statement to include the phrase "who have received one or more prior anti-HER2-based regimens" to describe prior therapies*** ***-Reordered Diarrhea and Hepatotoxicity under W&P to list Diarrhea first*** ***- Added a statement about severe diarrhea and frequency of diarrhea to Diarrhea under W&P***

		- Added a statement about severe hepatotoxicity to Hepatotoxicity under W&P ***- Added a reference to the trastuzumab and capecitabine labels to Embryo-Fetal Toxicity under W&P*** ***- Revised Adverse Reactions to add fatigue, hepatotoxicity, blood bilirubin increased, AST increased, abdominal pain, and headache to the list of common ARs*** ***- Revised Drug Interactions to add the qualifier "moderate" before CYP2C8 inducers*** ***- Under Drug Interactions, added a recommendation to reduce the dose of P-gp substrates where minimal concentration change could lead to serious or life-threatening consequences.*** ***- Removed Females of Reproductive Potential from Specific Populations***
Indications and Usage	**Included the phrase "who have received at least 3 prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting" to describe prior therapies in the indication statement**	***- Revised the indication to include the phrase "who have received one or more prior anti-HER2-based regimens" to describe prior therapies in the indication statement*** ***- Added "adult" to the indication statement*** ***- Removed "locally" before "advanced" in the indication statement***
	2.1 Recommended Dosage	***2.1 Recommended Dosage*** ***- Added a statement advising patients not to ingest tablets***

	(b) (4) **2.2 Dose Modifications** **Recommended** (b) (4)	***that are broken, cracked, or not otherwise intact*** ***- Removed*** (b) (4) ***- Included text with capecitabine dosage recommendation*** ***2.2 Dose Modifications*** ***-Revised*** (b) (4) ***to recommend permanent discontinuation if Grade 4 Diarrhea occurs*** ***Added 2.3 Dosage Modifications for Severe Hepatic Impairment and 2.4 Dosage Modifications for coadministration with strong CYP2C8 inhibitors***
Warnings and Precautions	**Information was provided in a different order** **Stated** (b) (4) **in 5.3**	***- Agreed to W&P for Diarrhea (5.1), Hepatotoxicity (5.2), and Embryo-Fetal Toxicity (5.3)*** ***-Revised order to increase prominence of Diarrhea under W&P*** ***- Revised text under Diarrhea (5.1) to list sequelae of severe diarrhea, add incidence of diarrhea by grade, and add incidence of dose modifications due to diarrhea*** ***-Revised text under Hepatotoxicity (5.2) to add the qualifier "severe" before hepatotoxicity, add incidences of ALT, AST, and total bilirubin increase, and the incidence of dose modifications for hepatotoxicity***

		- Revised text under Embryo-Fetal Toxicity (5.3) to include information on rats and provide animal to human exposure multiples at the recommended human dose ***- Added that females of reproductive potential should be warned of risk to fetus, added guidance for males with female partners of reproductive potential, and added references to the trastuzumab and capecitabine Full Prescribing Information in 5.3***
Adverse Reactions	**Separated Grade 3 and 4 AEs in different columns in Table 5: Adverse Reactions** **Did not present AEs by descending order of frequency in Table 5: Adverse Reactions** **In Table 5: Adverse Reactions, the grouping strategy for preferred terms was different than FDA's for anemia, stomatitis, AST increased, ALT increased, blood bilirubin increased. The table included** (b) (4) **rather than peripheral neuropathy. The table did not include hepatotoxicity.** **Did not include a table of laboratory abnormalities**	***- Revised clinical trial information to include the dosing regimen and duration of treatment with tucatinib.*** ***-Removed*** (b) (4) ***-Added abdominal pain and seizure to list of serious ARs, added hepatotoxicity to list of ARs leading to dose discontinuation and list of ARs leading to dose reduction*** ***- Added a list of the most common ARs (≥20%)*** ***-Revised Table 5 to a 4-column format with columns for "All Grade" and "Grade ≥3" ARs. Added a footnote to denote for which ARs there were no grade 4 observed*** ***-Adjusted frequencies of ARs in Table 5 based on the FDA's***

		grouping strategy for preferred terms ***-Added hepatotoxicity and creatinine increased to the table, and revised*** (b) (4) ***to peripheral neuropathy*** ***- Removed*** (b) (4) ***and only included in laboratory table due to grouped term hepatotoxicity in AR table*** ***-Added a table of laboratory abnormalities worsening from baseline*** ***-Made edits to the Increased Creatinine section to improve readability***
Drug Interactions	**Did not include information on moderate CYP2C8 inducers or moderate CYP2C8 inhibitors in 7.1**	***-Added information about moderate CYP2C8 inducers and moderate CYP2C8 inhibitors to Table 5 in 7.1*** ***- Removed the term*** (b) (4) ***to refer to CYP3A substrates and instead used the descriptor "where minimal concentration changes may lead to serious or life-threatening toxicities" in Table 6 in 7.2***
Use In Specific Populations	**Stated** (b) (4) **Stated** (b) (4)	***- Added references to the trastuzumab and capecitabine Full Prescribing Information in 8.1, 8.2, and 8.3*** ***- Revised the Risk Summary in 8.1 to more clearly outline embryo-fetal toxicities from animal studies and provide animal to human exposure multiples at the recommended human dose***

	Stated [redacted] (b) (4) **Did not include information about Geriatric Use**	***-Revised Animal Data in 8.1 to more clearly outline fetal effects in animal studies and to correct the maternal exposure data*** ***-Added a specific warning about fetal harm in pregnant women under 8.3*** ***-Completed 8.5: Geriatric Use*** ***-Under 8.6 Renal Impairment, stated that tucatinib with trastuzumab and capecitabine is not recommended in patients with severe renal impairment because capecitabine is contraindicated in this population, and added a reference to the Full Prescribing Information for capecitabine*** ***- Under 8.7 Hepatic Impairment, added information and a recommendation for dose reduction of tucatinib in patients with severe hepatic impairment***
[redacted] (b) (4)		
Description	--	***-Revised pharmacologic class from*** [redacted] (b) (4) ***to "kinase inhibitor"*** ***-Added information about the amount of potassium and sodium in each 50 mg tablet and each 150 mg tablet of tucatinib***

Clinical Pharmacology	**Included extensive information in 12.1 Mechanism of Action** **Stated that** (b) (4) **Stated that** (b) (4) **under Specific Populations in 12.3** **Stated** (b) (4)	***-Revised 12.1 to provide a more concise summary, remove educational and promotional language, and remove*** (b) (4) ***-Revised language in 12.2 to state that no large mean increase in QTc was detected in a TQT study,*** (b) (4) ***-Revised language in 12.2 to state that the exposure-response relationship has not been fully characterized*** ***- Revised language under Specific Populations (12.3) to include ranges for age, albumin, creatinine clearance, body weight, and categorical descriptors for race.*** ***- Revise Renal Impairment (12.3) to detail the effects in patients with mild to moderate impairment, and state that the effect in those with severe renal impairment is unknown*** ***-Revised Hepatic Impairment (12.3) to include specific information on tucatinib AUC in those with severe hepatic impairment and removed*** (b) (4) ***- Revised column heading for clarity under Drug Interaction Studies (12.3)***

		- Added information that tucatinib is not an inhibitor of UGT1A1 under In Vitro Studies (12.3)
Nonclinical Toxicology	**Included information that** (b) (4) [redacted]	***-Added information about the specific assays used to assess clastogenic potential*** ***-Added information that fertility studies in animals have not been conducted*** ***- Revised text to include specific effects seen in male rats*** ***-Corrected the exposure multiples comparing exposures in female and male rats to human exposure at the recommended dose***
Clinical Studies	**Text organized in a different order** **Included** (b) (4) [redacted] **Include** (b) (4) [redacted]	***- Added that randomization was 2:1*** ***- Added information about how HER2 positivity was determined*** ***-Revised and condensed text describing study treatment regimen*** ***-Added information about frequency of tumor assessments*** ***-Added information about percentage of patients with visceral metastases and deleted*** (b) (4) [redacted] ***-Added information about how many patients had received prior trastuzumab, pertuzumab, and T-DM1*** ***-Added that RECIST v1.1 criteria were used to assess efficacy endpoints***

		-Deleted information about (b) (4) ***-Condensed results for primary and key secondary endpoints into one table*** ***- Removed*** (b) (4) ***-Removed*** (b) (4)
How Supplied/Storage and Handling	**--**	***-Added guidance to store tucatinib in original contianer to protect from moisture*** ***-Added a statement that once, opened the product must be used within 3 months***
Patient Counseling Information	**--**	***-Revised text to add more information under Embryo-fetal Toxicity, added references to trastuzumab and capecitabine Full Prescribing Information under Embryo-fetal toxicity and Lactation.*** ***-Added a section on infertility***
PPI	**--**	***-Reformatted and made multiple content revisions to the proposed Patient Package Insert (PPI). Updated to be consistent with revisions to the Full Prescribing Information.*** ***- See the approved PPI and FDA OPDP/DMP reviews for full details***

12 Risk Evaluation and Mitigation Strategies (REMS)

Regulatory Authorities Assessment:

Based on the benefit-risk profile of tucatinib in combination with trastuzumab and capecitabine, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance. REMS are not required by the FDA for this new drug application.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The FDA did not issue any postmarketing requirements or commitments for this new drug application.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OB)

X

16 Division Director (Clinical)

X

17 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

18 Division Director (OCP)

X

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:
Financial disclosures and additional processes to minimize bias are described in Section 8.1.2 of the assessment aid.

The FDA's Assessment:
The initial sponsor of HER2CLIMB was Cascadian Therapeutics, Inc. Seattle Genetics, Inc. purchased Cascadian on March 8, 2018 and became the sponsor of HER2CLIMB on October 1, 2018. There were a total of 1924 principal investigators and sub-investigators who participated in HER2CLIMB. Out of this total, 214 were investigators under Cascadian only, 208 were investigators under Seattle Genetics only, and 1502 were investigators under both sponsors. There was complete financial disclosure information for 1805 out of 1924 investigators (93.8%). There was missing financial disclosure information for 119 out of 1924 investigators (6.2%) as listed here:

- **2 investigators under Cascadian only with missing financial disclosure forms (FDFs)**
- **8 investigators under Seattle Genetics only with missing FDFs**
- **17 investigators under both sponsors with missing Cascadian FDFs**
- **84 investigators under both sponsors with missing Seattle Genetics FDFs**
- **8 investigators under both sponsors missing both FDFs**

Out of the 1916 investigators with available financial disclosure information, 3 (0.16%) had disclosable financial interests. Given the small number of patients potentially impacted (n=11), the randomized and blinded nature of HER2CLIMB, and the use of a BICR to evaluate the primary endpoint, these disclosable financial interests were unlikely to impact the results of the study. Please also refer to section 8.1.2.

Covered Clinical Study (Name and/or Number):* ONT-380-206 (HER2CLIMB)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1924 unique investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 2		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2[a], [b], [c], and [f]): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 3 Sponsor of covered study: Seattle Genetics, Inc (formerly Cascadian Therapeutics, Inc.)		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) NA		
Is an attachment provided with the reason:	Yes ☐	No ☒ [a](Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

a. In form FDA 3454, Box 3 is not applicable for HER2CLIMB because the application does not include studies conducted by another party.

19.3. Nonclinical Pharmacology/Toxicology

Data:
NA

The Applicant's Position:
All nonclinical pharmacology and toxicology data are included in Section 5.

The FDA's Assessment:
NA

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The regulatory authorities' Assessment:
Population PK analysis

The sponsor submitted a population PK report entitled " Population Pharmacokinetic Modeling of Tucatinib".

Objectives: The objectives of this analysis were to develop a population pharmacokinetic (PK) model to characterize the PK profile of tucatinib and to assess the sources of variability in tucatinib PK.

Data: The population PK model was developed with data from pooled PK data with the studies in Table 45 except study HER2CLIMB. The final population PK model was based on 3918 plasma tucatinib concentrations from a total of 126 healthy subjects and 112 subjects with cancer from 5 independent studies. Clinical studies included in the population PK model are summarized in

Table **45**. Baseline characteristics in the population PK analysis dataset are summarized in Table 46, and

Table **47**.

