TUCATINIB RISK MANAGEMENT PLAN

RMP Version number: 2.1

Data lock point for this RMP: 20 December 2024

Date of final sign off: 15 September 2025

Rationale for submitting an updated RMP: The purpose of this RMP update is to add further characterisation of specific safety concerns (diarrhoea, hepatotoxicity, embryo-foetal toxicity and long-term safety) and additional pharmacovigilance information stemming from the completion of the post-approval measure /category 3 for SGNTUC-016/C4251001 (HER2CLIMB-02) (Clinical Study Report by Q2 2025).

Of note, the data presented in this RMP update corresponds to the primary CSR analysis of the HER2CLIMB-02 study with a data cut-off (DCO) of 29 June 2023. A subsequent, predefined, second interim analysis (OS IA2) for HER2CLIMB-02 occurred at 206 OS events with a DCO of 15 November 2024. [redacted]. The PFS and safety data were consistent with the primary analysis. No new safety risks were identified.

All participants have had the opportunity to be followed for at least 29 months since the last participant was enrolled in June 2022, and there is no evidence from the review of OS IA2 data to suggest a different safety profile with long-term use. A final OS analysis is planned at 253 OS events, [redacted]. As of 12 May 2025, [redacted] participants remain on tucatinib treatment. Therefore, the data from the final OS analysis is unlikely to show a different safety profile compared to the mature data set already available.

Summary of significant changes in this RMP:

On December 2023, Pfizer acquired Seagen, as such, the format and content of this RMP update may differ from the prior approved RMP.

Table 1. Summary of Significant Changes in this RMP

RMP Module:	Major Change(s):	Version Number and Date
PART I. PRODUCT OVERVIEW	Updated to reflect Pfizer as MAH.	V2.0, May 2025
PART II.Module SI Epidemiology of the indication(s) and target population(s)	Updated information through the DLP of 20 December 2024.	V2.0, May 2025
PART II.Module SII Nonclinical part of the safety specification	No changes.	
PART II.Module SIII Clinical trial exposure	Updated clinical exposure list of studies and tables to a data lock point (DLP) of 20 December 2024.	V2.0, May 2025

Table 1. Summary of Significant Changes in this RMP

RMP Module:	Major Change(s):	Version Number and Date
PART II.Module SIV Populations not studied in clinical trials	Updated information on "Population with relevant different ethnic origin" based on updated data through the DLP of 20 December 2024.	V2.0 May 2025
PART II.Module SV Post-authorisation experience	Updated post-authorisation exposure through DLP of 20 December 2024.	V2.0, May 2025
PART II.Module SVI Additional EU requirements for the safety specification	No changes.	
PART II.Module SVII Identified and potential risks	Updated risk characterisation with data from final CSR for pivotal studies HER2CLIMB and MOUNTAINEER. Added safety data from SGNTUC-016/C4251001 (HER2CLIMB-02).	V2.0, May 2025
PART II.Module SVIII Summary of the safety concerns	No changes.	V2.1, September 2025
PART III Pharmacovigilance plan (including post-authorisation safety studies)	Removal of Study SGNTUC-016/C4251001 (HER2CLIMB-02) from "Additional Pharmacovigilance Activities".	V2.0, May 2025
PART IV Plans for post-authorisation efficacy studies	No changes.	
PART V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)		
V.3 Summary of Risk Minimisation Measures	Removal of Study SGNTUC-016/C4251001 (HER2CLIMB-02 from Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern.	V2.0, May 2025
PART VI Summary of the risk management plan	No changes.	
Annexes		
Annex 1	No changes.	
Annex 2	Updated to reflect current study statuses.	V2.0, May 2025
Annex 3	Removal of SGNTUC-016 protocol	V2.0, May 2025
Annex 4	Removed legacy Seagen Hepatic Questionnaire and Adverse Experience Reporting Form and	V2.0, May 2025

Table 1. Summary of Significant Changes in this RMP

RMP Module:	Major Change(s):	Version Number and Date
	replaced with Pfizer Data Capture Aides for safety concerns of Hepatoxicity and Cardiotoxicity.	
Annex 5	No changes.	
Annex 6	No changes.	
Annex 7	Updated references	V2.0, May 2025
Annex 8	Added Summary of changes for the current version.	V2.1, September 2025

Other RMP versions under evaluation:

RMP version Number: 2.0

Submitted on: 18 June 2025

Procedure number: EMA/VR/0000280202

Details of the currently approved RMP:

Version number: 1.1

Approved with procedure: EMEA/H/C/005263/II/0010

Date of approval (opinion date): 16 March 2023

QPPV NAME: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ACS	American Cancer Society
AE	Adverse event
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
AUC	Area under the plasma concentration-time curve
BID	Twice per day
BRCA1	Breast cancer type 1
BRCA2	Breast cancer type 2
CI	Confidence interval
CNS	Central nervous system
CYP2C8	Cytochrome P450 2C8
CRC	Colorectal cancer
CSR	Clinical Study Report
CYP2C9	Cytochrome P450 2C9
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
CYP450	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DLP	Data lock point
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European public assessment report
ErbB1	Human epidermal growth factor receptor-1, also abbreviated as HER1
ErbB2	Human epidermal growth factor receptor-2, also abbreviated as HER2
ESMO	European Society for Medical Oncology
EU	European Union
FOLFOX	Folinic acid, Fluorouracil (5-FU), and Oxaliplatin.
FRESH	French Early Breast Cancer Cohort
GD	Gestation day
GEJ	Gastroesophageal junction
GI	Gastrointestinal
HER1	Human epidermal growth factor receptor-1, also abbreviated as ErbB1
HER2	Human epidermal growth factor receptor-2, also abbreviated as ErbB2
HER3	Human epidermal growth factor receptor-3, also abbreviated as ErbB3
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
HR	Hazard ratio
IBD	International birthdate
INN	International nonproprietary name

IV	Intravenous
LA/M	Locally-advanced/Metastatic LumA luminal-A
LVEF	Left Ventricular Ejection Fraction
MA	Marketing authorisation
MAH	Marketing authorisation holder
MATE	Multidrug and toxin extrusion MSD Merck Sharp & Dohme LLC
NAACCR	North American association of central cancer registries
NCCN	National comprehensive cancer network
NCI	National cancer institute
OCT2	Organic cation transporter 2
OR	Odds ratio
OS	Overall survival
OS IA2	Overall survival second interim analysis
PBS	Pharmaceutical benefits scheme
PFS	Progression free survival
P-gp	P-glycoprotein
pH	Potential of hydrogen
PI	Prescribing information
PIC	Powder-in-capsule
PL	Package leaflet
PO	Oral dose
PSUR	Periodic safety update report
QPPV	Qualified person for pharmacovigilance
RECIST	Response evaluation criteria in solid tumors
RMP	Risk management plan
SC	Subcutaneous
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
T-DM1	Trastuzumab emtansine
TKI	Tyrosine kinase inhibitor
UGT1A1	5'-diphospho-glucuronosyltransferase 1A1
UI	Uncertainty Interval
UK	United Kingdom
US	United States

TABLE OF CONTENTS

LIST OF TABLES

PART I. PRODUCT OVERVIEW

<table>
<tr><td>Active substance

(INN or common name)</td><td>Tucatinib</td></tr>
<tr><td>Pharmacotherapeutic group (ATC Code)</td><td>L01EH03</td></tr>
<tr><td>Marketing Authorisation Holder</td><td>Pfizer, Inc.</td></tr>
<tr><td>Medicinal products to which this RMP refers</td><td>1</td></tr>
<tr><td>Invented name(s) in the European Economic Area (EEA)</td><td>TUKYSA</td></tr>
<tr><td>Marketing authorisation procedure</td><td>Centralised</td></tr>
<tr><td>Brief description of the product:</td><td>Tucatinib is an orally administered, reversible human epidermal receptor type 2 (HER2)-targeted small molecule tyrosine kinase inhibitor (TKI).
Tucatinib is a potent inhibitor of HER2 in vitro, and in cellular signaling assays is >1000-fold more selective for HER2 compared to the closely related kinase epidermal growth factor receptor (EGFR).</td></tr>
<tr><td>Hyperlink to the Product Information:</td><td>The Summary of Product Characteristics (SmPC) and Package Leaflet is provided in Module 1.3.1.</td></tr>
<tr><td>Indication(s) in the EEA</td><td>TUKYSA is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally-advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.</td></tr>
<tr><td>Dosage in the EEA</td><td>The recommended dose is 300 mg tucatinib (two 150 mg tablets) taken twice daily continuously in combination with trastuzumab and capecitabine, at doses described in the table below.

Table 2. Dosage in the EEA
<table>
<tr><th>Treatment</th><th>Dose</th><th>Treatment Days</th><th>Timing relative to food intake</th></tr>
<tr><td>Tucatinib</td><td>300 mg orally twice daily</td><td>Continuously</td><td>With or without a meal</td></tr>
<tr><td>Capecitabine</td><td>1000 mg/m^2 orally twice daily</td><td>Days 1 to 14 every 21 days</td><td>Within 30 minutes after a meal</td></tr>
<tr><td>Trastuzumab Intravenous dosing</td><td></td><td></td><td></td></tr>
<tr><td>Initial dose</td><td>8 mg/kg IV</td><td>Day 1</td><td></td></tr>
<tr><td>Subsequent doses</td><td>6 mg /kg IV</td><td>Every 21 Days</td><td>NA</td></tr>
</table></td></tr>
</table>

	OR Subcutaneous (SC) dosing: 600 mg SC, Every 21 days
Pharmaceutical form and strengths	Tucatinib drug product is supplied as a round, yellow, film-coated, tablet in a 50 mg dosage strength and an oval-shaped, yellow, film-coated tablet in a 150 mg dosage strength for oral administration.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Incidence:

Breast cancer is the most common form of cancer in women worldwide,[1,2] and its burden is rising over the past decades. Over 2.3 million new cases and 685,000 deaths from breast cancer occurred globally in year 2020. In 2020, the highest age-standardized incidence rate of breast cancer was reported in Australia/New Zealand, Western Europe, and Northern America as 95.5, 90.7, and 89.4 per 100,000, respectively. In population <50 years, the highest age-standardized incidence rate was reported in 2020 in Western Europe, Australia/New Zealand, and in Southern Europe as 37.7, 36.0, and 34.9 per 100,000, respectively. In population 50+ years, the highest age-standardized incidence rate was reported in 2020 in Australia/New Zealand, Northern America, and in Northern Europe as 333.4, 311.2, and 302.9 per 100,000, respectively. [3]