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Table 45: Clinical Studies Included in Population PK Modeling

Study Number	Study Description	Tucatinib Dose (n)	PK Data Description
Phase 1 Studies in Healthy Subjects			
ARRAY-380-103	Relative BA study of tablet vs. PIC formulation Food effect evaluation Omeprazole DDI	300 mg (n = 12)	Intensive SD PK Note: PK data from the omeprazole DDI treatment period was not included in the PK model.
ONT-380-012	DDI study with itraconazole, rifampin, gemfibrozil, repaglinide, midazolam, tolbutamide, and digoxin Tablet formulation	Part A: 300 mg SD (n = 28) Part B: 300 mg SD (n = 28) Part C: 300 mg SD (n = 28) Part D: 300 mg BID × 10 days (n = 17) Part E: 300 mg BID × 14 days (n = 13)	Intensive SD PK from Parts A, B, and C Intensive SD and MD PK from Parts D and E Note: Only PK data from monotherapy treatments were included in the PK model.
Studies in Subjects with Cancer			
ARRAY-380-101	Phase 1, dose escalation HER2+ cancer PIC formulation	25 to 800 mg BID (n = 33 for dose escalation; n = 17 for dose expansion)	Intensive SD and MD PK Dose escalation Cycle 1 Day 1: Pre-dose to 24 hours post-dose Cycle 1 Day 3: Pre-dose to 4 hours post-dose

Study Number	Study Description	Tucatinib Dose (n)	PK Data Description
			Cycle 1 Day 15: Pre-dose to 12 hours post-dose Cycles 2 to 4 Day 1: Trough samples Expansion Cycle 1 Day 1: Pre-dose Cycle 1 Day 15 and Cycle 2 Day 1: Pre-dose to 12 hours post-dose Cycles 2 to 6 Day 1: Trough samples
ONT-380-004	Phase 1b in HER2+ mBC, in combination with T-DM1 Tablet formulation	300 mg BID (n = 32) 350 mg BID (n = 7)	Intensive SD and MD PK Day 1 of Cycles 1 (tucatinib only) and 2 (tucatinib + T-DM1): Pre-dose to 6 hours post-dose Day 1 of Cycles 3 to 6: 1 hour pre-dose
ONT-380-005	Phase 1b in HER2+ mBC, in combination with capecitabine (1A and 1B) or capecitabine + trastuzumab (3A and 3E) Tablet formulation	300 mg BID (n = 17) 350 mg BID (n = 3)	Intensive MD PK Days 14 and 21 of Cycle 1: Pre-dose to 6 hours post-dose Cycles 2 to 6: pre-dose

BA = bioavailability; BID = twice daily; DDI = drug-drug interaction; HER2+ = human epidermal growth factor receptor 2-positive; mBC = metastatic breast cancer; MD = multiple dose; n = number of subjects; PIC = powder in capsule; PK = pharmacokinetics; SD = single dose; T-DM1 = ado-trastuzumab emtansine.

Table 46: Summary of Continuous Covariates

Covariate	Mean (SD) Median [Minimum, Maximum]					
	Study ONT-380-005 (N = 24)	Study ARRAY-380-101 (N = 49)	Study ARRAY-380-103 (N = 12)	Study ONT-380-004 (N = 39)	Study ONT-380-012 (N = 114)	Total (N = 238)
Age (y)	50.5 (9.54) 50.0 [36.0, 70.0]	56.6 (9.55) 58.0 [31.0, 77.0]	29.4 (8.60) 26.0 [19.0, 45.0]	53.5 (12.1) 52.0 [31.0, 72.0]	42.8 (11.9) 43.5 [22.0, 65.0]	47.5 (13.1) 49.0 [19.0,77.0]
Albumin (g/dL)	4.08 (0.372) 4.10 [3.50, 4.90]	3.88 (0.592) 3.90 [2.50, 4.80]	4.53 (0.328) 4.50 [4.00, 4.90]	3.85 (0.338) 3.90 [3.10, 4.40]	4.58 (0.281) 4.60 [3.80, 5.20]	4.26 (0.508) 4.40 [2.50, 5.20]
ALP (IU/L)	126.0 (126.0) 92.5 [45.0, 685.0]	109.0 (51.4) 101.0 [13.0, 262.0]	61.8 (16.1) 58.0 [42.0, 93.0]	106.0 (89.2) 79.0 [25.0, 506.0]	71.2 (17.5) 68.0 [39.0, 152.0]	89.7 (63.0) 76.5 [13.0, 685.0]
ALT (IU/L)	32.5 (9.56) 31.0 [16.0, 62.0]	26.0 (15.6) 22.0 [11.0, 99.0]	22.8 (6.73) 21.5 [15.0, 34.0]	27.9 (22.8) 20.0 [7.00, 119.0]	20.3 (8.91) 19.0 [6.00, 58.0]	24.1 (14.1) 21.0 [6.00, 119.0]
AST (IU/L)	44.7 (20.3) 41.0 [21.0, 110.0]	36.1 (17.7) 29.0 [16.0, 93.0]	22.4 (3.45) 21.0 [18.0, 28.0]	29.2 (23.9) 22.0 [9.00, 155.0]	20.0 (4.32) 20.0 [8.00, 33.0]	27.4 (16.7) 22.0 [8.00, 155.0]
Bilirubin (mg/dL)	0.558 (0.253) 0.553 [0.199, 1.10]	0.450 (0.248) 0.400 [0.175, 1.40]	0.942 (0.271) 0.900 [0.700, 1.50]	0.468 (0.237) 0.398 [0.175, 1.17]	0.459 (0.221) 0.400 [0.100, 1.20]	0.494 (0.258) 0.400 [0.100, 1.50]
BMI (kg/m^2)	26.7 (4.88) 26.2 [18.4, 35.6]	26.3 (5.42) 26.0 [15.3, 46.0]	25.3 (2.89) 25.4 [21.3, 29.8]	28.4 (8.43) 25.7 [17.8, 55.2]	26.9 (2.77) 27.1 [19.7, 31.8]	26.9 (4.88) 26.4 [15.3, 55.2]
BSA (m^2)	1.78 (0.169) 1.78 [1.43, 2.11]	1.78 (0.218) 1.75 [1.47, 2.44]	1.90 (0.162) 1.85 [1.63, 2.12]	1.80 (0.250) 1.74 [1.30, 2.39]	1.93 (0.157) 1.92 [1.55, 2.34]	1.86 (0.200) 1.85 [1.30, 2.44]
CRCL (mL/min)	108.0 (30.0) 106.0 [68.2, 174.0]	98.7 (31.2) 96.0 [36.0, 195.0]	130.0 (25.8) 131.0 [88.6, 181.0]	101.0 (31.5) 91.3 [45.5, 166.0]	116.0 (21.8) 117.0 [74.2, 168.0]	110.0 (27.9) 108.0 [36.0, 195.0]

Covariate	Mean (SD) Median [Minimum, Maximum]					
	Study ONT-380-005 (N = 24)	Study ARRAY-380-101 (N = 49)	Study ARRAY-380-103 (N = 12)	Study ONT-380-004 (N = 39)	Study ONT-380-012 (N = 114)	Total (N = 238)
CRCLN (mL/min/ 1.73 m^2)	105.0 (26.6) 104.0 [64.6, 169.0]	95.6 (27.9) 93.6 [35.4, 183.0]	119.0 (22.0) 119.0 [77.8, 147.0]	95.1 (25.5) 89.7 [60.6, 156.0]	104.0 (17.6) 102.0 [65.3, 154.0]	102.0 (23.0) 100.0 [35.4,183.0]
Weight (kg)	71.3 (12.6) 74.3 [46.8, 93.2]	71.8 (17.6) 69.9 [45.5, 138.0]	76.2 (12.1) 72.2 [59.2, 93.4]	74.0 (20.9) 67.1 [40.7, 132.0]	79.8 (10.4) 78.7 [57.0, 99.5]	76.1 (14.8) 75.4 [40.7, 138.0]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; BMI = body mass index; BSA = body surface area; CRCL=creatinine clearance; CRCLN = body surface area-normalized creatinine clearance; N = number of subjects; SD = standard deviation.

Source: Table 6 on page 35-36 of Applicant's population PK report

Table 47: Summary of Categorical Covariates

Covariate	Value	ARRAY-380-101 (N = 49)	ARRAY-380-103 (N = 12)	ONT-380-012 (N = 114)	ONT-380-004 (N = 39)	ONT-380-005 (N = 24)	Overall (N = 238)
Race	White	39 (79.6%)	10 (83.3%)	67 (58.8%)	30 (76.9%)	22 (91.7%)	168 (70.6%)
	Black	4 (8.2%)	1 (8.3%)	44 (38.6%)	4 (10.3%)	0 (0.0%)	53 (22.3%)
	Other	2 (4.1%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (1.2%)
	Asian	4 (8.2%)	0 (0.0%)	1 (0.9%)	4 (10.3%)	1 (4.2%)	10 (4.2%)
	Amer. Indian	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	Nat. Hawaiian	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (4.2%)	2 (0.8%)
Gender	Female	44 (89.8%)	0 (0.0%)	21 (18.4%)	39 (100%)	24 (100%)	128 (53.8%)
	Male	5 (10.2%)	12 (100%)	93 (81.6%)	0 (0.0%)	0 (0.0%)	110 (46.2%)
Population	Subject with cancer	49 (100%)	0 (0.0%)	0 (0.0%)	39 (100%)	24 (100%)	112 (47.1%)
	Healthy subject	0 (0.0%)	12 (100%)	114 (100%)	0 (0.0%)	0 (0.0%)	126 (52.9%)
Tumor	Metastatic breast cancer	42 (85.7%)	0 (0.0%)	0 (0.0%)	39 (100%)	24 (100%)	105 (44.1%)
	Other	7 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (2.9%)

Covariate	Value	ARRAY-380-101 (N = 49)	ARRAY-380-103 (N = 12)	ONT-380-012 (N = 114)	ONT-380-004 (N = 39)	ONT-380-005 (N = 24)	Overall (N = 238)
	Healthy subject	0 (0.0%)	12 (100%)	114 (100%)	0 (0.0%)	0 (0.0%)	126 (52.9%)
Formulation	PIC	49 (87.5%)	12 (100%)[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)	61 (25.6%)
	Tablet	0 (0.0%)	12 (100%)[a]	114 (100%)	39 (100%)	24 (100%)	189 (79.4%)
NCI hepatic dysfunction category	Group A	34 (69.4%)	12 (100%)	109 (95.6%)	34 (87.2%)	14 (58.3%)	203 (85.3%)
	Group B1	13 (26.5%)	0 (0.0%)	0 (0.0%)	5 (12.8%)	10 (41.7%)	28 (11.8%)
	Group B2	2 (4.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
	Missing	0 (0.0%)	0 (0.0%)	5 (4.4%)	0 (0.0%)	0 (0.0%)	5 (2.1%)
ECOG status	1 (Restricted)	30 (53.6%)	0 (0.0%)	0 (0.0%)	23 (59.0%)	7 (29.2%)	60 (25.2%)
	0 (Fully active)	16 (28.6%)	12 (100%)	114 (100%)	16 (41.0%)	17 (70.8%)	175 (68.6%)
	2 (Only self-care)	3 (5.36%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.18%)
Combination drug	Monotherapy	49 (100%)	12 (100%)	114 (100%)	1 (2.56%)[b]	0 (0.0%)	176 (73.9%)
	T-DM1	0 (0.0%)	0 (0.0%)	0 (0.0%)	38 (97.4%)	0 (0.0%)	38 (16.0%)
	Capecitabine	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (45.8%)	11 (4.6%)
	Capecitabine + Trastuzumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (54.2%)	13 (5.5%)

[a] Subjects in Study ARRAY-380-103 received both the PIC and tablet formulations.
[b] One subject in Study ONT-380-004 was recorded as receiving only a single dose of tucatinib and no T-DMI and was thus assigned to monotherapy in the analysis dataset.
Number (percentage) of subjects in category provided.
ECOG = Eastern Cooperative Oncology Group; NCI = National Cancer Institute; PIC = powder in capsule; T-DM1 = ado-trastuzumab emtansine.