Based on GLOBOCAN data, an estimated 2.3 million (95% uncertainty interval (UI): 2.3, 2.3) new cases and 670,000 (95%UI: 650,000, 680,000) deaths from breast cancer occurred in 2022, corresponding to 25.0% of new cases and 15.5% of cancer-related deaths among females when non-melanoma skin cancers were excluded.[4]

In the US, estimated cases of new ductal carcinoma in situ and invasive breast cancer and deaths among women of all ages in 2022 were reported to be 51,400, 287,850 and 43,250, respectively.[5]

Approximately 1% of breast cancer cases occur in men.[6] Invasive breast cancer occurred in 234,190 new cases and there were approximately 40,730 breast cancer deaths in 2015.[7] The incidence rate is specifically high in North America, Western Europe and Australia with an age standardised rate of more than 90 per 100,000 women. In the European Union (EU-28), 404,920 new cases of breast cancer and 98,755 deaths occurred in 2018. The highest age standardised incidence rate was observed in Belgium (113.2 per 100,000), while the highest mortality rate was observed in Croatia (18.2 per 100,000).[8]

Between 15% and 30% of breast cancers overexpress the HER2 receptor and are classified as HER2+ breast cancer.[9,10,11,12,13] Historically, HER2+ breast cancer tends to be more aggressive and more likely to recur than HER2-negative breast cancer[9,13,14]. HER2+ breast cancer also disproportionately affects younger patients, where the proportion of HER2 positivity is higher compared to older patients.[15]

The HER2+ breast cancers comprise about 10% to 20% of new breast cancer diagnoses in the United States and Europe and is more frequent in younger patients. In a study in Norway, 27% of subjects 20 to 39 years had HER2+ disease; this proportion decreased to 12.4% for ages 70 to 79 and 11.2% after age 80.[16] A study in Germany showed a higher proportion of HER2+ breast cancers in premenopausal women (21% versus 16% in postmenopausal women).[17] In the United States, 20.0% of breast cancer patients below age 50 have HER2+ disease[18], down to 10.7% in patients above age 75.

Prevalence:

Per Global Cancer Observatory 2022 data, 5-year prevalence of breast cancer in both sexes was 3,197,043 in Asia, 2,296,495 in Europe, and 1,332,343 in Northern America.[19]

Demographics of target population in the proposed indication

The incidence of breast cancer is higher in white women compared to South Asian and/or Black women,[20,21] however a study in the United Kingdom (UK) showed ethnic differences are mostly due to differences in known risk factors for the disease.[20]

Based on the cancer registrations for invasive breast cancer in women in England aged ≥25 years during 2011–2019 with a recorded ethnicity extracted from the National Cancer Registration and Analysis Service, the age-standardized incidence rate was highest for white women (199.6 (95 % CI 198.9–200.3)), and lowest for Black African women (118.2 (95 % CI 111.6–125.1)).[22]

In the US, based on the data from the North American Association of Central Cancer Registries (NAACCR), of all estimated cases of new ductal carcinoma in situ and invasive breast cancer among women of all ages in 2022, the highest proportion of cases were reported to be in age-group of 60-69 years (31% and 29%, respectively).[5]

In the US, based on the data from the North American Association of Central Cancer Registries (NAACCR), breast cancer incidence rates are highest in White women (133.7 per 100,000), followed closely by Black women (127.8 per 100,000), and are lowest in Hispanic (99.2 per 100,000) and Asian Pacific Islander women (101.3 per 100,000). [5]

In the US, based on the data from the North American Association of Central Cancer Registries (NAACCR), incidence rates of HR-positive/HER2-negative breast cancer are highest in White women (141 cases per 100,000), followed by American Indian/Alaska Native and Black women (112 per 100,000) among women aged 20 years and older. [5]

Risk factors for the disease

The risk factors associated with breast cancer (National Cancer Institute [23,24] include:

- age
- genetic alterations (eg, breast cancer type 1 [BRCA1], breast cancer type 2 [BRCA2], and others)
- mammographic breast density
- family history
- personal history of breast cancer
- radiation therapy
- alcohol consumption

- long-term hormone therapy
- high body weight
- low physical activity

Among women aged 40-49 years, a meta-analysis of 66 studies reported that extremely dense breasts on mammography or first-degree relatives with breast cancer were associated with at least a 2-fold increase in risk for breast cancer. Prior breast biopsy, second-degree relatives with breast cancer, or heterogeneously dense breasts were associated with a 1.5- to 2.0-fold increased risk; current use of oral contraceptives, nulliparity, and age 30 years or older at first birth were associated with a 1.0- to 1.5-fold increased risk of breast cancer. [25]

The main existing treatment options:

First-line treatment for most patients with HER2+ metastatic breast cancer is a combination of trastuzumab plus pertuzumab and chemotherapy. However, within 2 years, the majority of patients treated with this combination will progress.[26,27] Fam-trastuzumab deruxtecan-nxkin is the recommended second-line systemic therapy for recurrent unresectable (local or regional) or stage IV (M1) disease per guidelines from the National Comprehensive Cancer Network (NCCN) Guidelines published in 2025 and based on the results of a phase 3 randomized study that showed clinically meaningful and statistically significant improvements in both progression free survival and overall survival.[28,29,30] The tucatinib+trastuzumab and capecitabine regimen and T-DM1 are the recommended treatment options in the third line setting. In the fourth line setting and beyond optima sequence is not known since there is no single established standard of care[31,32] and no approved therapies have demonstrated clinically meaningful improvements in progression free survival or overall survival. [33,34,35] Preferred regimens for these patients based on American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and NCCN guidelines include trastuzumab-based combinations, other TKIs or margetuximab.[29,30]

Natural history of the indicated condition in the population, including mortality and morbidity:

Seventy-seven (77%) to 86% of breast cancer patients in Europe survive up to 5 years after diagnosis. The rate varies by country but generally, the survival rate is higher in Western Europe compared to Central and Eastern Europe.[1,2,36] Five-year survival of breast cancer patients in different European countries has approached a ceiling of 85% (highest survival in northern Europe). While Sweden had a 5-year survival rate of 89% in 2014, Slovakia, Romania, and Poland had survival rates of 73% to 75%.[37] Differences in survival between countries are probably due to differences in stage at diagnosis, access to good care, screening, and differences in cancer biology.[38]

A population-based cohort of 3,197 systemically untreated breast cancer patients were identified within the registry of the Danish Breast Cancer Cooperative Group and in the study population there were 970 deaths compared with expected death of 737 women, which was

an excess mortality of 233 deaths (Standardized mortality ratio = 1.32, 95% CI = 1.24 to 1.40). Mortality rates were 2356 per 100000 person-years in the study population and 1790 per 100,000 person-years in the general population of women.[39]

The HER2+ subtype has been shown to be more aggressive than other breast cancer subtypes. The HER2+ subtype are reported to be associated with bone metastasis (odds ratio [OR] = 1.6), brain metastasis (OR: 2.8 to 5), liver metastasis (OR: 3.4 to 5.4) and lung metastasis (OR: 2.0 to 3.0) and survival is much lower in patients with HER2+ disease compared with HER2-negative disease (hazard ratio [HR]: 5.65).[21] In a study on Swiss cancer registries patients, the overall survival hazard ratio was 3.5 times higher (ie, poorer survival) in HER2-enriched patients than luminal-A (LumA)-Like (high estrogen receptor/progesterone receptor expression) subtype.[40]

Important co-morbidities:

Significant co-morbidities for patients with breast cancer include peripheral vascular disease, dementia, chronic pulmonary disease, liver diseases, and renal diseases.[41] These comorbid conditions exist in the population; however, those are not specific to breast cancer patients. In the cited reference, Charlson comorbidity score was calculated using these co-morbidities for prognosis. The prevalence of co-morbidities among women treated for breast cancer aged older than 66 is 32.2%, a statistic comparable to those without cancer at 31.8%. A nationwide retrospective study with the published FRESH (French Early Breast Cancer Cohort) cohort identified all women with non-metastatic breast cancer newly diagnosed between 01 January 2011 to 31 December 2017.[42] Of these 235, 368 patients, the following comorbid conditions were reported: (1) cardiovascular, n=60,146 (25.6%), (2) endocrine and metabolism, n=51,588 (21.9%), (3) psychiatric disorders, n=30,372 (12.9%), (4) pulmonary disorders, n=10,883 (4.6%).

Of the 33,099 women who had incident invasive breast cancer with inpatient and outpatient hospital discharge data within 2 years after breast cancer diagnosis identified from the Missouri Cancer Registry in the US between 2002-2012, 2852 (9%) had cardiovascular disease, 2637 (12%) had type 2 diabetes mellitus and 12,988 (39%) had hypertension at baseline.[43]

A retrospective chart review conducted in 548 women with early breast cancer (Stage I-III) seen at breast cancer clinics of a single institution in the US identified hypertension (39.6%), hypercholesterolemia or hyperlipidemia (20.8%), diabetes (10.6%), stomach or intestinal disorders (16.9%) as the most frequent comorbidities. [44]

A retrospective cohort study using provincial linked administrative health datasets from British Columbia, Canada, between 2000 and 2013 included 12,127 women diagnosed with breast cancer between 2005 and 2009 and reported the following comorbidities measured up to 5 years prior to the diagnosis of breast cancer: (1) ischemic heart disease, 13.2%, (2) heart failure, 4.7%, (3) depression, 34.2%, (4) cerebrovascular disease, 3.3%, (5) diabetes, 14.9%, (6) osteoporosis, 16.0%, and (7) hypothyroidism, 16.9% .[45]

A retrospective, rolling cohort study using Pharmaceutical Benefits Scheme (PBS) dispensing claims data from Australia for the period 01 January 2003 to 31 December 2014 included 4,278 women with hormone dependent breast cancer who initiated endocrine therapy .[46] In this cohort, at least one dispensing record for a cardiovascular condition up to 12 months prior to initiation of endocrine therapy was present in 64% of women; medications for pain or pain-inflammation (51%), gastric acid disorders (41%), hyperlipidemia (36%) and depression (22%) were also frequently dispensed.

Module SII. Non-Clinical Part of the Safety Specification

Table 3. Key Safety Findings and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
Toxicity:		
• Acute or repeat-dose toxicity • Hepatotoxicity	In the 28- and 90-day nonclinical studies there were reversible hepatocellular and/or hepatobiliary effects, including generally minimal (≤2.5–fold) increases in serum markers of liver injury (including aspartate aminotransferase [AST], alanine aminotransferase [ALT], and bilirubin), liver weight increases, and centrilobular hepatocyte hypertrophy. These changes occurred at doses ≥3 mg/kg twice daily (BID) in rats (0.09-fold human exposures based on AUC_{12h}) and ≥10 mg/kg BID for cynomolgus monkeys (1.5 and 0.15-fold human exposure based on the 28- and 90-day studies, respectively). At non-tolerated doses in cynomolgus monkeys (30 and 45 mg/kg BID; 4- and 7–fold human exposures), liver was reported as friable, with hepatocyte cytoplasmic swelling and rarefaction, without any changes in serum liver parameters. There were no hepatic histologic changes indicating hepatocellular injury (eg, hepatic degeneration, inflammation, or necrosis) in any nonclinical study.	In clinical studies: elevated AST, ALT, and bilirubin (Grade 1 to 4) have been observed and were reversible with dose modification except in cases of progressive metastatic liver disease. Hepatotoxicity is considered an important identified risk. This risk will be monitored in the periodic safety update report (PSUR).
• Acute or repeat-dose toxicity • GI toxicity	In repeat-dose 28- and 90-day nonclinical studies, gastrointestinal clinical signs including vomiting and/or watery feces were observed in rats administered a non-tolerated dose of 100 mg/kg BID (21–fold human exposure; dose reduction to 60 mg/kg BID after approximately 1 week) and in cynomolgus monkeys at ≥2.5 mg/kg BID (0.04-fold human exposure). There were no histologic changes associated with the gastrointestinal tract except in	In clinical studies, the most common adverse reactions have been mild to moderate (Grade 1 or 2) gastrointestinal reactions and included nausea, diarrhoea, and vomiting. Most events have been manageable with dose modifications and treatment with anti-diarrhoeals and anti-emetics as needed.

Table 3. Key Safety Findings and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
	rats at non-survivable doses (gastrointestinal erosions and ulcers). * Human AUC_{12h} was 3.47 (μg·h/mL), determined in Clinical Study ONT-380-012, Part D.	
• Toxicity reproductive/developmental toxicity	A preliminary embryo-foetal development study (Study 20144956) in rabbits (6 dams/group) indicates that tucatinib caused embryo-foetal toxicity in the absence of significant maternal toxicity. Pregnant New Zealand White rabbits were administered either vehicle or suspensions of tucatinib orally twice daily on gestation days (GD) 7 through 19 at 0, 60, 90, 120, and 150 mg/kg/day. All surviving rabbits were euthanized on GD 29 and examined. The area under the plasma concentration-time curve (AUC) (0-12 hr) at 90 mg/kg/day in rabbits was approximately the same exposure as participants dosed with the recommended dose of 300 mg BID (ARRAY-380-103, a phase 1 clinical pharmacology study). These data indicate that tucatinib is a selective embryo-foetal toxicant in rabbits. Foetal external and visceral malformations were observed at ≥90 mg/kg/day, including domed heads with severe dilation of the lateral and third ventricles. Other malformations included hyperflexed forepaw, herniated umbilicus, organ malposition, and vascular malformations and variations Foetal skeletal variations corresponding to the domed heads were observed at 90, 120, and 150 mg/kg/day. Microscopic changes in female reproductive organs, and male mammary gland and prostate were observed in repeat-dose rat toxicity studies at 0.92-fold human exposure. The changes included uterine atrophy, vaginal mucification, changes in corpora lutea, lobular atrophy of the male mammary gland, and decreased organ weights (decreased uterus/cervix and prostate weights). During the recovery phase, these changes were partially or fully reversible.	There was one pregnancy reported in a participant enrolled in the HER2CLIMB (H2C) trial and treated on the tucatinib arm. The participant chose to undergo an elective termination of pregnancy. No pregnancies were reported in participants in the MOUNTAINEER and HER2CLIMB-02 trials. Women of reproductive potential are advised of the potential risk of taking tucatinib while pregnant. Women of reproductive potential are also advised to use effective contraception during treatment and for at least 1 week after the last dose. Information is presented in sections 4.4 and 4.6 of the SmPC as well as section 2 of the package leaflet (PL) to minimise risk of pregnancy and provide guidance regarding breastfeeding while taking tucatinib.

Table 3. Key Safety Findings and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
	Reproductive changes were not observed in monkeys.	
Genotoxicity	Tucatinib has been evaluated *in vitro* and *in vivo* for genotoxicity. Tucatinib was negative in bacterial and mammalian mutagenesis assays, and in the mouse micronucleus test.	No impact on human usage is anticipated.
• General Safety pharmacology: - Cardiovascular system including potential effect on QT interval prolongation	In an *in vitro* human ether-a-go-go related gene (hERG)-channel assay, tucatinib showed inhibition only at very high doses. In telemeterized cynomolgus monkeys, there was no effect of tucatinib on cardiovascular function. In nonclinical studies conducted with tucatinib, left ventricular ejection fraction (LVEF) was not specifically measured; however, in repeat-dose studies up to 90 days with tucatinib in rats and cynomolgus monkeys, the evaluations of in-life clinical signs, blood pressure, heart rate, and morphologic evaluations of lung and heart did not show any evidence of decreased LVEF or its sequelae.	A dedicated TQT study (ONT-380-011) demonstrated no effect of tucatinib on QT prolongation, thus no impact on human usage is anticipated.
• Nervous system	In nonclinical repeat-dose studies up to 90 days in rats and cynomolgus monkeys, there were no changes in any endpoint, including neurological and histologic evaluations, indicating any effect of tucatinib on the brain. There were no effects of tucatinib on neurobehavioral function in rats.	No impact on human usage is anticipated.
• Respiratory	There were no effects of tucatinib on respiratory function in rats.	No impact on human usage is anticipated.
• Other	There were no effects of oral tucatinib on gastrointestinal propulsion in rats. Gastric secretion, acidity, and irritation were increased only at the highest dose tested. In nonclinical repeat-dose studies up to 90 days in rats and cynomolgus monkeys, there were no in-life or histologic observations indicating any effect of tucatinib on skin.	No impact on human usage is anticipated.
• Carcinogenicity	Carcinogenicity studies have not been conducted with tucatinib.	Carcinogenicity studies have not been conducted with tucatinib.
Other toxicity-related information	Tucatinib is a substrate of cytochrome P450 2C8 (CYP2C8) and cytochrome P450 3A (CYP3A). Tucatinib is an inhibitor of CYP2C8 and P-glycoprotein (P-gp) in vitro and a	The potential of tucatinib to be a drug-drug interaction (DDI) perpetrator or victim was evaluated in the 2 clinical DDI studies (ONT380-012 and

Table 3. Key Safety Findings and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
	metabolism-dependent inactivator of CYP3A. Tucatinib inhibited organic cation transporter 2 (OCT2)/multidrug and toxin extrusion (MATE) 1/2-K-mediated transport of metformin and creatinine in vitro.	SGNTUC-020), a physiologically- based pharmacokinetic analysis, and in nonclinical *in vitro* and *in vivo* systems. Tucatinib is a strong inhibitor of CYP3A, the increase in midazolam-exposure in a DDI study was 5.7-fold. Tucatinib exposure was reduced ~50% when co-administered with strong CYP2C8/CYP3A inducers. Tucatinib exposure was increased ~3-fold when co-administered with strong CYP2C8 inhibitors. Gastric potential of hydrogen (pH) modulation with omeprazole did not impact tucatinib absorption. Tucatinib is a weak inhibitor of P-gp. Caution is recommended when co-administering with digoxin or other P-gp substrates with narrow therapeutic windows. Tucatinib is a weak inhibitor of CYP2C8, MATE1/2-K, and was not an inhibitor of cytochrome P450 2C9 (CYP2C9). Tucatinib inhibits ATE1/MATE2-K-mediated transport of metformin and OCT2/MATE1-mediated transport of creatinine. The observed serum creatinine increase in clinical studies with tucatinib is due to inhibition of tubular secretion of creatinine via OCT2 and MATE1. Information is presented in sections 4.4 and 4.5 of the SmPC regarding possible drug interactions with tucatinib.

Module SIII. Clinical Trial Exposure

The exposure data presented in this European Union Risk Management Plan (EU RMP) include participants in Legacy Seagen/Pfizer-sponsored completed and ongoing studies.

Cumulatively through the data lock point (DLP) for clinical studies in this RMP (20 December 2024), there are 14 completed studies and 9 ongoing clinical studies[1] for tucatinib described below.

Completed Clinical Studies:

- Study ARRAY-380-101 is a phase 1, open-label, multiple dose study that assessed the safety, tolerability and pharmacokinetics of tucatinib in adult subjects with advanced solid malignancies in the United States and Canada.

- Study ARRAY-380-102 is a phase 1, open-label, single-dose, four-period study that assessed pharmacokinetics, relative bioavailability and safety of single 300 mg doses of tucatinib administered as 4 oral tucatinib formulations in fasted healthy adult subjects in the United States.

- Study ARRAY-380-103 is a phase 1, open-label, single-dose, four-period study that compared the administration of the 300 mg tucatinib tablet with the 300 mg powder-in-capsule (PIC) formulation in the fasted state in healthy subjects as an assessment of relative bioavailability between the two formulations in the United States.

- Study ONT-380-004 is a phase 1b, open-label study to assess the safety and tolerability of tucatinib combined with ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1) in adult subjects with HER2+ metastatic breast cancer in the United States and Canada. Enrollment has been completed; the data cut-off date for the primary analysis was 31 January 2018.

- Study ONT-380-005 is a phase 1b, open-label study to assess the safety and tolerability of tucatinib in adult subjects with HER2+ metastatic breast cancer following combination treatment of tucatinib + capecitabine; tucatinib + trastuzumab; or tucatinib + capecitabine + trastuzumab in the United States.

- Study ONT-380-008 is a phase 1, open-label study of the absorption, metabolism, and excretion of [^{14}C]-tucatinib following a single oral dose (PO) in healthy male and female subjects in the United States.

- Study ONT-380-009 is a phase 1, open-label, nonrandomized, single-dose parallel group study to assess the safety, tolerability, and pharmacokinetics in fasted, hepatically-impaired male and female subjects and fasted matched-control healthy subjects administered 300 mg of tucatinib in the United States.

[1] Includes one study (SGNDV-004) from the Disitamab Vedotin clinical development program in which tucatinib is being used as a study drug.

- Study ONT-380-011 is a phase 1, randomized, partially double-blind, placebo- and positive-controlled study to evaluate the effect of tucatinib on cardiac repolarization in healthy subjects in the United States.

- Study ONT-380-012 is a phase 1, open-label, fixed-sequence, 5-part, drug-drug interaction study of tucatinib to evaluate the effects of CYP3A4 and CYP2C8 inhibition and induction on the pharmacokinetics of the substrates of CYP3A4, CYP2C8, CYP2C9, and P-gp in healthy subjects in the United States.