Source: Table 7 on page 36-37 of Applicant's population PK report

Reviewer's comment*: PK data from the pivotal study HERCLIMB supporting this application was not included in the population PK analysis due to lack of recording time of dosing. However, the population PK dataset has included sufficient subjects in healthy volunteers and cancer patients which would allow it to characterize the PK profile of tucatinib. The reviewer also noted that the PK data in study ONT-380-004 and ONT-380-005 are very sparse and highly variable.*

Model Development: Nonlinear mixed-effects modeling software (NONMEM®) (version 7.3), a software package for nonlinear mixed-effects analysis (b) (4) was used for population PK modeling. SAS version 9.4 was used for data preparation. R version 3.5.3 was used for graphical analysis, model diagnostics, and statistical summaries. Xpose® and Pearl speaks NONMEM (PsN®) (b) (4)

were used for model diagnostics and facilitation of tasks such as covariate testing and bootstrap.

Base Model: The base model was developed in 2 stages. In the first stage, data from healthy subjects in Studies ARRAY-380-103 and ONT-380-012 were used to establish the absorption model and estimate the effects of formulation, administration of tucatinib with a high-fat meal, and administration of tucatinib 2 hours after breakfast on tucatinib absorption. A 2-compartment model with linear elimination and first-order absorption preceded by an absorption Tlag was found to provide an adequate fit to the healthy data. The model estimated an 11% decrease in Frel with the capsule compared to the tablet, a 38.1% decrease in the first-order absorption rate constant (Ka) with a high-fat meal relative to the fasted state, and a 43.9% increase in Frel when tucatinib is administered with a high-fat meal or 2 hours after breakfast relative to administration in the fasted state. These effects were considered to apply only to healthy subjects.

In the second stage, the final base model was established by fitting the model selected from the first stage to the entire analysis dataset containing data from both healthy subjects and subjects with cancer. With the exception of Tlag, the absorption-related parameters (i.e., Ka and the effects of formulation and prandial state on Ka and Frel in healthy subjects) were fixed to the values estimated in the first stage. The effect of formulation on Frel was applied only to healthy subjects and not subjects with cancer.

Parameter estimates for the base model are presented in Table 48. All parameters were precisely estimated, with relative standard errors (RSEs) ≤ 9.3%. Goodness-of-fit plots for the base model are shown in Figure 6 and Appendix 1.4, and they indicate an adequate model fit to the data. No marked systematic trends were seen in the residual diagnostic plots.

Table 48: Tucatinib Base Model Parameter Estimates

	Fixed Effects		BSV CV%		
Parameter	Estimate	RSE	Estimate	RSE	Shrinkage
CL/F (L/h)	103	3.8%	60.8%	5.3%	0.7%
Vc/F (L)	183	7.0%	186%	3.8%	4.6%
Q/F (L/h)	57.4	4.8%	50.0%	7.5%	30.4%
Vp/F (L)	787	6.4%	83.3%	8.7%	25.4%
Ka (1/h)	0.3146 Fixed				

	Fixed Effects		BSV CV%		
Parameter	Estimate	RSE	Estimate	RSE	Shrinkage
Tlag (h)	0.327	0.3%			
Frel, fasted	1 Fixed				
Ka ~ high-fat meal fractional change (healthy subjects only)	-0.3805 Fixed				
Frel ~ capsule fractional change (healthy subjects only)	-0.11 Fixed				
Frel ~ high-fat meal or 2 hours after breakfast (healthy subjects only)	0.4393 Fixed				
Additive res. error SD (ng/mL)	0.001 Fixed				
Proportional res. error CV	40.1%	0.8%			6.6%

BSV = between-subject variability; CL/F = apparent clearance; CV = coefficient of variation; Frel = relative bioavailability; Ka = first-order absorption rate constant; Q/F = apparent inter-compartmental clearance; Res. = residual; RSE = relative standard error; SD = standard deviation; Tlag = lag time; Vc/F = apparent central volume; Vp/F = apparent peripheral volume of distribution.

Covariate Analysis: The covariates tested in the stepwise covariate search were selected based on a statistically significant reduction in the univariate screening step ($p < 0.01$) or on clinical interest and were as follows:

- Apparent clearance (CL/F): body weight, race, CRCLN, age, NCI hepatic dysfunction category, Eastern Cooperative Oncology Group performance status monotherapy, capsules versus Phase 1b patient combination therapy, tablet)
- Apparent central volume of distribution (Vc/F): body weight and albumin
- Apparent inter-compartmental clearance (Q/F): weight
- Apparent peripheral volume of distribution (Vp/F): weight
- Ka: fasted state versus unknown prandial state (i.e., dosing without regard to
- food; applied only to subjects with cancer)

The covariates added to the model during the forward addition step were population on CL/F, body weight on Q/F, albumin on Vc/F, unknown prandial state on Ka, and body weight on CL/F, in that order. No covariates were removed in the backward elimination step.

The Applicant mentioned that a comparison between the capsule and tablet formulations in subjects with cancer was confounded by the fact that the only data from the tablet formulation in subjects with cancer were from combination therapy studies ONT-380-004 and ONT-380-005, whereas the only data from the capsule formulation in subjects with cancer were from ARRAY-380-101, in which tucatinib was given as monotherapy. Therefore, rather than categorizing the population covariate as healthy subjects versus subjects with cancer, the population covariate was defined as 3 categories:

1) Healthy subjects (Studies ARRAY-380-103 and ONT-380-012)
2) Phase 1a subjects with cancer receiving tucatinib monotherapy in the capsule formulation, i.e., Phase 1a patient monotherapy, capsules (Study ARRAY-380-101)
3) Phase 1b subjects with cancer receiving tucatinib tablets in combination with T-DM1 or trastuzumab and capecitabine, i.e., Phase 1b patient combination therapy, tablet (Studies ONT-380-004 and ONT-380-005)

Only female subjects with cancer participated in Studies ONT-380-004 and ONT-380-005, in which tucatinib was co-administered with T-DM1, capecitabine, trastuzumab, or trastuzumab + capecitabine. Thus, gender was confounded with combination therapy and study. Consequently, gender was not included in the covariate search.

Final Model

The final population PK model was a 2-compartment model with linear elimination, with a first-order absorption preceded by a lag time (Tlag). The parameter estimates for the final population PK model for tucatinib are presented in **Table 49**. Goodness-of-fit plots are presented in **Figure 23** and the VPC plots are shown in Figure 24.

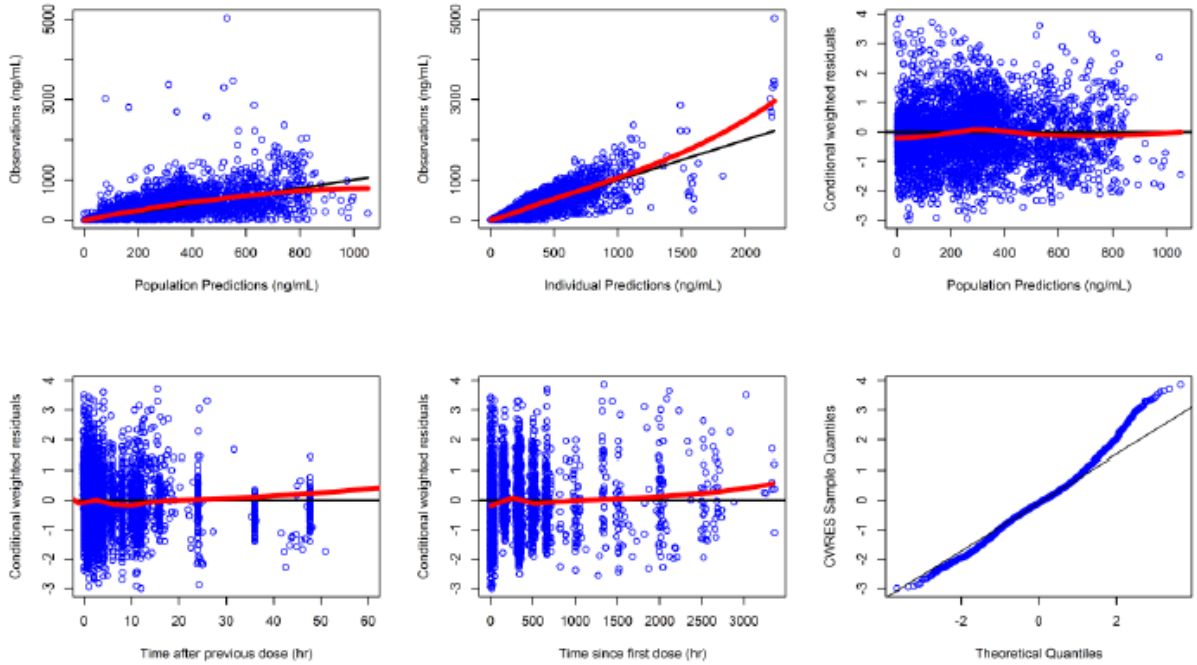
Table 49: Final Model Parameter Estimates for Tucatinib PK

	Fixed Effects		BSV CV%		
Parameter	Estimate	RSE	Estimate	RSE	Shrinkage
CL/F (L/h), healthy subjects	131	4.8%	43%	4.5%	3.1%
Vc/F (L)	157	12.7%	182%	4.5%	7.0%
Q/F (L/h)	56.9	6.1%	62.5%	6.6%	18.5%
Vp/F (L)	573	5.1%	62.5%	6.6%	18.5%
Ka (1/h)	0.3146 Fixed				
Tlag (h)	0.328	0.3%			
Frel, fasted	1 Fixed				
Ka ~ high-fat meal fractional change	-0.3805 Fixed				
Ka ~ unknown prandial state fractional change	-0.122	17.4%			
Frel ~ capsule fractional change (healthy subjects only)	-0.110 Fixed				
Frel ~ high-fat meal or 2 hours after breakfast fractional change	0.4393 Fixed				
CL/F ~ Phase 1a subjects with cancer monotherapy capsule (Study ARRAY-380-101) fractional change	-0.133	48.6%			
CL/F ~ Phase 1b subjects with cancer tablet combo. therapy (Studies ONT-380-004 and ONT-380-005) fractional change	-0.563	6.0%			
CL/F ~ weight exponent	0.567	28.3%			
Q/F ~ weight exponent	0.488	39.6%			
Vc/F ~ albumin exponent	-2.24	33.1%			
Additive res. error SD (ng/mL)	0.001 Fixed				
Proportional res. error CV	40.6%	0.8%			5.7%

BSV = between-subject variability; CL/F = apparent clearance; combo. = combination; CV = coefficient of variation; Frel = relative bioavailability; Ka = first-order absorption rate constant; PK = pharmacokinetic; Q/F = apparent inter-compartmental clearance; Res. = residual; RSE = relative standard error; SD = standard deviation; Tlag = lag time; Vc/F = apparent central volume; Vp/F = apparent peripheral volume of distribution.