- Study SGNTUC-015 is a phase 1, open-label, safety, tolerability and pharmacokinetic study of tucatinib (ONT-380) in healthy Japanese and Caucasian subjects in the United States.

- Study SGNTUC-020 is a phase 1, open-label, fixed-sequence, drug-drug interaction study to evaluate the effects of tucatinib on the pharmacokinetics of a MATE substrate (metformin) in healthy subjects in the United States.

- Study ONT-380-206 (HER2CLIMB)/ C4251010 is a global, pivotal, randomized, double-blind, controlled study of tucatinib versus placebo in combination with capecitabine and trastuzumab in subjects with previously-treated, unresectable locally-advanced or metastatic HER2+ breast cancer in the United States, Canada, Europe, Israel, and Australia. The data cut-off date for the primary analysis was 04 September 2019. The final analysis of safety for study closure was 12 September 2022.

- Study SGNTUC-017 (MOUNTAINEER)/ C4251002 is a global, phase 2, open-label study of tucatinib combined with trastuzumab in subjects with HER2+ metastatic colorectal cancer (CRC). The data cut-off date for the primary analysis was 28-March-2022. The data cut-off date for the final analysis was 02 November 2023.

- Study SGNTUC-022 (MOUNTAINEER-02)/C4251004 is a phase 2/3 randomized, double-blind, placebo-controlled, active comparator study of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously-treated, locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal cancer.

<u>Ongoing Clinical Studies:</u>

- Study SGNTUC-016 (HER2CLIMB-02)/C4251001 is a global, randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic (LA/M) HER2+ breast cancer. The data cut-off date for the primary analysis was 29 June 2023.

- Study SGNTUC-019/C4251003 is a phase 2 basket study of tucatinib and trastuzumab in solid tumors with HER2 alterations in subjects with previously-treated, locally-advanced unresectable or metastatic solid tumors.

- Study SGNTUC-024/C4251005 is a phase 1b dose escalation study of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy for HER2+ Subjects with unresectable or metastatic HER2+ esophageal adenocarcinoma, gastroesophageal junction (GEJ) adenocarcinoma, gastric adenocarcinoma, colorectal carcinoma (CRC), cholangiocarcinoma, and gallbladder carcinoma.

- Study SGNTUC-025 (HER2CLIMB-04)/C4251006 is a phase 2 study of tucatinib plus trastuzumab deruxtecan in subjects with previously-treated unresectable locally-advanced or metastatic HER2+ breast cancer.

- Study SGNTUC-028 (HER2CLIMB-05)/C4251007 is a randomized, double-blind, phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for subjects with LA/M HER2+ breast cancer who have had prior treatment with a taxane, trastuzumab, and pertuzumab.

- Study SGNTUC-029 (MOUNTAINEER-03)/C4251008 is an open-label randomized phase 3 study of tucatinib in combination with trastuzumab and mFOLFOX6 versus mFOLFOX6 given with or without either cetuximab or bevacizumab as first-line treatment for subjects with HER2+ metastatic colorectal cancer.

- MK7119-001/C4251013 is a phase 2 open-label, single arm study of tucatinib (MK-7119) in combination with trastuzumab and capecitabine in participants with previously-treated locally-advanced unresectable or metastatic HER2+ breast cancer.

- Study MK7119-002/C4251016 is a is a Phase 1 study in China to investigate the safety and pharmacokinetics of tucatinib (MK-7119) in participants with HER2+ advanced breast cancer, gastric or gastroesophageal junction adenocarcinoma and colorectal cancer.

- SGNDV-004/C5731004 is a Phase 1b/2 open-label study of disitamab vedotin in combination with other anticancer therapies in solid tumors.

Across these 23 clinical studies, a total of 2831 participants, with and without cancer, received at least dose of tucatinib or blinded therapy as of 20 December 2024. Clinical trial exposure to tucatinib in participants with cancer is presented herein by age and gender (Table 4), dose (Table 4), duration or exposure (Table 5) and race (Table 6).

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib Monotherapy				
Adults (18-64 years)	4	57	1.02	19.88

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Elderly (>=65 years)	5	11	1.18	4.26
65-74 years	5	10	1.18	3.95
75-84 years	0	1	0	0.31
85+ years	0	0	0	0
Total	9	68	2.21	24.14
Tucatinib+T-DM1 <Includes BLINDED>				
Adults (18-64 years)	2	526	1.23	510.17
Elderly (>=65 years)	0	101	0	84.37
65-74 years	0	89	0	74.47
75-84 years	0	12	0	9.90
85+ years	0	0	0	0
Total	2	627	1.23	594.54

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; TDM1= trastuzumab emtansine; SGNDV= disitamab vedotin

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).

Cutoff date: 20 December 2024

Table 4 Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib+Trastuzumab				
Adults (18-64 years)	70	96	70.51	55.33
Elderly (>=65 years)	59	68	31.66	26.40
65-74 years	38	54	23.62	19.40
75-84 years	20	12	7.92	6.71
85+ years	1	2	0.12	0.29
Total	129	164	102.17	81.72
Tucatinib Monotherapy Crossover to Tucatinib+Trastuzumab				
Adults (18-64 years)	6	11	2.20	8.36
Elderly (>=65 years)	8	3	6.36	1.39
65-74 years	6	3	3.82	1.39
75-84 years	2	0	2.54	0
85+ years	0	0	0	0
Total	14	14	8.57	9.75

Table 4 Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and eucovorin/levoleucovorin; TDM1= trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date +)/365.25 and summed for all the participants in the row. Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024.

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib+Trastuzumab+FOLFOX (includes Blinded)				
Adults (18-64 years)	75	56	42.31	34.95
Elderly (>=65 years)	45	15	32.51	7.79
65-74 years	38	11	26.10	6.20
75-84 years	6	4	5.62	1.58
85+ years	1	0	0.79	0
Total	120	71	74.82	42.74
Tucatinib+Trastuzumab Deruxtecan				
Adults (18-64 years)	1	47	0.16	47.89
Elderly (>=65 years)	1	21	0.11	18.95
65-74 years	1	18	0.11	16.02
75-84 years	0	3	0	2.93
85+ years	0	0	0	0
Total	2	68	0.27	66.84

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T-DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib+Capecitabine				
Adults (18-64 years)	0	9	0	4.95

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Elderly (>=65 years)	0	2	0	1.08
65-74 years	0	2	0	1.08
75-84 years	0	0	0	0
85+ years	0	0	0	0
Total	0	11	0	6.03
Tucatinib+Trastuzumab+Capecitabine				
Adults (18-64 years)	3	401	2.21	385.19
Elderly (>=65 years)	0	93	0	60.46
65-74 years	0	81	0	53.35
75-84 years	0	12	0	7.11
85+ years	0	0	0	0
Total	3	494	2.21	445.65

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; TDM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib+Trastuzumab+Capecitabine after Crossover from Placebo+Trastuzumab+Capecitabine				
Adults (18-64 years)	0	24	0	15.58
Elderly (>=65 years)	0	2	0	0.30
65-74 years	0	1	0	0.25
75-84 years	0	1	0	0.05
85+ years	0	0	0	0
Total	0	26	0	15.89
Tucatinib+Trastuzumab+Pembro+CAPOX				
Adults (18-64 years)	3	1	2.01	1.14
Elderly (>=65 years)	3	1	0.80	0.49
65-74 years	2	1	0.67	0.49
75-84 years	1	0	0.14	0
85+ years	0	0	0	0
Total	6	2	2.81	1.64

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female

a.Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; TDM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib+Trastuzumab+Pembro+FOLFOX				
Adults (18-64 years)	2	1	1.79	1.73
Elderly (>=65 years)	1	0	0.16	0
65-74 years	0	0	0	0
75-84 years	1	0	0.16	0
85+ years	0	0	0	0
Total	3	1	1.95	1.73
Tucatinib+Trastuzumab+Fulvestrant				
Adults (18-64 years)	0	16	0	13.01
Elderly (>=65 years)	0	15	0	15.07
65-74 years	0	14	0	13.03
75-84 years	0	1	0	2.04
85+ years	0	0	0	0
Total	0	31	0	28.08

a.Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; TDM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024.

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib+Trastuzumab+Ramucirumab+Paclitaxel				

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Adults (18-64 years)	13	0	11.19	0
Elderly (>=65 years)	3	1	1.20	0.98
65-74 years	3	1	1.20	0.98
75-84 years	0	0	0	0
85+ years	0	0	0	0
Total	16	1	12.39	0.98
Tucatinib+Trastuzumab+Pertuzumab <Includes BLINDED>				
Adults (18-64 years)	0	544	0	548.79
Elderly (>=65 years)	0	106	0	103.27
65-74 years	0	89	0	87.52
75-84 years	0	17	0	15.75
85+ years	0	0	0	0
Total	0	650	0	652.05

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; TDM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).

Cutoff date: 20 December 2024.

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population[a] (continued)

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
Tucatinib +SGNDV				
Adults (18-64 years)	2	6	0.36	1.18
Elderly (>=65 years)	0	1	0	0.08
65-74 years	0	0	0	0
75-84 years	0	1	0	0.08
85+ years	0	0	0	0
Total	2	7	0.36	1.26

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; TDM1 = trastuzumab emtansine.

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).

Cutoff date: 20 December 2024

Table 4. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Age Group and Gender: Safety Population

Age Group	Participants		Participant-Years	
	Male	Female	Male	Female
All Treatment Regimens Total				
Adults (18-64 years)	181	1795	135.00	1648.14
Elderly (>=65 years)	125	440	74.00	324.90
65-74 years	93	374	56.71	278.14
75-84 years	30	64	16.38	46.46
85+ years	2	2	0.91	0.29
Total	306	2235	208.99	1973.03

Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; TDM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).

Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a] (continued)

Dose of Tucatinib	Participant	Participant-Years
Tucatinib Monotherapy[b]		
25 mg BID	3	0.62
50 mg BID	3	0.54
100 mg BID	3	0.62
200 mg BID	3	0.93
300 mg BID	30	11.81
500 mg BID	4	1.37
600 mg BID	24	8.11
650 mg BID	3	1.23
800 mg BID	4	1.12
Total	77	26.35

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

b. Includes 50 participants from ARRAY-380-101 who received powder in capsule.

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.

Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a] (continued)

Dose of Tucatinib	Participant	Participant-Years
Tucatinib+T-DM1 <Includes BLINDED>		
300 mg BID	50	42.19
350 mg BID	7	5.89
Blinded BID	572	547.69
Total	629	595.76
Tucatinib+Trastuzumab		
300 mg BID	289	180.80
350 mg BID	4	3.09
Total	293	183.89

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
b.Includes 50 participants from ARRAY-380-101 who received powder in capsule.
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.
Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a] (continued)

Dose of Tucatinib	Participant	Participant-Years
Tucatinib Monotherapy Crossover to Tucatinib+Trastuzumab		
300 mg BID	28	18.32
Total	28	18.32
Tucatinib+Trastuzumab+FOLFOX (includes BLINDED)		
150 mg BID	5	1.43
300 mg BID	23	21.14
Blinded BID	163	94.98
Total	191	117.56

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
b. Includes 50 participants from ARRAY-380-101 who received powder in capsule.
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.
Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a] (continued)

Dose of Tucatinib	Participant	Participant-Years
Tucatinib+Trastuzumab Deruxtecan		
300 mg BID	70	67.11
Total	70	67.11
Tucatinib+Capecitabine		
300 mg BID	7	4.65
350 mg BID	4	1.38
Total	11	6.03
Tucatinib+Trastuzumab+Capecitabine		
300 mg BID	497	447.85
Total	497	447.85

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, MK-7119-001, MK-7119-002, SGNDV-004

b. Includes 50 participants from ARRAY-380-101 who received powder in capsule.

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.

Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a] (continued)

Dose of Tucatinib	Participant	Participant-Years
Tucatinib+Trastuzumab+Capecitabine after Crossover from Placebo+Trastuzumab+Capecitabine		
300 mg BID	26	15.89
Total	26	15.89
Tucatinib+Trastuzumab+Pembro+CAPOX		
300 mg BID	8	4.45
Total	8	4.45
Tucatinib+Trastuzumab+Pembro+FOLFOX		
300 mg BID	4	3.68
Total	4	3.68

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

b. Includes 50 participants from ARRAY-380-101 who received powder in capsule.

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.

Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a] (continued)

Dose of Tucatinib	Participant	Participant-Years
Tucatinib+Trastuzumab+Fulvestrant		
300 mg BID	31	28.08
Total	31	28.08
Tucatinib+Trastuzumab+Ramucirumab+Paclitaxel		
300 mg BID	17	13.37
Total	17	13.37
Tucatinib+Trastuzumab+Pertuzumab <Includes BLINDED>		
Blinded BID	650	652.05
Total	650	652.05

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
b. Includes 50 participants from ARRAY-380-101 who received powder in capsule.
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.
Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a] (continued)

Dose of Tucatinib	Participant	Participant-Years
Tucatinib+SGNDV		
1.25 mg BID	6	1.30
1.5 mg BID	3	0.33
Total	9	1.62

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
b. Includes 50 participants from ARRAY-380-101 who received powder in capsule.
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.
Cutoff date: 20 December 2024

Table 5. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Dose: Safety Population[a]

Dose of Tucatinib	Participant	Participant-Years
All Treatment Regimens Total[b]		
1.25 mg BID	6	1.30
1.5 mg BID	3	0.33

25 mg BID	3	0.62
50 mg BID	3	0.54
100 mg BID	3	0.62
150 mg BID	5	1.43
200 mg BID	3	0.93
300 mg BID	1080	859.36
350 mg BID	15	10.35
500 mg BID	4	1.37
600 mg BID	24	8.11
650 mg BID	3	1.23
800 mg BID	4	1.12
Blinded BID	1385	1294.72
Total	2541	2182.03

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

b. Includes 50 participants from ARRAY-380-101 who received powder in capsule.

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Parcipitant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories.

Cutoff date:20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib Monotherapy		
<1 month	9	0.56
1 to <3 months	31	4.87
3 to <6 months	24	8.56
>=6 months	13	12.36
Total	77	26.35
Tucatinib+T-DM1 <Includes BLINDED>		
<1 month	15	0.73
1 to <3 months	129	20.70
3 to <6 months	129	48.62
>=6 months	356	525.71
Total	629	595.76

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.

b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004

CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.

Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).

Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib+Trastuzumab		
<1 month	19	0.99
1 to <3 months	108	16.87
3 to <6 months	61	22.63
>=6 months	105	143.40
Total	293	183.89
Tucatinib Monotherapy Crossover to Tucatinib+Trastuzumab		
<1 month	0	0
1 to <3 months	5	0.78
3 to <6 months	11	4.15
>=6 months	12	13.40
Total	28	18.32

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participants (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib+Trastuzumab+FOLFOX (Includes BLINDED)		
<1 month	9	0.55
1 to <3 months	32	5.87
3 to <6 months	46	17.65
>=6 months	104	93.48
Total	191	117.56
Tucatinib+Trastuzumab Deruxtecan		
<1 month	1	0.06
1 to <3 months	12	1.84
3 to <6 months	12	4.49
>=6 months	45	60.72
Total	70	67.11

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, MK-7119-001, MK-7119-02, SGNDV-004: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib+Capecitabine		
<1 month	0	0
1 to <3 months	2	0.29
3 to <6 months	3	1.05
>=6 months	6	4.69
Total	11	6.03
Tucatinib+Trastuzumab+Capecitabine		
<1 month	26	1.14
1 to <3 months	93	15.40
3 to <6 months	111	43.24
>=6 months	267	388.07
Total	497	447.85

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib+Trastuzumab+Capecitabine after Crossover from Placebo+Trastuzumab+Capecitabine		
<1 month	3	0.08
1 to <3 months	5	0.74
3 to <6 months	8	3.25
>=6 months	10	11.82
Total	26	15.89

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib+Trastuzumab+Pembro+CAPOX		
<1 month	1	0.07
1 to <3 months	2	0.31
3 to <6 months	3	1.44
>=6 months	2	2.63
Total	8	4.45

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib+Trastuzumab+Pembro+FOLFOX		
<1 month	0	0
1 to <3 months	1	0.16
3 to <6 months	1	0.26
>=6 months	2	3.26
Total	4	3.68
Tucatinib+Trastuzumab+Fulvestrant		
<1 month	1	0.06
1 to <3 months	8	1.29
3 to <6 months	4	1.54
>=6 months	18	25.19
Total	31	28.08

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib+Trastuzumab+Ramucirumab+Paclitaxel		
<1 month	0	0
1 to <3 months	2	0.41
3 to <6 months	4	1.38
>=6 months	11	11.58
Total	17	13.37
Tucatinib+Trastuzumab+Pertuzumab <Includes BLINDED>		
<1 month	4	0.23
1 to <3 months	63	10.91
3 to <6 months	58	21.66
>=6 months	525	619.26
Total	650	652.05

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b] (continued)

Duration of Exposure	Participants	Participant-Years
Tucatinib +SGNDV		
<1 month	0	0
1 to <3 months	7	0.92
3 to <6 months	2	0.70
>=6 months	0	0
Total	9	1.62

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 19, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV= disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 6. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Duration of Exposure: Safety population[a,b]

Duration of Exposure	Participants	Participant-Years
All Treatment Regimens Total		
<1 month	88	4.46
1 to <3 months	500	81.37
3 to <6 months	477	180.63
>=6 months	1476	1915.57
Total	2541	2182.03

a. Data for duration of exposure from Study MK7110-001/C4251013 were available through 17 October 2024 as the transfer of data from Merck to Pfizer was on-going at the data cutoff date.
b. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib Monotherapy		
Asian	29	11.55
Black or African American	5	1.95
Other	2	1.11
White	41	11.74
Unknown/Not Given/Missing	0	0
Total	77	26.35
Tucatinib+T-DM1 <Includes BLINDED>		
Asian	247	225.05
Black or African American	25	19.78
Other	15	9.88
White	246	251.56
Unknown/Not Given/Missing	96	89.48
Total	629	595.76

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib+Trastuzumab		
Asian	93	46.70
Black or African American	13	2.78
Other	2	2.84
White	148	109.23
Unknown/Not Given/Missing	37	22.35
Total	293	183.89
Tucatinib Monotherapy Crossover to Tucatinib+Trastuzumab		
Asian	0	0
Black or African American	2	0.75
Other	0	0
White	22	16.02
Unknown/Not Given/Missing	4	1.55
Total	28	18.32

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC- 019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib+Trastuzumab+FOLFOX (Includes BLINDED)		
Asian	102	61.23
Black or African American	4	2.84
Other	1	0.54
White	71	49.10
Unknown/Not Given/Missing	13	3.85
Total	191	117.56
Tucatinib+Trastuzumab Deruxtecan		
Asian	4	2.12
Black or African American	8	6.43
Other	0	0
White	56	57.62
Unknown/Not Given/Missing	2	0.94
Total	70	67.11

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years

Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib+Capecitabine		
Asian	0	0
Black or African American	0	0
Other	0	0
White	10	5.61
Unknown/Not Given/Missing	1	0.42
Total	11	6.03
Tucatinib+Trastuzumab+Capecitabine		
Asian	85	74.12
Black or African American	42	28.30
Other	3	1.26
White	306	286.20
Unknown/Not Given/Missing	61	57.97
Total	497	447.85

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note:Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib+Trastuzumab+Capecitabine after Crossover from Placebo+Trastuzumab+Capecitabine		
Asian	1	0.24
Black or African American	1	0.48
Other	1	0.86
White	19	12.11
Unknown/Not Given/Missing	4	2.20
Total	26	15.89
Tucatinib+Trastuzumab+Pembro+CAPOX		
Asian	7	2.97
Black or African American	0	0

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Other	0	0
White	1	1.49
Unknown/Not Given/Missing	0	0
Total	8	4.45

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib+Trastuzumab+Pembro+FOLFOX		
Asian	2	0.42
Black or African American	0	0
Other	0	0
White	2	3.26
Unknown/Not Given/Missing	0	0
Total	4	3.68
Tucatinib+Trastuzumab+Fulvestrant		
Asian	11	8.60
Black or African American	1	0.99
Other	0	0
White	15	14.76
Unknown/Not Given/Missing	4	3.72
Total	31	28.08

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant -time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib+Trastuzumab+Ramucirumab+Paclitaxel		

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Asian	9	7.13
Black or African American	0	0
Other	0	0
White	8	6.25
Unknown/Not Given/Missing	0	0
Total	17	13.37
Tucatinib+Trastuzumab+Pertuzumab <Includes BLINDED>		
Asian	226	249.62
Black or African American	19	20.83
Other	23	26.69
White	266	251.87
Unknown/Not Given/Missing	116	103.04
Total	650	652.05

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participantss in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a] (continued)

Race	Participants	Participant-Years
Tucatinib +SGNDV		
Asian	1	0.08
Black or African American	0	0
Other	0	0
White	8	1.54
Unknown/Not Given/Missing	0	0
Total	9	1.62

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Table 7. Summary of Tucatinib Treatment Exposure in Participants with Cancer by Race: Safety population[a]

Race	Participants	Participant-Years
All Treatment Regimens Total		
Asian	817	689.83
Black or African American	120	85.13
Other	47	43.19
White	1219	1078.35
Unknown/Not Given/Missing	338	285.53
Total	2541	2182.03

a. Safety population: ARRAY-380-101, ONT-380-004, ONT-380-005, ONT-380-206, SGNTUC-016, SGNTUC-017, SGNTUC-019, SGNTUC-022, SGNTUC-024, SGNTUC-025, SGNTUC-028, SGNTUC-029, MK-7119-001, MK-7119-002, SGNDV-004
CAPOX = capecitabine and oxaliplatin; FOLFOX = fluorouracil, oxaliplatin, and leucovorin/levoleucovorin; T- DM1 = trastuzumab emtansine; SGNDV=disitamab vedotin
Participant-time (years) is calculated for each participant (end of tucatinib treatment date - first dose date + 1)/365.25 and summed for all the participants in the row.
Note: Participants who crossed over to a different tucatinib combination are summarized in a separate category (i.e., they are not counted in their original or post-crossover categories).
Cutoff date: 20 December 2024

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
Participants who have received previous treatment with cumulative dose of doxorubicin >360 mg/m^2 or treatment with another anthracycline with cumulative dose approximately equivalent to >360 mg/m^2 doxorubicin[2]	HER2-directed therapies have the potential to cause cardiotoxicity especially in the elderly when combined with anthracycline-based chemotherapy regimens. Previous exposure to high cumulative doses of anthracyclines may impair cardiac function and may increase risk of cardiotoxicity.	Yes	Not applicable.
Participants who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing	Events of hepatotoxicity were observed in tucatinib studies, but these events and laboratory abnormalities were primarily	Yes	Not applicable.

[2] Exclusion criterion not applicable in study SGNTUC-017/ C4251002 (MOUNTAINEER) which was conducted in patients with HER2+ Metastatic Colorectal Cancer.

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
cholangitis, or other known chronic liver disease	Grades 1 and 2, transient, asymptomatic reversible, and manageable with dose modification. However, the hepatic safety profile in participants with chronic liver conditions is unknown.		
Participants with central nervous system (CNS) disease were excluded if they met any of the following criteria: • Untreated brain lesions >2.0 cm in size unless approved by the study medical monitor • Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total dose of >2 mg of dexamethasone (or equivalent) • Any brain lesion requiring immediate local therapy • Poorly controlled generalised or complex partial seizures or signs of neurologic progression due to brain metastases notwithstanding CNS directed- therapy	At the time of study initiation, the effect of tucatinib on brain metastases was not definitively characterised, and these participants were excluded in case systemic therapy was not adequate for participants with rapidly progressing disease. In addition, cerebral edema was an adverse event of special interest at the time of study initiation, and it was unknown if there was a risk of developing cerebral edema in participants with pre-existing brain metastases.	No	Analysis of data from ONT-380-206 do not indicate that cerebral edema is a risk associated with tucatinib. In addition, participants with brain metastases on the study had a statistically significant and clinically meaningful improvement in progression free survival.
Participants with a history of other malignancy	Due to competing risks of death due to other active cancer, the treatment effect of tucatinib in breast cancer would be confounded. This population was excluded from clinical studies to enable clearer interpretation of data.	No	The safety profile is not anticipated to be different in this population.
Participants with known impaired cardiac function or clinically significant cardiac disease	HER2-directed therapies have the potential to cause cardiotoxicity.	No	The risk of cardiac toxicity has been evaluated in the tucatinib clinical program. QT

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
			prolongation was studied in ONT-380-011 and the effect on LVEF function was studied in ONT-380-206, SGNTUC-017, and SGNTUC-016. The safety profile is not anticipated to be different in this population
Participants known to be human immunodeficiency virus (HIV) positive	Due to competing risks of death due to intercurrent HIV-associated illness, the treatment effect of tucatinib in breast cancer would be confounded	No	The safety profile is not expected to differ in this population.
Participant is pregnant, breastfeeding, or planning a pregnancy	In nonclinical studies, increased resorptions, decreased percentages of live foetuses, and skeletal, visceral, and external malformations were observed in foetuses at doses approximately equivalent to the human exposure at the recommended dose based on AUC. It is not known whether tucatinib is transferred into human milk.	No	Pregnant and lactating women are exclusion criteria in the tucatinib clinical program. Embryo-foetal toxicity has been adequately characterised in nonclinical studies.
Participants that have used a strong cytochrome CYP2C8 or cytochrome CYP3A4 inducer or inhibitor within 3 to 5 elimination half-lives of the inhibitor or inducer prior to the start of tucatinib treatment	Non-clinical studies predict that tucatinib would be metabolized in the human liver primarily by CYP2C8 and CYP3A4. Participants taking a concomitant medication that is a strong CYP2C8 or CYP3A4 inhibitor or inducer were excluded from clinical studies to enable clearer interpretation of data.	No	The safety profile has been adequately characterised in the tucatinib nonclinical and clinical program.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 9. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development program.
Patients with relevant co-morbidities: • Patients with hepatic impairment	A total of 37 participants (0.10 person-years) were exposed to tucatinib in Study ONT-380-009. Participants included those with normal hepatic function (15 participants), mild hepatic dysfunction (8 participants), moderate hepatic dysfunction (8 participants), and severe hepatic dysfunction (6 participants)
• Patients with renal impairment	Not included in the clinical development program because tucatinib is predominantly hepatobiliary eliminated.
• Patients with cardiovascular disease	Not included in the clinical development program.
• Immunocompromised patients	Not included in the clinical development program.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	In the clinical development program, the majority of participants in the clinical development program were either White or Asian (See Table 7).
Subpopulations carrying relevant genetic polymorphisms	Participants enrolled were characterised by a biomarker, not based on genetic testing. Thus, this subpopulation is not applicable to the clinical development program.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

As of the DLP of 20 December2024, post-authorisation use of tucatinib was reported in the countries presented in Table 10.

SV.1.1. Method Used to Calculate Exposure

Methodology

Pfizer has updated the methodology for estimating post-marketing exposure from the methodology presented in the prior RMP version 1.1 dated November 2022. In alignment with the US patient estimates, the international patient exposure calculation now uses the US real-world data ratio of standard units per new patient start (8.2 SU/patient). The standard unit is now 18,000 milligrams, which is a higher monthly dosage than the legacy-Seagen international regional assumptions 16,740 mg/ month. The new calculation also assumes 8.2 SU vs. 6 months of treatment per new patient. Using a higher divisor creates a lower estimate of treated patients per package. This methodology change was made to standardise

calculations of patient estimates across all countries and, to base the ratio of patient/shipped drugs on actual clinical experience taken from US Claims data where accurate.

Of note, following Pfizer's acquisition and integration with Seagen, access to legacy-Seagen databases used to obtain sales data was discontinued. As such, it is not possible to calculate the current post-marketing exposure using legacy-Seagen's methodology.

For US and Canada, cumulative patient exposure through commercial distribution and free drug product was estimated based on the following calculations:

- Tucatinib channel and distribution partners provide anonymised patient level data, allowing for the analysis of a subset of our patients on therapy. Data are not provided for all tucatinib patients, or across all channels. Through this anonymised patient data, the MAH calculates the number of standardised bottles a new tucatinib patient receives when they start therapy in a given period. This is calculated by dividing the number of unique patients starting tucatinib for the first time by the total number of standardised tucatinib bottles dispensed by the entity. For instance, if the channel partner distributed 100 standardised bottles and indicated that 60 patients started tucatinib, the result would be 100 divided by 60, or 1.67 standardised bottles per new patient. Next, the number of standardised bottles per new patient is multiplied against the total number of standardised bottles distributed across all channels not providing anonymised patient level data in the same period. This results in the estimated number of new patients receiving tucatinib in a given period for the channel(s) in which anonymised patient data is not provided. Finally, the number of unique new patients is added from each channel (estimated or provided) into 1 combined estimate of patient exposures.
- Standardised tucatinib bottles are the monthly equivalents, in mg, of the HER2CLIMB regimen that are shipped out to a patient. For instance, 1 bottle containing 6000 mg would equal ~0.33 standardised bottles, in that the HER2CLIMB regimen stipulated 18,000 mg/period. This standardisation allows for multiple National Drug Codes and Stock Keeping Units to be compared equally.

The following calculations were used for rest of the markets, including those covered by Swixx and Genesis distribution partners and Merck:

- Total mg (150 mg pack) = Number of Tablets distributed × 150 mg
- Total mg (50 mg pack) = Number of Tablets distributed × 50 mg

For worldwide consistency, patients are estimated using the real-world clinical experience tracked through Pfizer specialty pharmacy claims. The US ratio of standardised 18,000 bottles per new patient start is used to calculate patients in all countries from the milligrams of tucatinib calculated from shipments to those countries.

From first marketing authorisation on 17 April 2020 through DLP of 20 December 2024, the cumulative number of patients exposed to tucatinib, by country and overall, are presented in Table 10.

Table 10. Estimated Cumulative Product Patient Exposure of Tucatinib

Country/Market	Cumulative Patient Exposure Since Launch through 20 December 2024 (Total Number of Patients Exposed)
US	11,263
France	1772
Germany	1687
Canada	831
Italy	648
Swixx Market[a]	630
United Kingdom	543
Genesis – Greece, Cyprus and Malta	378
Spain	316
Netherlands	191
Switzerland	159
Austria	135
Bahrain/Kuwait/United Arab Emirates[b]	109
Singapore[b]	94
Belgium	90
Saudi Arabia[b]	86
Denmark	48
Portugal	45
Finland	38
Sweden	35
Israel[b]	25
Norway	21
China (Hong Kong SAR)[b]	19
Ireland	17
Australia[b]	10
Argentina[b]	7
Oman/Qatar[b]	3
Luxembourg	1
Iceland	1
Total	**19,202**

SAR=Special Administrative Region

a [redacted] is a distribution partner covering the collection of exposure from the following 11 countries in Central and Eastern Europe: Estonia, Latvia, Lithuania, Poland, Czech Republic, Slovakia, Hungary, Bulgaria, Croatia, Romania, and Slovenia.
b Pfizer data for 1 Oct - 20 Dec 2024; Merck interval data collected from launch through 30 Sep 2024

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

There is no evidence to suggest a potential for drug abuse or misuse in the tucatinib clinical development program. Tucatinib inhibits phosphorylation of HER2 and human epidermal growth factor receptor-3 (HER3), resulting in inhibition of downstream cell-signaling and

cell-proliferation, and induces death in HER2 driven tumour cells. Thus, the mechanism of action is not consistent with pathways typically associated with addiction.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 11. Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Risks with minimal clinical impact on participants (in relation to the severity of the indication treated)	Nausea, vomiting, stomatitis, weight decrease, arthralgia, epistaxis, rash, drug-drug interactions
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	None
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the prescribing information (PI) are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised)	None
Known risks that do not impact the risk-benefit profile	None
Other reasons for considering the risks not important	None

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks 1:

Diarrhoea:

Risk-benefit impact:

Treatment-emergent adverse events (TEAEs) of diarrhoea observed across tucatinib studies were mainly low-grade and manageable with dose modifications and treatment with anti-diarrhoeals on an “as needed” basis. Prophylactic use of anti-diarrhoeals was not required per protocol in most tucatinib studies.