Source: Table 9 on page 42 of Applicant's population PK report

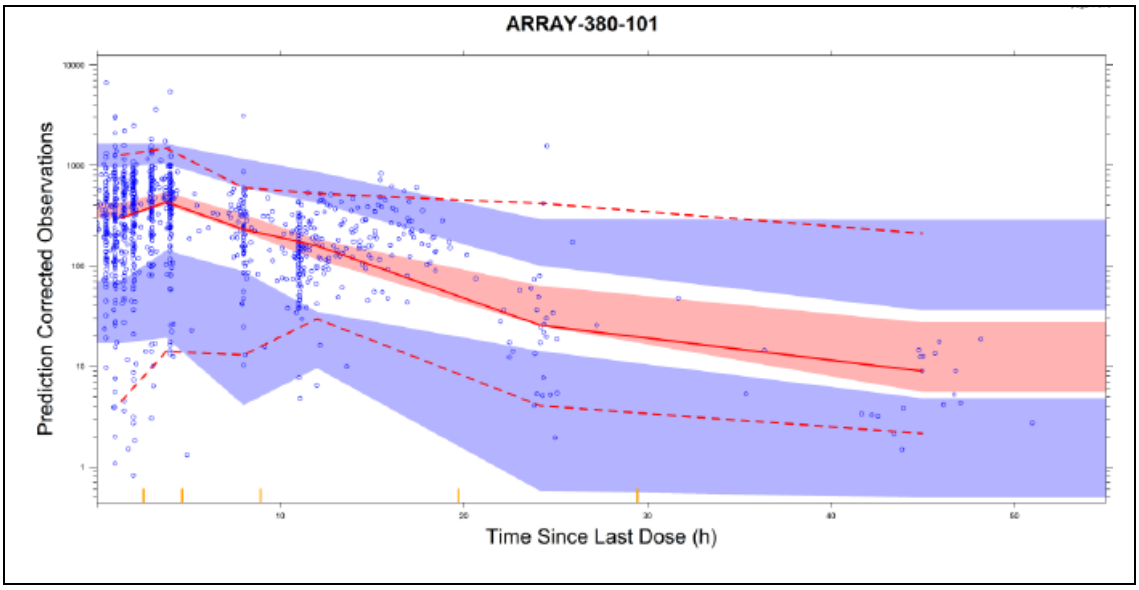
Figure 23: Goodness-of-Fit Plots for the Final Model

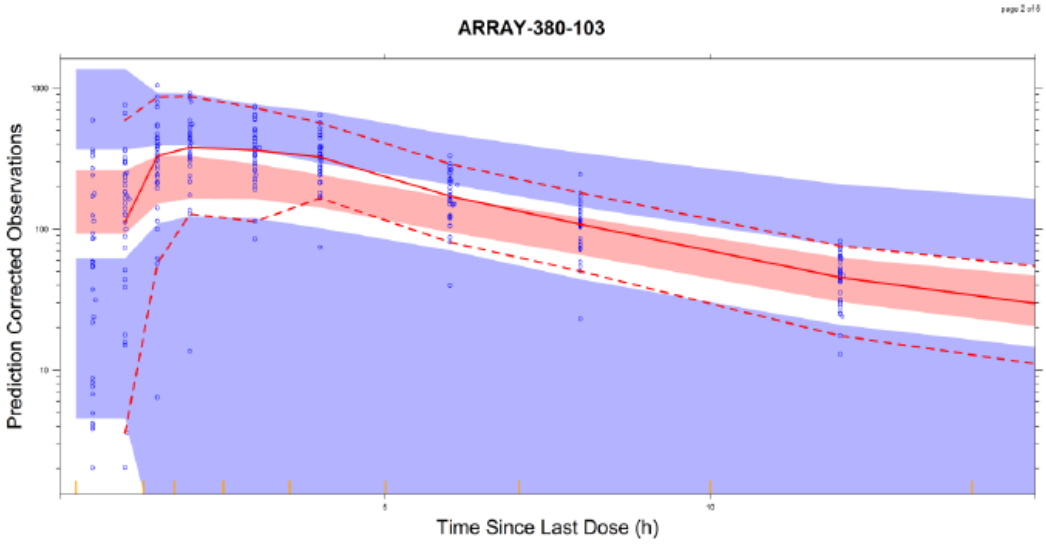


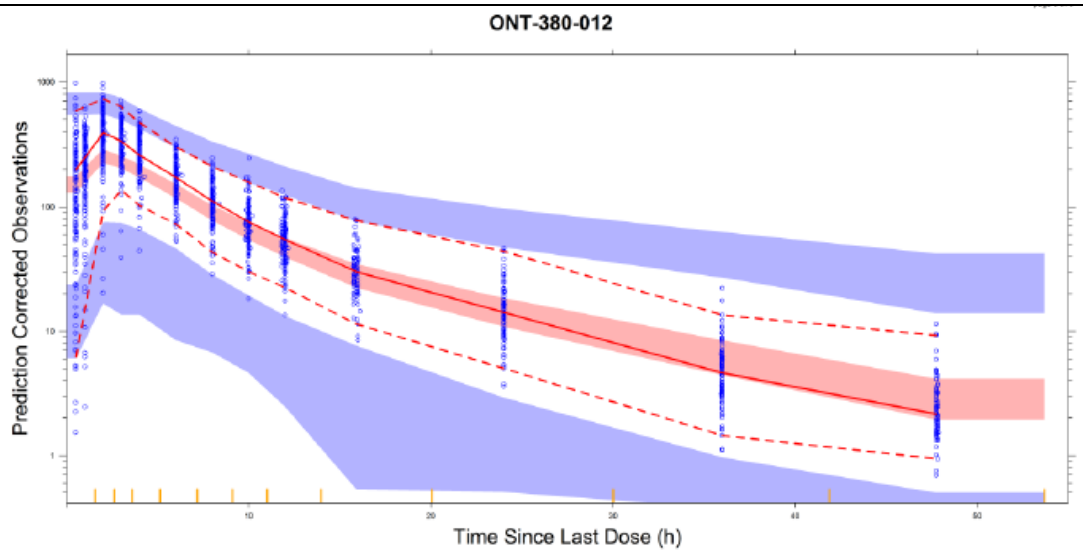
Note:Open circles are individual data points. Red solid lines are LOESS smooth regression lines. Black solid lines are lines of identity for the observations versus predictions and quantile-quantile plots, and y =0for the plots of CWRES. CWRES = conditional weighted residual; LOESS = locally estimated scatter plot smoothing

Source: Figure 1.25 on page 94 of Appliant's population PK report

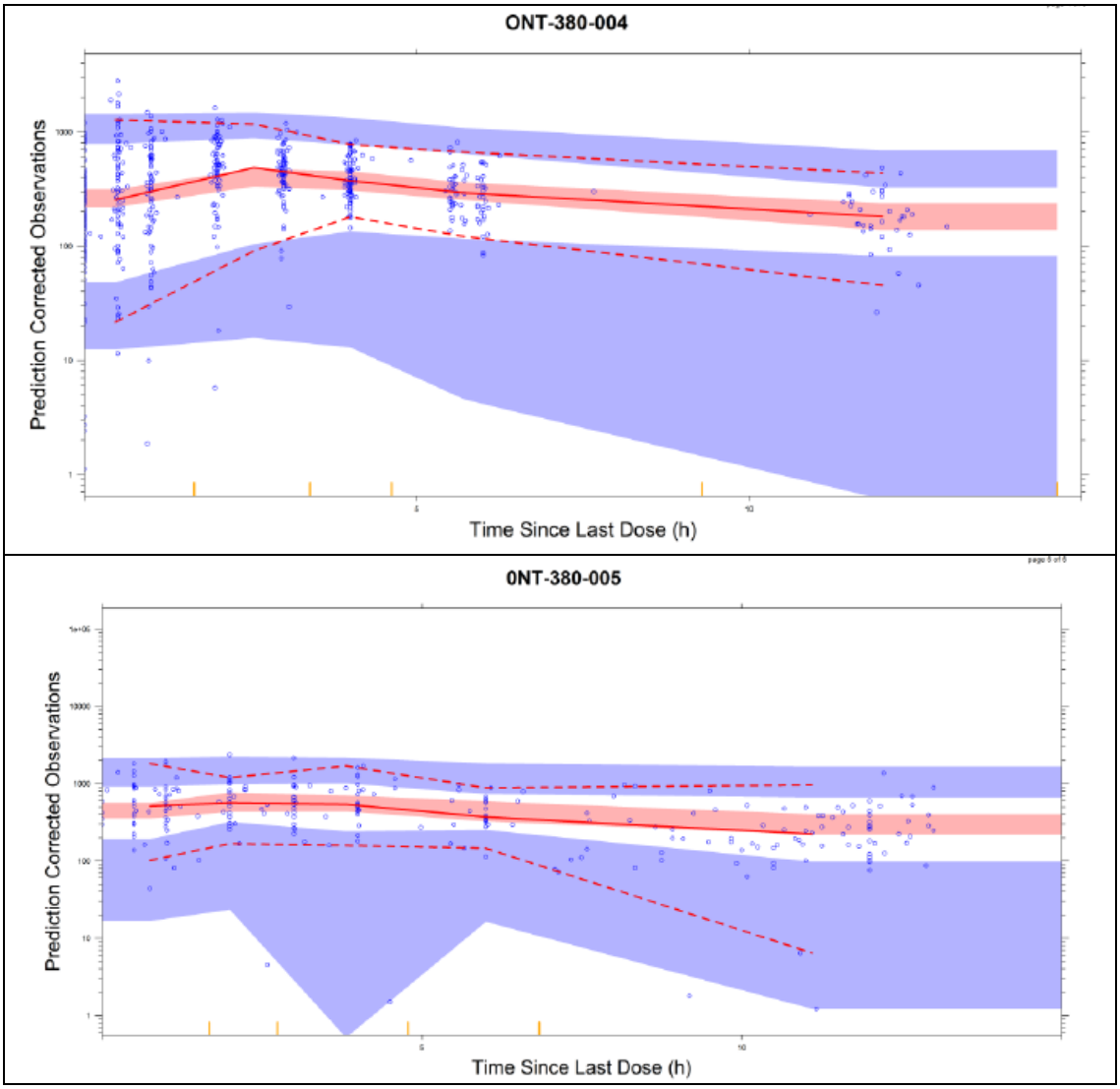
Figure 24: VPC Plots by Study







Blue open circles represent observed data points. The red solid line is the observed median, and the red dashed lines are the observed 5th and 95th percentiles. The red-shaded area is the 95% PI of the simulated median, and the blueshaded areas are the 95% PI of the simulated 5th and 95th percentiles. PI = prediction interval; VPC = visual predictive check



The following covariate effects on tucatinib PK were identified:

- Increase in relative bioavailability (Frel) for tucatinib administration with a high-fat meal or 2 hours after breakfast relative to administration in the fasted state
- Decrease in bioavailability in healthy subjects with the capsule formulation relative to the tablet formulation
- Slower absorption rate (i.e., decrease in first-order absorption rate constant [Ka]) for administration with a high-fat meal in healthy subjects or in the unknown prandial state (i.e., tucatinib administration without regard to a meal) in subjects relative to administration in the fasted state
- Increase in CL/F with increasing body weight

- Increase in apparent inter-compartmental clearance (Q/F) with the increase in body weight
- Decrease apparent central volume of distribution (Vc/F) with increasing serum albumin

Based on the population PK analysis, the proposed label by the Applicant stated (b) (4)