In ongoing studies combining tucatinib with trastuzumab and FOLFOX or with trastuzumab deruxtecan, risk mitigation strategies, including the use of antidiarrhoeal prophylaxis, have been mandated because of 1) a higher rate of diarrhoea events observed (SGNTUC-024), 2) a higher rate of diarrhoea events anticipated given the same combination as SGNTUC-24 (SGNTUC-029), and 3) an increased rate of dose modifications secondary to low-grade gastrointestinal events (nausea and/or vomiting concurrent with diarrhoea) (SGNTUC-025).

In HER2CLIMB, 82% of participants who received tucatinib experienced diarrhoea, including 13% with Grade 3 diarrhoea and 0.5% with Grade 4 diarrhoea. Both participants who developed Grade 4 diarrhoea subsequently died, with diarrhoea as a contributor to death. Diarrhoea led to dose reduction in 6% of participants and treatment discontinuation in 1% of participants.

In MOUNTAINEER (tucatinib in combination with trastuzumab; 64% of participants who received any study treatment experienced diarrhoea; including 3.5% of participants with Grade 3 diarrhoea. No Grade 4 or higher diarrhoea events were reported. Diarrhoea led to tucatinib dose reduction in 2.3% participants. No participants discontinued tucatinib due to diarrhoea.

The risk-benefit impact is considered minimal as adequate risk communication and minimisation measures, including dose modifications, are in place in the SmPC.

Important Identified Risks 2:

Hepatotoxicity:

Risk-benefit impact:

AEs of transaminase and bilirubin elevations have been reported early in tucatinib treatment, and were primarily low-grade, transient, and manageable with dose modifications.

In HER2CLIMB, 6% of participants who received tucatinib had a Grade 3 or higher adverse event (AE) of ALT increase, 5% had a Grade 3 or higher AE of AST increase, and 1.7% had a Grade 3 or higher AE of bilirubin increase. Hepatotoxicity led to dose reduction of tucatinib in 9% of participants and discontinuation of tucatinib in 1.5% of participants.

In MOUNTAINEER (tucatinib in combination with trastuzumab), (any grade) AEs of increased ALT, AST, or bilirubin occurred in 9% of participants who received any study treatment. Grade 3 or 4 events occurred in 4.6% of participants. Hepatotoxicity led to dose reduction of tucatinib in 3.5% participants and discontinuation of tucatinib in 2.3% participants.

The risk-benefit impact is considered minimal as adequate risk communication and minimisation measures, including dose modifications, are in place in the SmPC.

Important Potential Risk 1:

Embryo-foetal toxicity

Risk-benefit impact:

The risk-benefit impact is considered minimal as adequate risk communication and minimisation measures are in place in the SmPC. Prescribers are informed that tucatinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with tucatinib and that the pregnancy status of women of childbearing potential should be verified prior to initiating treatment with tucatinib. Female patients of childbearing potential are advised to avoid becoming pregnant and to use an effective method of

contraception while receiving treatment with tucatinib and for up to 1 week after ending treatment. Male patients with female partners of reproductive potential are advised to use an effective method of contraception while receiving treatment with tucatinib and for at least 1 week after ending treatment.

Missing information 1:

Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin

Risk-benefit impact: Although cardiotoxicity was not seen specifically for tucatinib, HER2-directed therapies have the potential to cause cardiotoxicity, especially in the elderly when combined with anthracycline-based chemotherapy regimens. Cardiotoxicity with tucatinib is not considered a potential risk but there is a possibility that this could potentially be seen in patients with other significantly cardiotoxic chemotherapy agents and therefore the safety profile in this patient population may be different.

Missing information 2:

Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease

Risk-benefit impact: In Study ARRAY-380-101, the dose limiting toxicity of tucatinib as monotherapy was found to be transient, reversible Grade 3 elevation of transaminases. Events of hepatotoxicity have also been observed 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 a study examining tucatinib treatment in participants with mild, moderate, or severe hepatic impairment, the safety profile showed that overall, a single oral dose of tucatinib 300 mg was considered to be safe and well tolerated in participants with normal hepatic function or with mild, moderate, or severe hepatic impairment. The hepatic safety profile is not known in participants with chronic conditions that impact the liver.

Missing information 3:

Long-term safety

Risk-benefit impact: Ongoing clinical trials will provide additional information about the safety of tucatinib with long term use. There is no evidence to suggest a different safety profile with long-term use.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

There were no new safety concerns noted during this RMP.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The characterisation of the important identified and important potential risks are derived from data from 3 clinical trial studies as well as post-marketing data from the Global Safety Database.

The 3 clinical trials used to characterise the important identified and important potential risks are:

- Study ONT-380-206 (HER2CLIMB)/ C4251010. The study is completed and DLP for the final analysis is 12 September 2022.
- Study SGNTUC-017 (MOUNTAINEER)/ C4251002. The study is completed and the DLP for the final analysis 02 November 2023.
- Study SGNTUC-016 (HER2CLIMB-02)/ C4251001 is currently on-going. The DLP used for safety characterisation is 29 June 2023 which aligns with the cut-off of the primary analysis.

The DLP used for the analysis of post-marketing data from the Global Safety Database was 20 December 2024.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Table 12. Important Identified Risk: Diarrhoea

Potential mechanisms	EGFR is highly expressed on colonic epithelial cells and regulates ion transport by EGF driven signaling in EGFR-EGFR homodimers. While HER2 expression is lower, it contributes to this regulation by forming competing EGFR-HER2 heterodimers. Inhibition of signaling by kinase inhibitors disrupts the regulation of ion transport and results in secretory diarrhoea. This type of diarrhoea has a different underlying mechanism than diarrhoea that results from insults such as mucosal damage or inflammation.[47,48,49] Tucatinib is a highly selective HER2 tyrosine kinase inhibitor. Its selectivity for HER2 over EGFR is >1000-fold in cellular assays of phosphorylation inhibition, therefore the ability of tucatinib to inhibit EGFR kinase activity that leads to GI toxicity is expected to be low. Any pharmacology driven GI toxicity after tucatinib treatment would be expected to be due to inhibition of HER2 kinase activity.
Evidence source and strength of evidence	Tucatinib nonclinical, clinical studies and post-marketing data. In the clinical development program, participants who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of diarrhoea events than participants who received trastuzumab and capecitabine alone.
Characterisation of the risk	**Clinical Trial Data:** ***Frequency*** In the HER2CLIMB tucatinib arm of safety population (n=404), 81.9% of participants developed diarrhoea. The majority of diarrhoea events reported were Grade 1 to 2 in severity (68.5%). Grade 3 events were observed in 12.9% and Grade 4 events were

Table 12. Important Identified Risk: Diarrhoea

	observed in 0.5% of participants across this population. Both participants who developed Grade 4 diarrhoea subsequently died, with diarrhoea as a contributor to death. A total of 17 participants (4.2%) developed serious events (any grade). In the MOUNTAINEER study, TEAEs of diarrhea occurred in 66.3% of participants in the tucatinib + trastuzumab cohort. The majority of diarrhoea events reported were Grade 1 (48.8%) and Grade 2 (14.0%). Grade 3 events were observed in 3.5% of participants. No Grade 4 or higher diarrhoea events were reported and no SAEs were reported. In the HER2CLIMB-02 study, TEAEs of diarrhea occurred in 56.7% in the tucatinib +T-DM1 arm. The majority of events were either Grade 1 (35.9%) or Grade 2 (16.0%). Grade 3 diarrhoea occurred in 11 participants (4.8%) in the tucatinib+T-DM1 arm. There were no reported events of Grade ≥ 4 TEAEs. In the tucatinib+T-DM1 arm, there were 3 participants (1.3%) with SAEs of diarrhoea. ***Severity***: Diarrhoea was observed across tucatinib studies. Events were mainly Grades 1 and 2. In the HER2CLIMB tucatinib arm of safety population, the majority of diarrhoea events reported were Grades 1 to 2 in severity. Grade 3 events were observed in 12.9% and Grade 4 events were observed in 0.5% of participants. In MOUNTAINEER (tucatinib in combination with trastuzumab), the majority of diarrhoea events reported were Grades 1 to 2 in severity. Grade 3 events occurred in 3.5% of participants. No Grade 4 or higher diarrhoea events were reported. In the HER2CLIMB-02 tucatinib+T-DM1 arm of the study, the majority of events were Grades 1 to 2 in severity. Grade 3 diarrhoea occurred in 11 participants (4.8%) in the tucatinib+T-DM1 arm. There were no reported events of Grade ≥4 AEs. ***Reversibility***: In non-clinical trials, GI clinical observations, including watery feces were rapidly reversible. In the HER2CLIMB tucatinib arm of safety population, diarrhoea was manageable with dose modifications and treatment with anti-diarrhoeals on an “as needed” basis, and 81.3% of events resolved, with a median time to resolution of 7.5 days. In MOUNTAINEER (tucatinib in combination with trastuzumab), diarrhoea was manageable with dose modifications and treatment with anti-diarrhoeals on an “as needed” basis, and 64.9% of events resolved, with a median time to resolution of 57.0 days. In HER2CLIMB-02 tucatinib+T-DM1 arm, diarrhoea was manageable with dose modifications and treatment with anti-diarrhoeals on an “as needed” basis, and 80.5% of events resolved, with a median time to resolution of 4 days. ***Long-term outcomes*** The onset of diarrhoea was early (median onset was 12.0 days in the HER2CLIMB tucatinib arm), and the incidence of diarrhoea was similar throughout treatment cycles. The majority (81.3%) of events resolved. In MOUNTAINEER (tucatinib in combination with trastuzumab), the onset of diarrhoea was early (median onset was 13.0 days). The majority (64.9%) of events resolved. In HER2CLIMB-02 tucatinib+T-DM1 arm of the study, median time to onset of the first event of diarrhoea was 6 days; the majority (80.5%) of events resolved. The occurrence of diarrhoea is not anticipated to impact long-term outcomes.