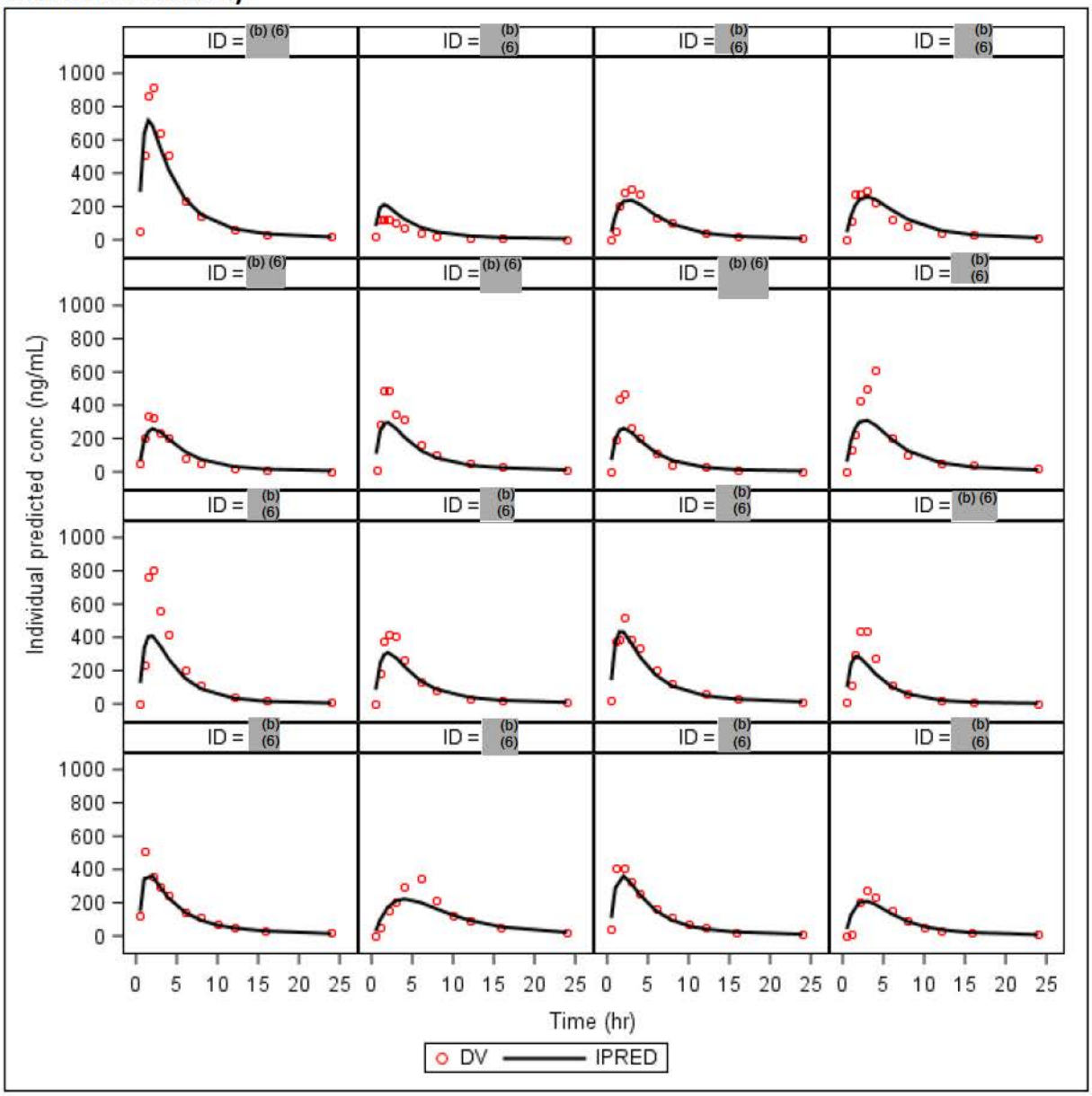
Reviewer's Comment: *As indicated by the VPC plots above and individual plots shown in Figure 1.23 in the report, the fitting of PK data in subjects enrolled in study ONT-380-004 and ONT-380-005 was poor. The sample size in these subjects was limited and the PK data were highly variable, suggesting that poor data quality might have affected the results of the analysis. The PK and exposure estimates of subjects in study ONT-380-004 and ONT-380-005 were not reliable and use of the estimates in these subjects should be with caution.*

Independent analysis was conducted by the FDA reviewer. Representative individual plots of PK profile of tucatinib in healthy volunteers are shown in Figure 25 . While the general conclusions of the population PK analysis are acceptable, multiple flaws were identified. As indicated in Figure 25 below Cmax of many subjects in healthy volunteers were under estimated, suggesting that the parameter of Ka was not well estimated. Despite these flaws, the concentration in the last few points were well captured indicating that the estimate of clearance is accurate.

Overall, despite few flaws identified in the analysis, the reviewer agrees with the Applicant's conclusions from the population PK analysis on effect of covariates except for the following:

- *Decrease in apparent clearance (CL/F) in subjects with cancer (i.e., Phase 1a subjects with cancer receiving tucatinib monotherapy in the capsule formulation [ARRAY-380-101] and Phase 1b subjects with cancer receiving tucatinib tablets in combination therapy with T-DM1 or trastuzumab and capecitabine [ONT-380-004 and ONT-380-005]) compared to healthy subjects*

Figure 25: Representative Individual plots of tucatinib PK profile in healthy volunteers (data shown first 24 hours)



Source: Reviewer's plot based on results of the Applicant's final model

PBPK Analysis

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK reports to support the intended uses.

- R_SEAT_1B Final PK Report: Development of a physiologically based pharmacokinetic model for tucatinib and primary metabolite ONT-993, using the Simcyp population-based simulator, and subsequent prediction of DDI as perpetrator or victim of drug-drug interactions;
- R-SEAT-1B_PK_APPX_C: Development of a fit-for-purpose PBPK model for tucatinib and primary metabolite ONT-993, using the Simcyp population-based simulator, and subsequent prediction of DDI as perpetrator of CYP3A4, CYP2C8, CYP2C9 or MATE1/2k inhibition;
- R-SEAT-1B_PK_APPX_D: Extension of a previously developed PBPK model for tucatinib and primary metabolite ONT-993 within the Simcyp population-based simulator to enable evaluation of potential CYP and transporter mediated drug-drug interactions as victim.

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to FDA's information requests (IRs) submitted on February 5, 2020, and concluded the followings.

- The tucatinib and its metabolite ONT-993 PBPK models are adequate to predict the tucatinib and ONT-993 PK profiles following a single dose administration (300 mg) and multiple does administration (300 mg, bid) in healthy subjects.
- The tucatinib PBPK model is adequate to predict the effect of itraconazole (a strong CYP3A4 inhibitor) on tucatinib PK following multiple dose administration of tucatinib (300 mg, BID) and multiple dose administration of itraconazole (200 mg, QD). Model predicted tucatinib geometric mean AUC ratio was 1.09 with itraconazole in healthy subjects.
- The tucatinib PBPK model is adequate to predict the effect of gemfibrozil (a strong CYP2C8 inhibitor) on tucatinib PK following multiple dose administration of tucatinib (300 mg, BID) and multiple dose administration of gemfibrozil (600 mg, BID). Model predicted tucatinib geometric mean AUC ratio was 4.35 with gemfibrozil in healthy subjects.
- The tucatinib PBPK model is adequate to predict the effect of carbamazepine (a strong CYP3A4 inducer) on tucatinib PK following multiple dose administration of tucatinib (300 mg, BID) and multiple dose administration of carbamazepine (400 mg, BID). Model predicted tucatinib geometric mean AUC ratio was 0.70 with carbamazepine in healthy subjects.
- The tucatinib PBPK model is adequate to predict the effect of phenytoin (a strong CYP3A4 inducer) on tucatinib PK following multiple dose administration of tucatinib (300 mg, BID) and multiple dose administration of phenytoin (300 mg, QD). Model predicted tucatinib geometric mean AUC ratio was 0.84 with phenytoin in healthy subjects.
- The tucatinib PBPK model is adequate to predict the effect of tucatinib on raltegravir (a UGT1A1 substrate) and rosuvastatin (an OATP1B1/3 substrate) PK following multiple dose administration of tucatinib (300 mg, BID) and a single dose administration of raltegravir and rosuvastatin. Model predicted changes in the exposure of raltegravir and rosuvastatin were not considered clinically significant when coadministered with multiple dose of tucatinib in healthy subjects.

Applicant's PBPK Modeling Effort

PBPK software

Simcyp V17 (Simcyp Ltd, UK) was used by the Applicant to develop the PBPK models and DDI predictions. The reviewer used the same software and version for analyses.

Model development

Tucatinib

The tucatinib model consisted of a first order absorption and a whole-body PBPK model. The absorption rate constant (ka) and lag time (T_{lag}) were estimated to be 0.6 1/h and 0.5 hr, respectively, based on the observed tucatinib PK in healthy subjects in Study ARRAY-380-103. The $f_{u,gut}$ (unbound fraction in enterocytes) was set to be 1.0. The $P_{eff,man}$ (permeability in man) was predicted to be $2.19X10^{-4}$ cm/s based on the permeability data in Caco-2 cells.

The whole-body full PBPK model was used to simulate tucatinib distribution. The volume of distribution (V_{ss}, 2.08 L/kg) was predicted using Method 1 in Simcyp and subsequently optimized based on the observed tucatinib PK in healthy subjects in Study ARRAY-380-103 using a global Kp scalar of 0.4.

Tucatinib oral clearance (124 L/h) after a single dose of 300 mg tablets under fasted condition in Study ARRAY-380-103 was used for the retrograde calculation of unbound hepatic intrinsic clearance by CYP2C8 and CYP3A4. The percentages of tucatinib metabolized by CYP3A4 and CYP2C8 were assigned as 10% and 75% according to the clinical DDI study results with itraconazole and gemfibrozil, respectively. The rest of the metabolism was assigned as the additional human liver microsome clearance (15%). Renal elimination was not considered in the model because the majority of tucatinib clearance was attributed to metabolic elimination, with minimal drug excreted unchanged in urine.

The in vitro Ki values of CYP2C8 (0.17 µM) and CYP2C9 (4.57 µM) were used in the tucatinib model to simulate the observed repaglinide (a CYP2C8 substrate) and tolbutamide (a CYP2C9 substrate) DDI.

Based on in vivo clinical DDI study results, a 20-, 20-, and 15-fold reduction in the in vitro Ki values for MATE, OCT2 and P-gp, respectively, were incorporated in the model to simulate the observed DDI with metformin (a MATE and OCT2 substrate) and digoxin (a P-gp substrate).

The in vitro reversible inhibition constant (Ki=0.805 µM), in vitro inactivation rate constant (kinact=0.66) and a 3-fold reduction in the in vitro inactivation constant (KI=0.18 µM) for CYP3A4 were incorporated in the model to simulate the observed DDI with midazolam.

The in vitro Ki of UGT1A1 or OATP1B1 and OATP1B3 were applied in the model to predict the DDI of tucatinib as perpetrator when co-administered with a single dose raltegravir or rosuvastatin. A sensitivity analysis of UGT1A1 or OATP1B1 and OATP1B3 Ki values were conducted to assess the effect on raltegravir or rosuvastatin exposure.

Metabolite ONT-993

The whole-body full PBPK model was used to simulate ONT-993 distribution with a predicted V_{ss} of 0.513 L/kg. The B/P value of 0.60 was predicted using Simcyp predictor. The total clearance was estimated based on the clinical PK data in the fasted tablet cohort in Study ARRAY-380-103. 100% of CYP2C8 responsible for the metabolism of tucatinib was assigned in the model for the formation of ONT-993. The in vitro irreversible inactivation parameter values of CYP3A4 (KI=0.17 µM and kinac=0.9/h) and in vitro Ki value of MATE1/2-K (0.22 µM) were used in the ONT-993 model to simulate the observed DDI with midazolam (a CYP3A4 substrate) and metformin (a MATE and OCT2 substrate).

Victim and perpetrator drug models

The default PBPK models of itraconazole, gemfibrozil, rifampicin, carbamazepine, phenytoin, midazolam, repaglinide, tolbutamide, digoxin, rosuvastatin and raltegravir in SimCYP were used without any modification for DDI prediction.

The regulatory authorities' assessment

1. The adequacy of tucatinib PBPK model to predict the effect of tucatinib on repaglinide (a CYP2C8 substrate), tolbutamide (a CYP2C9 substrate), and digoxin (a P-gp substrate) or the effect of tucatinib and ONT-993 on metformin (a MATE1/2-K and OCT2 substrate) was not reviewed by the FDA, since the Applicant has already submitted clinical DDI study reports, which provided adequate information for the DDI liability evaluation between tucatinib as perpetrator with repaglinide, tolbutamide, digoxin and metformin.
2. Tucatinib has a high permeability. The formulation of tucatinib is an amorphous solid dispersion formulation. It was indicated that at least 70-fold higher concentration achieved with this amorphous solid dispersion formation compared to the free drug species (Pharmaceutical development). In addition, the total radioactivity recovered in the urine as unchanged drug or metabolites plus in the feces as oxidative metabolites was ~70% (ONT-380-008 CSR). Therefore, the fraction of dose absorbed in intestine is expected to be moderate to high. Based on this information, P-gp and BCRP in the intestine are expected to be saturated under clinical condition. Inhibition or induction of P-gp or BCRP would not expected to result in clinically significant DDI.
3. The Applicant's estimated fmCYP3A4 and fmCYP2C8 for tucatinib were 0.10 and 0.75, respectively, which were based on the DDI study results with itraconazole, gemfibrozil, and rifampin. An information request was issued requesting the Applicant to re-estimate the fmCYP3A4 and fmCYP2C8 due to the following reasons.
    - The estimated fmCYP3A4 and fmCYP2C8 based on the clinical DDI study results were not consistent with those estimated based on the in vitro phenotyping study results. The in vitro phenotyping study with recombinant CYP enzymes indicated that CYP3A4 was the major enzyme for the hepatic metabolism of tucatinib. The Applicant estimated the fraction metabolized by CYP3A4 and CYP2C8 to be 73% and 27%, respectively, based on the tucatinib depletion rate in the presence of recombinant CYP3A4 or CYP2C8.

- Applicant estimated fmCYP3A4 and fmCYP2C8 for tucatinib based on the clinical DDI study results with itraconazole, gemfibrozil and rifampin. Rifampicin is a strong CYP3A4 inducer and a moderate CYP2C8 inducer. The rifampicin model used in Applicant's simulation only incorporated rifampicin mediated CYP3A4 induction effect but not the CYP2C8 induction effect.

4. The effect of a moderate CYP2C8 inhibitor on tucatinib exposure has not been evaluated in the clinical trial and using PBPK modeling and simulation approach. Since a strong CYP2C8 inhibitor, gemfibrozil, increased tucatinib AUC by 3 fold, an information request was issued requesting the Applicant to evaluate the DDI liability of tucatinib with a moderate CYP2C8 inhibitor.
5. The clinical DDI study with midazolam indicated that tucatinib is a relatively strong CYP3A4 inhibitor. In vitro study showed that tucatinib possessed both reversible and time dependent inhibitory effects on CYP3A4. The DDI study with itraconazole was conducted following multiple-dose of itraconazole and a single dose of tucatinib. An information request was issued requesting the Applicant to simulate the DDI liability of tucatinib as a victim with CYP3A modulators following multiple dose of tucatinib and CYP3A modulators.
6. Although rifampicin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) was used in the Applicant's simulations for DDI assessment, the DDI liability between tucatinib and a strong CYP3A inducer but not a CYP2C8 inducer was not evaluated. An information request was issued requesting the Applicant to simulate the DDI liability of tucatinib as a victim with a strong CYP3A inducer but not a CYP2C8 inducer following multiple dose of tucatinib and the CYP3A inducer.

In the response to the FDA's IR, the Applicant re-estimated the fmCYP3A4 and fmCYP2C8 for tucatinib based on the clinical DDI study results with itraconazole and gemfibrozil only. DDI study results with rifampin were excluded for tucatinib fm estimation due to the impact of rifampin on both CYP2C8 and CYP3A4 and the rifampin mediated CYP2C8 induction effect was not verified yet. The Applicant re-estimated fmCYP3A4 and fmCYP2C8 were 15% and 70%, respectively. Table 50 showed the Applicant's model verification results and the simulated DDI results using the re-estimated fmCYP3A4 and fmCYP2C8 values. Since the re-estimated fmCYP3A4 (15%) and fmCYP2C8 (70%) are still not consistent with those (CYP3A4: 73% and CYP2C8: 27%) estimated based on the in vitro phenotyping study results, and the predicted DDI with itraconazole and gemfibrozil were slightly underestimated and overestimated, respectively, as compared to the clinical observed DDI, the FDA reviewer reevaluated the in vitro phenotyping study results and further refined the tucatinib model to better capture the tucatinib and ONT-993 PK profiles and the observed DDI with itraconazole and gemfibrozil. Refer to "FDA's Model refinement and verification" for the details.

Table 50: Observed and simulated tucatinib geometric mean PK parameters following a single dose (300 mg) or multiple dose (300 mg, bid) administration of tucatinib in healthy subjects.

Observed and simulated tucatinib or midazolam geometric mean Cmax and AUC ratios in the presence and absence of a CYP modulator in healthy subjects.

			Without CYP modulator/substrate						With CYP modulator/substrate				Sources
			Cmax (ng/mL)			AUC (ng*h/mL)			Cmax ratio		AUC ratio		
			Obs.	Pred.	$R_{Pred/Obs}$	Obs.	Pred.	$R_{Pred/Obs}$	Obs.	Pred.	Obs.	Pred.	
Applicant's refined model	300 mg, SD, w/ or w/o itraconazole	Tucatinib	488	378	0.77	3350	2814	0.84	1.32	1.24	1.34	1.26	ONT-380-012, Part A
		ONT-993	62	47	0.76	512	323	0.63					
	300 mg, SD, w/ or w/o gemfibrozil	Tucatinib	410	375	0.92	2480	2765	1.12	1.62	1.81	3.04	3.42	ONT-380-012, Part C
		ONT-993	49	51	1.04	415	348	0.84					
	300 mg, bid, w/ or w/o midazolam	Tucatinib	554	550	0.99	3120[a]	3376	1.08	3.01	2.51	5.74	5.71	ONT-380-012, Part E
		ONT-993	87	74	0.85	522[a]	443	0.85					
FDA's model	300 mg, SD, w/ or w/o itraconazole	Tucatinib	488	386	0.80	3350	2833	0.85	1.32	1.27	1.34	1.36	ONT-380-012, Part A
		ONT-993	62	56	0.90	512	386	0.75					
	300 mg, SD, w/ or w/o gemfibrozil	Tucatinib	410	385	0.94	2480	2835	1.14	1.62	1.63	3.04	3.00	ONT-380-012, Part C
		ONT-993	49	48	0.98	415	328	0.80					
	300 mg, bid, w/ or w/o midazolam	Tucatinib	554	592	1.07	3120[a]	374[a]	1.20	3.01	2.43	5.74	5.70	ONT-380-012, Part E
		ONT-993	87	68	0.78	522[a]	534[a]	1.02					

a: geometric mean AUC0-12h
Source: from FDA's reviewer's simulations using Applicant's refined final model and FDA's model

In the response to the FDA's IR, the Applicant assessed the effect of a moderate CYP2C8 inhibitor on the PK of tucatinib. A hypothetic sensitive CYP2C8 substrate was developed based on the rosiglitazone (a moderately sensitive CYP2C8 substrate) model by increasing the fmCYP2C8 from approximately 50% to 90% for rosiglitazone. The Applicant modified the lower end and higher end of the Ki values in the gemfibrozil and its metabolite, gemfibrozil 1-O-β glucuronide models to mimic moderate CYP2C8 inhibition effect to achieve >2 to <5-fold increase in the AUC of a sensitive CYP2C8 substrate. The Applicant's approach can be used for risk assessment purpose to provide a range of potential DDI magnitude. However, this approach cannot be used to inform tucatinib dose adjustment because the predicted high end of AUCR of tucatinib with a moderate CYP2C8 inhibitor was 3, which was similar to the observed AUCR with a strong CYP2C8 inhibitor using this approach and there were

uncertainties associated with the predicted lower end of AUCR with a moderate CYP2C8 inhibitor.

FDA's Model refinement and verification

Reanalysis of fmCYP3A4 and fmCYP2C8 based on phenotyping study results

In the PBPK report "R-SEAT-1B_PK_APPX_D", the Applicant provided the following calculation for tucatinib fraction metabolized by CYP2C8 and CYP3A4.

Table 3.17-1. Calculated in vitro *intrinsic clearance and fraction metabolized by CYP3A4 and CYP2C8*

CYP	k (min^{-1})	V (ml)	enzyme (pmol)	CL_{int} (µl/min/pmol)	*In* vivo Abundance (pmol/mg)	ISEF	Scaled CL_{int} (µl/min/mg)	fm (%)
2C8	0.0449	1.60	80.00	0.90	24	0.43	9.27	26.90
3A4	0.0383	0.20	10.00	0.77	137	0.24	25.19	73.10

Source: PBPK report R-SEAT-1B_PK_APPX_D

The intersystem extrapolation factor (ISEF) value for CYP2C8 used in the Applicant's calculation was 0.43 which was obtain from Chen et al, 2011[1]. However, Chen et al 2011 reported that the ISEF value for CYP2C8 was 1.41. FDA reviewer recalculated the tucatinib fraction metabolized by CYP2C8 and CYP3A4 based on an ISEF value of 1.41 for CYP2C8. The recalculated fmCYP3A4 was 0.45 and fmCYP2C8 was 0.55.

Re-estimation of fmCYP3A4 and fmCYP2C8 based on DDI study results

The fmCYP3A4 and fmCYP2C8 were re-estimated based on the clinical DDI study results with itraconazole and gemfibrozil and tucatinib and ONT-993 plasma concentration-time profiles in the DDI studies. Table 51**:** showed the fu,gut, fmCYP3A4 and fmCYP2C8 values used in the Applicant's refined model and FDA's model. The re-estimated fmCYP2C8 is close to that from phenotyping study results. In vitro study indicated that multiple CYP enzymes along with CYP3A4 were involved in the formation of other metabolites except for ONT-993, hence it is reasonable to have a lower fmCYP3A4 as compared to the fmCYP3A4 re-estimated based on the phenotyping study results.

Model verification results were shown in Table 54 and Figure 26. After model verification with the clinical PK and DDI data, FDA's model was applied to assess the DDI liability of tucatinib as victim or perpetrator with enzyme modulators or enzyme and transporter substrates.

[1] Chen Y, Liu L, Nguyen K, Fretland AJ. Utility of intersystem extrapolation factors in early reaction phenotyping and the quantitative extrapolation of human liver microsomal intrinsic clearance using recombinant cytochromes P450. Drug Metab Dispos. 2011;39(3):373-82.

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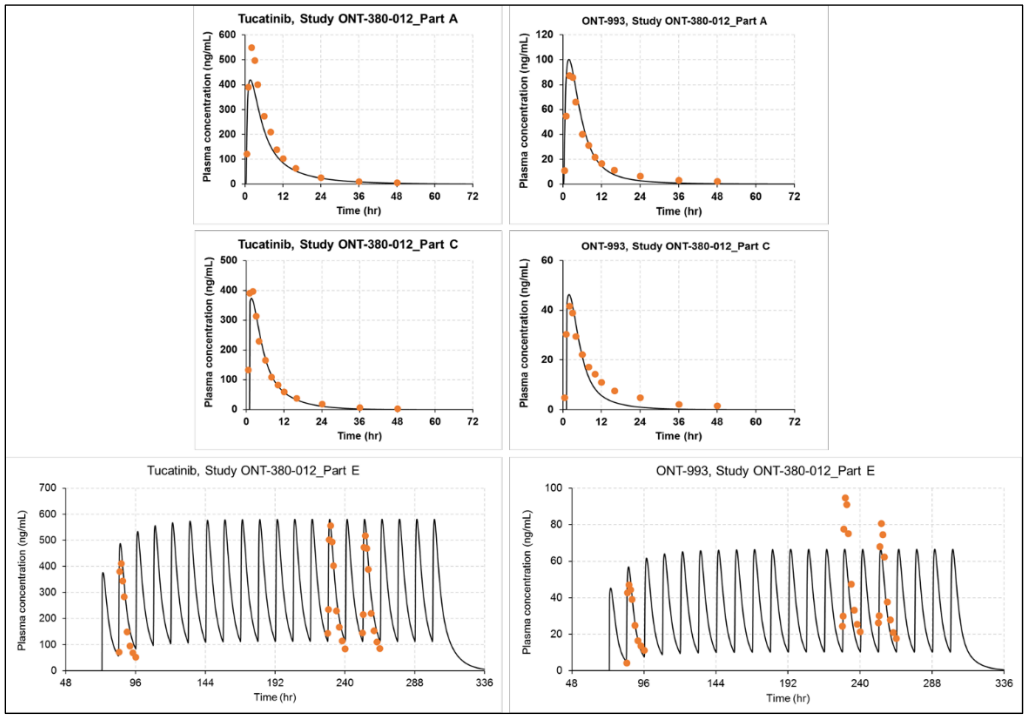
Table 51: fu,gut, fmCYP3A4 and fmCYP2C8 values implemented in the Applicant's refined model and FDA's model

	fu,gut	fmCYP3A4	fmCYP2C8
Applicant's refined model	1.0	0.15	0.70
FDA's model	0.118	0.27	0.61
Phenotyping study[a]		0.45	0.55

a: refer to "Reanalysis of fmCYP3A4 and fmCYP2C8 based on phenotyping study results"

Figure 26: Observed (dots) and simulated (lines, FDA refined model) tucatinib and metabolite ONT-993 plasma concentration-time profiles (geometric mean) following a single dose (300 mg) or multiple dose (300 mg, bid) administration of tucatinib in healthy subjects.



PBPK model application

The developed PBPK model was used to simulate the DDI for tucatinib and ONT-993 in the following scenarios.

- To predict the effect of itraconazole (a strong CYP3A inhibitor) or gemfibrozil (a strong CYP2C8 inhibitor) on the PK of tucatinib following multiple dose administration of tucatinib and multiple dose administration of itraconazole or gemfibrozil in healthy subjects.
- To predict the effect of carbamazepine (a strong CYP3A inducer) or phenytoin (a strong CYP3A inducer) on tucatinib PK following multiple dose administration of tucatinib and

multiple dose administration of carbamazepine or phenytoin in healthy subjects. Carbamazepine and phenytoin were selected by the FDA reviewer to evaluate the effect of a strong CYP3A4 inducer but not a CYP2C8 inducer on tucatinib PK at steady-state.

- To predict the effect of tucatinib on the PK of raltegravir (a UGT1A1 substrate) and rosuvastatin (an OATP1B1/3 substrate) in healthy subjects.

Results

1. **Can FDA refined tucatinib PBPK model describe tucatinib and metabolite ONT-993 PK in healthy subjects?**

   Yes. The FDA refined tucatinib and ONT-993 models were able to capture the observed tucatinib and metabolite ONT-993 PK profiles following a single dose administration (300 mg) or multiple dose administration (300 mg, bid) in healthy subjects. (Figure 26 andTable 54).

2. **Can FDA refined tucatinib PBPK model predict the effect of tucatinib on the PK of midazolam (a sensitive CYP3A4 substrate)?**

   Yes. The FDA refined tucatinib model was able to simulate the observed effect of tucatinib on the PK of midazolam in healthy subjects. The tucatinib mediated TDI of CYP3A4 was appropriately quantified based on the clinical observed DDI study results between tucatinib and midazolam (Table 54).

3. **Can FDA refined tucatinib PBPK model predict the effect of itraconazole (a strong CYP3A inhibitor) and gemfibrozil (a strong CYP2C8 inhibitor) on the PK of tucatinib following multiple dose administration of tucatinib and itraconazole or gemfibrozil in healthy subjects?**

   Yes. The FDA refined tucatinib model was able to simulate the observed effect of itraconazole or gemfibrozil on tucatinib PK following a single dose administration of tucatinib and multiple dose administration of itraconazole or gemfibrozil in healthy subjects (Table 54). As compared to the effect of itraconazole or gemfibrozil on the single dose tucatinib PK, the effect of itraconazole on multiple dose tucatinib exposure was decreased (AUCR: 1.34 vs 1.09), whereas the magnitude of DDI between multiple dose of tucatinib and multiple dose of gemfirbrozil was increased (AUCR: 3.04 vs 4.35). (Table 54 and **Table 52**)

4. **Can FDA refined tucatinib PBPK model predict the effect of carbamazepine (a strong CYP3A inducer) and phenytoin (a strong CYP3A4 inducer) on the PK of tucatinib following multiple dose administration of tucatinib and CYP3A inducers in healthy subjects?**

   Yes. The refined tucatinib model was able to predict the effect of carbamazepine or phenytoin on tucatinib PK following multiple dose administration of tucatinib and multiple dose administration of carbamazepine or phenytoin in healthy subjects. The model predicted tucatinib AUCR is 0.70 or 0.84 when coadministered with carbamazepine or phenytoin at steady-state in healthy subjects (**Table 52**).

Table 52. Model predicted tucatinib (300mg bid) Cmax and AUC ratios in the presence and absence of a CYP3A modulator at steady-state in healthy subjects

CYP3A modulators	CmaxR	AUCR
Itraconazole (a strong CYP3A inhibitor), 200 mg, QD	1.07	1.09
Gemfibrozil (a strong CYP2C8 inhibitor), 600 mg, BID	2.97	4.35
Carbamazepine (a strong CYP3A4 inducer), 400 mg, BID	0.72	0.70
Phenytoin (a strong CYP 3A4 inducer), 300 mg, QD	0.86	0.84

5. Can FDA refined tucatinib PBPK model predict the effect of tucatinib on the PK of raltegravir (a UGT1A1 substrate) in healthy subjects?

Yes. In vitro studies indicated that tucatinib is a UGT1A1 inhibitor with an in vitro determined Ki value of 1.81 □M. The model predicted raltegravir exposure was not significantly affected by concomitant tucatinib using the in vitro determined UGT1A1 Ki value (AUCR=1.04). The reviewer further conducted a sensitivity analysis of tucatinib UGT1A1 Ki to assess the effect on the predicted raltegravir exposure. The simulated raltegravir AUC ratios were 1.27 and 1.45 with 10- and 20-fold lower UGT1A1 Ki values, respectively than the in vitro determined. In vivo effect of tucatinib on a UGT1A1 substrate is expected to be weak unless there are potential safety concerns with the UGT1A1 substrate.

6. Can FDA refined tucatinib PBPK model predict the effect of tucatinib on the PK of rosuvastatin (an OATP1B1/3 substrate) in healthy subjects?

Yes. In vitro studies indicated that tucatinib is an OATP1B1/3 inhibitor with an in vitro determined OATP1B1 Ki value of 5 □M and OATP1B3 Ki value of 4 □M. The model predicted rosuvastatin exposure was not significantly affected by concomitant tucatinib using the in vitro determined OATP1B1/3 Ki values (AUCR = 1.0) or 10-fold lower OATP1B1/3 Ki values (AUCR=1.03) than the in vitro determined. The reviewer noticed the version difference between Simcyp V17 and Simcyp V19 with respect to the rosuvastatin PBPK model. Simcyp V19 was also used to evaluate the effect of tucatinib on rosuvastatin exposure and no difference was found in the predicted rosuvastatin AUC ratios in the presence and absence of tucatinib using Simcyp V17 or V19. Therefore, the rosuvastatin exposure would not be expected to be significantly affected by concomitant tucatinib.

Bioanalytical Method Summary

Validated bioanalytical assays using liquid chromatography with tandem mass spectrometry (LC-MS/MS) were used throughout the tucatinib clinical program to quantify tucatinib, ONT-993, co-administered drugs and metabolites(**Table 53**)

Table 53: Summary of validated analytical methods

Analyte[a]	Validation Laboratory	Method Number	Validation Report Number/ Summary Table in Appendices	Bioanalytical Report	Clinical Study Number
Tucatinib ONT-993	(b) (4)	(b) (4) 916[b]	1916[d] 1916 Amendment 2 1916 Amendment 3 Table 5-2, Table 5-3	1827 CP10-001 BA-12-001	ARRAY-380-101 ARRAY-380-102 ARRAY-380-103
Tucatinib ONT-993		ONT3HPP[b] (Plasma)	8373099[d] Table 5-4, Table 5-5	8373100 8373071 8373072 8373070	ONT-380-008 ONT-380-009 ONT-380-011 ONT-380-012
Tucatinib ONT-993		ONT3HUP (Urine)	8385605[d] Table 5-6, Table 5-7	8373100	ONT-380-008
Tucatinib ONT-993		TM17-396[b]	AV14-ONT380-01 Addendum 1[d] AV14-ONT380-01 Addendum 3[d,e] Table 5-8, Table 5-9, Table 5-10	AD16-950, AD19-849	ONT-380-206 SGNTUC-020
Tucatinib ONT-993		TM17-433[b]	AV17-ONT380-01[d] AV17-ONT380-01 Addendum 1[d,e] Table 5-11, Table 5-12	AD19-931	SGNTUC-015
Tucatinib ONT-993 Capecitabine 5'-DFCR 5'-DFUR		TM14-281[b]	AV14-ONT380-01[d], AV14-ONT380-01 Addendum 2[d,e] Table 5-8, Table 5-9, Table 5-10	AD14-747 AD14-734 Amendment 1 AD16-950	ONT-380-004 ONT-380-005 ONT-380-206 (Batches 1-3)
5-FU FBAL		TM14-286	AV14-5FU-01[d], AV14-5FU-01 Addendum 2[d,e] Table 5-13, Table 5-14	AD14-734, AD14-734 Amendment 1	ONT-380-005
Moxifloxin		MXNHPC[c]	2100-788, 8225508 Table 5-16, Table 5-17	8373072	ONT-380-011
(b) (4)		TM14-277	(b) (4) (b) (4) Addendum 1[d,e] Table 5-18, Table 5-19	(b) (4)	ONT-380-004
Metformin		TM18-500 (Plasma)	AV18-Metformin-01 Addendum 1[e,f] Table 5-20, Table 5-21	AD19-849	SGNTUC-020
Metformin		TM18-503 (Urine)	AV18-Metformin-02 Addendum 1[e] Table 5-20, Table 5-22	AD19-849	SGNTUC-020
Gemfibrozil		GEMFHPC[c]	8395822 Table 5-25, Table 5-28	8373070	ONT-380-012
Iohexol		(b) (4) L-043	(b) (4) 186747-B Table 5-23, Table 5-24	SGB637UF-186372-A	SGNTUC-020
Rifampin		RIFHPC[c]	8251-203 Table 5-25, Table 5-26	8373070	ONT-380-012
Digoxin		DGNHPC[c]	8274044 Table 5-25, Table 5-27	8373070	ONT-380-012
Repaglinide		REPGHPP	8395746[d] Table 5-25, Table 5-30	8373070	ONT-380-012
Itraconazole Hydroxy-Itraconazole		ITRHPC[c]	8294126 Table 5-25, Table 5-29	8373070	ONT-380-012
Midazolam 1'-hydroxymidazolam 4-hydroxymidazolam		MHHHPC[c]	8280288 Table 5-25, Table 5-31	8373070	ONT-380-012
Tolbutamide Hydroxy tolbutamide 4-Carboxy tolbutamide		TLBUHPC[c]	8352-993 Table 5-25, Table 5-32	8373070	ONT-380-012

Source: 2.7.1 summary of biopharmaceutic studies and associated analytical methods, Table 1-4.

For QC samples, acceptance criteria were set as average precision ≤15.0% and %bias ± 15.0% of nominal. All methods in the cross validation passed the QC predefined acceptance criteria. The results of the cross validation demonstrated that the 5 different assays produced sample concentration results similar to one another, and comparison of the methods yield consistent measurement of tucatinib and ONT-993.

Table 54: Absolute difference of QC mean bias % between TM17-396 and cross validation methods

	Tucatinib			ONT-993		
Method	3.00 ng/mL	50.0 ng/mL	800 ng/mL	3.00 ng/mL	50.0 ng/mL	800 ng/mL
TM14-281	4.4	1.0	7.2	3.0	4.6	4.2
TM17-433	0.4	1.6	9.6	5.3	12.0	2.6
1916	0.3	9.0	4.0	10.6	15.2	0.5
ONT3HPP	3.6	5.0	12.5	11.7	9.4	10.4

Source: 2.7.1 summary of biopharmaceutic studies and associated analytical methods, Table 1-4.

Validation summary tables for bioanalytical methods supporting HER2CLIMB is in (Table 55).

Table 55: Summary Method Performance

Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	AV14-ONT380-01 Table 3-1 Table 3-2 Table 3-3 Table 3-4 Table 3-5
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Tucatinib: -1.9% to 3.6% ONT-993 -1.5% to 1.0% Capecitabine: -3.8% to 2.8% 5'-DFCR: -1.0% to 1.0% 5'-DFUR: -2.0% to 2.0%	AV14-ONT380-01 Table 3-1 Table 3-2 Table 3-3 Table 3-4 Table 3-5
	Cumulative precision (%CV) from LLOQ to ULOQ	Tucatinib: ≤5.8% ONT-993: ≤6.8% Capecitabine: ≤6.1% 5'-DFCR: ≤6.1% 5'-DFUR: ≤7.7%	AV14-ONT380-01 Table 3-1 Table 3-2 Table 3-3 Table 3-4 Table 3-5
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs	Tucatinib: -4.4% to 7.0% ONT-993: -5.2% to 5.7% Capecitabine: -3.3% to 3.4% 5'-DFCR: -2.8% to 3.8% 5'-DFUR: -2.0% to 8.0%	AV14-ONT380-01 Table 3-6 Table 3-7 Table 3-8 Table 3-9 Table 3-10
	Inter-batch %CV QCs	Tucatinib: ≤8.7% ONT-993: ≤11.6% Capecitabine: ≤8.2% 5'-DFCR: ≤9.1% 5'-DFUR: ≤12.7%	AV14-ONT380-01 Table 3-6 Table 3-7 Table 3-8 Table 3-9 Table 3-10
	Total Error (TE)	Tucatinib: 15.7% ONT-993: 17.3% Capecitabine: 11.6% 5'-DFCR: 12.9% 5'-DFUR: 20.7%	Sum of largest bias and CV reported for analytes.
Selectivity & matrix effect	Blank interference 6 lots were tested, no significant interfering peaks were found that eluted at the retention times of all analytes. Matrix factor 6 lots of unpooled matrix tested The precision of the IS normalized matrix factor was acceptable for all analytes IS-Normalized Matrix Factor %CV Tucatinib: 3.2% ONT-993: 13.0% Capecitabine: 3.2% 5'-DFCR: 2.2% 5'-DFUR: 9.3%		AV14-ONT380-01 Table 3-46 Table 3-47 Table 3-48 Table 3-49 Table 3-50 Table 3-31 Table 3-32 Table 3-33 Table 3-34 Table 3-35

Interference & specificity	Multi-analyte selectivity Individual QCs of tucatinib, ONT-993, capecitabine, 5'-DFCR, and 5'-DFUR were quantified against the calibration curve containing all 5. All passed the QC criteria. Coadmin selectivity Tucatinib, ONT-993, capecitabine, 5'-DFCR and 5'-DFUR will not be affected by the presence of DM1 (50 ng/mL), which is released by the coadiminstered ADC, TDM-1. Metabolite selectivity All analytes passed and will not be affected by 5-fluorouracil (250 ng/mL) and α-fluoro-β-alanine (10000 ng/mL).	AV14-ONT380-01 Table 3-51 Table 3-52 Table 3-53 Table 3-54 Table 3-55 Table 3-61 Table 3-62 Table 3-63 Table 3-64 Table 3-65 Table 3-56 Table 3-57 Table 3-58 Table 3-59 Table 3-60
Hemolysis effect	Analysis of tucatinib, ONT-993, capecitabine, 5'-DFCR, and 5'-DFUR has been validated in up to 1% hemolyzed human K_2EDTA plasma. One lot was tested. All analytes passed in 10% hemolyzed human K_2EDTA plasma, except ONT-993 which did not meet acceptance criteria. Tucatinib: %Bias <11.7%; %CV <6.6% Capecitabine: %Bias <9.5%; %CV <6.4% 5'-DFCR: %Bias <8.0%; %CV <2.5% 5'-DFUR: %Bias <10.0%; %CV <9.3% 1% hemolyzed human K_2EDTA plasma ONT-993: %Bias <12.0%; %CV <10.1%	AV14-ONT380-01 Table 3-16 Table 3-17 Table 3-18 Table 3-19 Table 3-20
Lipemic effect	All samples passed. One lot was tested. Tucatinib: %Bias within 5.2%; %CV within 7.8% ONT-993: %Bias within 14.4%; %CV within 7.3% Capecitabine: %Bias within 8.0%; %CV was within 6.0% 5'-DFCR: %Bias was within 6.0%; %CV within 4.5% 5'-DFUR: %Bias was within 4.7%; %CV within 5.6%	AV14-ONT380-01 Table 3-21 Table 3-22 Table 3-23 Table 3-24 Table 3-25
Dilution linearity & hook effect	NA	NA
Bench-top/process stability	Bench-top plasma stability demonstrated for 6 hours at ambient conditions. Tucatinib: %Bias within 11.5%; %CV within 5.9% ONT-993: %Bias within 7.0%; %CV within 5.5% Capecitabine: %Bias within 6.4%; %CV was within 9.5% 5'-DFCR: %Bias was within 7.6%; %CV was within 5.4% 5'-DFUR: %Bias was within 9.3%; %CV was within 9.3% Bench-top plasma stability demonstrated for 6 hours on ice Tucatinib: %Bias within 12.5%; %CV within 4.9% ONT-993: %Bias within 10.7%; %CV within 4.4% Capecitabine: %Bias within 12.4%; %CV was within 6.6% 5'-DFCR: %Bias was within 7.6%; %CV was within 12.2% 5'-DFUR: %Bias was within 10.7%; %CV was within 5.6%	AV14-ONT380-01 Table 3-71 Table 3-72 Table 3-73 Table 3-74 Table 3-75 AV14-ONT380-01 Addendum 2 Table 4-21 Table 4-22 Table 4-23 Table 4-24 Table 4-25
Freeze-Thaw stability	3 freeze-thaw cycles across analytes tucatinib, ONT-993, capecitabine, 5'-DFCR and 5'-DFUR. Tucatinib: %Bias within 10.5%, %CV within 8.7% ONT-993: %Bias within 15.0%; %CV within 9.8% Capecitabine: %Bias within 5.3%; %CV within 10.8% 5'-DFCR: %Bias within 6.4%; %CV within 7.3% 5'-DFUR: %Bias within 11.3%; %CV within 10.1%	AV14-ONT380-01 Table 3-76 Table 3-77 Table 3-78 Table 3-79 Table 3-80

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Long-term storage	Tucatinib, capecitabine, 5'-DFCR and 5'-DFUR samples stored at -70°C are stable for up to 1119 days and for 95 days at -20°C. For ONT-993, QCs are stable for up to 602 days at -70ºC and DQCs are stable up to 1119 days at -70 ºC. Stability at -20ºC for ONT-993 has been established within AV14-ONT-380-01 Addendum 1 (Table 5-10). Long-term storage testing is ongoing. -70°C Tucatinib: %Bias within 3.5%; %CV was within 3.9% ONT-993: %Bias within 9.0%; %CV within 5.4% (DQC only) Capecitabine: %Bias within 5.5%; %CV within 4.5% 5'-DFCR: %Bias within 12.7%; %CV within 3.0% 5'-DFUR: %Bias within 4.7%; %CV within 11.2% -20°C Tucatinib: %Bias within 5.0%; %CV was within 5.1% Capecitabine: %Bias within 9.3%; %CV within 10.0% 5'-DFCR: %Bias within 14.7%; %CV within 5.6% 5'-DFUR: %Bias within 5.3%; %CV within 7.8%	AV14-ONT380-01 Addendum 2 Table 4-26 Table 4-27 Table 4-28 Table 4-29 Table 4-30 Table 4-31 Table 4-32 Table 4-33 Table 4-34 Table 4-35
Parallelism	NA	NA
Carry over	Analyte carryover met acceptance criteria for all batches for capecitabine, 5'-DFCR and 5'-DFUR. Analyte carryover failed for 10 out of 15 analytical batches for tucatinib. Analyte carryover failed for 15 out of 20 analytical batches for ONT-993. These results indicate that bioanalytical sample batches should be monitored for carryover.	AV14-ONT380-01 Table 3-66 Table 3-67 Table 3-68 Table 3-69 Table 3-70

FDA considered the bioanalytical method used in current submission is acceptable to support clinical pharmacology program of tucatinib.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
NA

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Wei Chen	OOD/DHOT	Sections:5/Nonclinical Pharmacology /Toxicology	Select one: x Authored ___ Approved
	Signature: Wei Chen -S Digitally signed by Wei Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wei Chen -S, 0.9.2342.19200300.100.1.1=1300221221 Date: 2020.04.16 09:46:37 -04'00'			
Nonclinical Team Leader	Tiffany Ricks	OOD/DHOT	Sections: 5/Nonclinical Pharmacology /Toxicology	Select one: x Authored x Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2020.04.16 10:13:50 -04'00'			
Nonclinical Team Division Director	John Leighton	OOD/DHOT	Sections: 5/Nonclinical Pharmacology /Toxicology	Select one: ___ Authored x Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2020.04.16 10:20:47 -04'00'			
Clinical Pharmacology Reviewer	Huiming Xia	OCP/DCP1	Sections: 6/Clinical Pharmacology	Select one: x Authored ___ Approved
	Signature: Huiming Xia -S Digitally signed by Huiming Xia -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Huiming Xia -S, 0.9.2342.19200300.100.1.1=2001860291 Date: 2020.04.16 10:18:20 -04'00'			
Pharmacometrics Reviewer	Fang Li	OCP/DPM	Sections: 19.4/Population PK	Select one: x Authored ___ Approved
	Signature: Fang Li -S Digitally signed by Fang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fang Li -S, 0.9.2342.19200300.100.1.1=1300430137 Date: 2020.04.16 12:29:12 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORE/ APPROVED
Pharmacometrics Team Leader	Jingyu (Jerry) Yu	OCP/DPM	Sections: 19.4/Population PK	Select one: ___ Authored x Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2020.04.16 09:35:31 -04'00'			
PBPK Reviewer	Jianghong Fan	OCP/DPM	Sections: 19.4/PBPK	Select one: X Authored ___ Approved
	Signature: Jianghong Fan -S Digitally signed by Jianghong Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianghong Fan -S, 0.9.2342.19200300.100.1.1=2001454698 Date: 2020.04.16 14:03:53 -04'00'			
PBPK Team Leader	Xinyuan (Susie) Zhang	OCP/DPM	Sections: 19.4/PBPK	Select one: ___ Authored X Approved
	Signature: Xinyuan Zhang -S Digitally signed by Xinyuan Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xinyuan Zhang -S, 0.9.2342.19200300.100.1.1=2000431943 Date: 2020.04.16 11:32:21 -04'00'			
Clinical Pharmacology Team Leader	Pengfei Song	OCP/DCP1	Sections: 6/Clinical Pharmacology	Select one: X Authored X Approved
	Signature: Pengfei Song -S Digitally signed by Pengfei Song -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pengfei Song -S, 0.9.2342.19200300.100.1.1=2000464900 Date: 2020.04.16 11:17:45 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OCP/DCP1	Sections: 6	Select one: ___ Authored x Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.04.16 13:37:13 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Joyce Cheng	OB/DBV	Sections: 8/Statistical and Clinical Evaluation including 8.1 and 8.3	Select one: x Authored ___ Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2020.04.16 10:48:34 -04'00'			
Statistical Team Leader	Mallorie Fiero	OB/DBV	Sections: 8/Statistical and Clinical Evaluation including 8.1 and 8.3	Select one: X Authored X Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S Date: 2020.04.16 10:26:59 -04'00'			
Clinical Reviewer	Mirat Shah	OOD/DO1	Sections: 1/Executive Summary, 2/Therapeutic Context, 3/Regulatory Background, 4/Significant Issues from Other Review Disciplines, 7/Sources of Clinical Data, 8/Statistical and Clinical Evaluation including 8.1, 8.2, and 8.4, 9/Advisory Committee Meeting, 10/Pediatrics, 11/Labeling Recommendations, 12/Risk Evaluation and Mitigation, 13/Post-Marketing Requirements, 19/Appendices including 19.1 and 19.2	Select one: x Authored ___ Approved
	Signature: Mirat Shah -S Digitally signed by Mirat Shah -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mirat Shah -S, 0.9.2342.19200300.100.1.1=2002232060 Date: 2020.04.16 11:44:33 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORE/ APPROVED
Division Director (OB)	Shenghui Tang	OB/DBV	Sections: 8	Select one: x Authored x Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2020.04.16 13:31:55 -04'00'			
Associate Director for Labeling (ADL)	William Pierce	OND/OOD	Sections: Prescribing Information; Labeling Recommendations	Select one: X Authored X Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2020.04.16 11:07:45 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Suparna Wedam	OOD/DO1	Sections: All	Select one: X Authored X Approved
	Signature: Suparna B. Wedam -S Digitally signed by Suparna B. Wedam -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011069340, cn=Suparna B. Wedam -S Date: 2020.04.16 09:39:25 -04'00'			
Deputy Division Director (Clinical)	Laleh Amiri-Kordestani	OOD/DO1	Sections: All	Select one: ___ Authored X Approved
	Signature: Laleh Amiri-kordestani -S Digitally signed by Laleh Amiri-kordestani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014338688, cn=Laleh Amiri-kordestani -S Date: 2020.04.16 15:36:39 -04'00'			
Deputy Director	Marc Theoret	OND/OOD	Sections: All	Select one: ___ Authored x Approved
	Signature:			

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04/16/2020 06:32:53 PM

MARC R THEORET
04/17/2020 08:59:26 AM
My signature indicates that I have considered the assessments and recommendations included in this Review in determining the regulatory action