Table 12. Important Identified Risk: Diarrhoea

<table>
<tr><td></td><td>

Impact on quality of life

Diarrhoea, mainly severe events, may diminish quality of life.

On the tucatinib arm of the HER2CLIMB study, the majority of the diarrhoea events reported were mild in nature. Diarrhoea events were reported commonly and more frequently on the tucatinib arm compared to the control arm. Diarrhoea led to treatment discontinuation in 1% of participants.

In MOUNTAINEER (tucatinib in combination with trastuzumab), the majority of the diarrhoea events reported were mild in nature. No tucatinib dose discontinuation due to diarrhoea was reported.

In HER2CLIMB-02 tucatinib+T-DM1 arm of the study, the majority of the diarrhoea events reported were mild in nature. TEAEs of diarrhoea led to tucatinib discontinuation in 1 participant (0.4%).

Post-marketing data[3]

Cumulatively through 20 December 2024, there were 803 cases (803/4439; 18.1% of the cumulative post-marketing dataset reporting events coded to the PT Diarrhoea. Of the 803 cases, 717 cases were medically confirmed. The characterisation of these 803 cases is provided below:

MedDRA PT	No. Events	Serious events	H	F	R	RS	NR	U
Diarrhoea	803	91	72	1	176	1	75	557

F= Fatal; H=Hospitalization; NR=Not resolved at the time of the last information received; R =Resolving/Resolved; RS=Resolved with sequelae; U= Unknown at the time of last information received

</td></tr>
<tr><td>Risk factors and risk groups</td><td>No specific risk groups at increased risk for diarrhoea have been identified with tucatinib treatment. Risk factors that could potentially be associated with an increased risk of diarrhoea include antibiotic use, side effects of other medications, intestinal abnormalities, food intolerance, and/or general wasting syndromes associated with cancer.</td></tr>
<tr><td>Preventability</td><td>Events were mainly Grades 1 and 2 and were manageable with dose modifications and treatment with anti-diarrhoeals. Prophylactic use of anti-diarrhoeals was not required per protocol in most tucatinib studies.

In ongoing studies combining tucatinib with trastuzumab and FOLFOX or with trastuzumab deruxtecan, risk mitigation strategies, including the use of antidiarrhoeal prophylaxis, have been mandated because of 1) a higher rate of diarrhoea events observed (SGNTUC-024), 2) a higher rate of diarrhoea events anticipated given the same combination as SGNTUC-24 (SGNTUC-029), and 3) an increased rate of dose modifications secondary to low-grade gastrointestinal events (nausea and/or vomiting concurrent with diarrhoea) (SGNTUC-025).</td></tr>
<tr><td>Impact on the risk-benefit balance of the product</td><td>Based on available information, the risk of diarrhoea with tucatinib treatment does not impact the overall positive benefit-risk balance of the product in the context of oncology care. More data are being collected regarding this risk and any potential impact to the benefit-risk balance will continue to be evaluated.</td></tr>
</table>

[3] The post-marketing data is derived from the Global Safety Database and includes data from serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources.

Table 12. Important Identified Risk: Diarrhoea

Public health impact	Cases of diarrhoea have been reported in participants treated with tucatinib; however, the public health impact is not considered to be high.

Table 13. Important Identified Risk: Hepatotoxicity

Potential mechanisms	HER2 has been shown to be expressed on hepatocytes.[50] Nonclinical studies show no evidence of adverse effects on liver for rats or cynomolgus monkeys treated with tucatinib. Findings of minimal to mild increases in serum liver enzymes and bilirubin were observed in rats and cynomolgus monkeys administered tucatinib. However, there was no histologic evidence of tucatinib-related liver injury associated with these biochemical changes, which is consistent with an adaptive response of the liver caused by induction of enzymes by tucatinib.[51] Non-adverse generally minimal (≤2.5-fold) increases in serum markers of liver injury (including AST, ALT, and bilirubin), liver weight increases, and centrilobular hepatocyte hypertrophy occurred at ≥6 mg/kg/day in rats and ≥20 mg/kg/day in cynomolgus monkeys treated with tucatinib. However, histologically, there was no evidence of liver injury, including no hepatic or biliary degeneration, inflammation, necrosis, fibrosis, or other sequelae of damage in any animal. Monkeys on the 28-day toxicity study euthanized moribund after approximately a week of dosing had histologic liver changes of hepatocyte swelling and rarefaction, but these animals had no evidence of hepatocellular injury and no changes in ALT, AST, and/or bilirubin. Therefore, the nonclinical studies do not show evidence of adverse effects on liver for rats or cynomolgus monkeys treated with tucatinib. Taken together, the generally minimally increased serum enzymes, liver weights, and centrilobular hypertrophy and the lack of histologic evidence of hepatocellular and hepatobiliary injury suggest that increased transaminases are consistent with an adaptive response of the liver caused by induction of enzymes by tucatinib.[51]
Evidence source and strength of evidence	Tucatinib nonclinical, clinical studies and post-marketing sources. In the clinical development program, participants who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of hepatotoxicity events than participants who received trastuzumab and capecitabine alone.
Characterisation of the risk	**Clinical Trial Data:** ***Frequency*** In the HER2CLIMB tucatinib arm of safety population (n=404), 45.0% developed hepatotoxicity, of which, 10.4% were Grade 3 or higher. A total of 2 participants (0.5%) developed serious events (any grade), and there have been no fatal events reported in this population to date. In MOUNTAINEER (tucatinib in combination with trastuzumab), 10.5% of participants developed hepatotoxicity AEs; of which, 4.7% participants were Grade 3 or higher. None of the events was serious and there have been no fatal events reported in this population to date. In HER2CLIMB-02, TEAEs of hepatotoxicity were reported in 56.7% of participants in the tucatinib+T-DM1 arm. The rate of Grade ≥3 hepatotoxicity events was 28.6% which included 1 Grade 5 event; not related to tucatinib by the investigator. Treatment-emergent SAEs of hepatoxicity were reported in 4.3% of participants in the tucatinib +T-DM1 arm. ***Severity****:*

Table 13. Important Identified Risk: Hepatotoxicity

	In the HER2CLIMB tucatinib arm of safety population, the majority of hepatotoxicity events reported were Grades 1 to 2 in severity; 5.9% of participants who received tucatinib had a Grade 3 or higher AE of ALT increase, 5.0% had a Grade 3 or higher AE of AST increase, and 1.0% had a Grade 3 or higher AE of bilirubin increase. In MOUNTAINEER (tucatinib in combination with trastuzumab), ALT/AST/Total bilirubin laboratory elevations relative to baseline were primarily Grade 1 to 2 in severity. Grade 3 or higher increases in ALT, AST, or bilirubin occurred in 3.5%, 2.3%, or 1.2% of participants, respectively. In HER2CLIMB-02 study, in the tucatinib+T-DM1 arm, 24.2% of participants had Grade 3, and 3.9% of participants had Grade 4 hepatotoxicity TEAEs. There was also 1 (0.4%) Grade 5 fatal event (PT Hepatic failure) in the tucatinib+T-DM1 arm. This participant had metastases in the liver and grade 2 AST elevation at baseline and the cause of death was hepatic failure, which was per the investigator related to cirrhosis of the liver (possibly associated with T-DM1) as well as liver metastases and unrelated to treatment with tucatinib. In the tucatinib + T-DM1 arm, Grade 3 or higher increases in ALT or AST occurred in 16.5% of participants and bilirubin increased occurred in 0.4% of participants. ***Reversibility**:* In non-clinical trials, the observations are consistent with an adaptive response of the liver caused by induction of enzymes by tucatinib. The changes were generally minimal and reversible. In the HER2CLIMB tucatinib arm of safety population, hepatotoxicity was manageable with dose modifications and discontinuations with 82.1% of events resolved. In MOUNTAINEER (tucatinib in combination with trastuzumab), hepatotoxicity was manageable with dose modifications, discontinuations, and standard medical care with 62.5% events resolved. Tucatinib dose modifications or discontinuations due to hepatotoxicity events were low (5.8%). In HER2CLIMB-02 tucatinib + T-DM1 arm, hepatotoxicity was manageable with dose modifications, discontinuations, and standard medical care with 73.9% events resolved. Hepatoxicity TEAEs led to treatment discontinuation in 6.9% of participants in tucatinib+T-DM1 arm. ***Long-term outcomes*** The onset of hepatotoxicity AEs was early (median onset 37.0 days in the HER2CLIMB tucatinib arm and median onset 33.0 days in HER2CLIMB-02 tucatinib+T-DM1) and late in MOUNTAINEER (tucatinib in combination with trastuzumab) (median onset 104.0 days) and the majority of events resolved. The occurrence of hepatotoxicity is not anticipated to impact long-term outcomes. ***Impact on quality of life*** Hepatotoxicity, mainly severe events, may diminish quality of life. On the tucatinib arm of the HER2CLIMB study, the majority of the hepatotoxicity events reported were primarily Grade 1 and 2. Hepatotoxicity events were reported commonly and more frequently on the tucatinib arm compared to the control arm. In MOUNTAINEER (tucatinib in combination with trastuzumab), ALT/AST/Total bilirubin laboratory elevations were primarily Grade 1 (36.5%, 24.7%, and 17.6%, respectively) and were generally not clinically significant. Grade 3 or higher AST increased/bilirubin occurred in 5.9% of participants, Grade 3 or higher ALT increased

Table 13. Important Identified Risk: Hepatotoxicity

occurred in 4.8% of participants and there have been no fatal events reported in this population to date.

In HER2CLIMB-02, Hepatotoxicity was very commonly observed in the tucatinib+T-DM1 arm. The overall incidence rate was 56.7%. The frequency of Grade ≥ 3 hepatotoxicity events was 28.6% which included 1 Grade 5 event; not related to tucatinib by the investigator. There was a higher frequency of hepatic events in the tucatinib+T-DM1 arm than in the placebo+T-DM1 arm, mostly increased transaminases which were transient and manageable with dose modifications.

Post-marketing data[3]

Cumulatively through 20 December 2024, there 365 cases reporting (365/4439; 8.2%) of the cumulative post-marketing dataset) reporting events coded to the 517 relevant PTs on the Drug-related hepatic disorders-comprehensive search SMQ (narrow). Of the 365 cases, 336 cases are medically-confirmed. Information for the most frequently (n≥ 2) is provided in the table below.

MedDRA PT	No. Events	Serious events	H	F	R	RS	NR	U
All PTs	**517**	**180**	**43**	**2**	**120**	**1**	**27**	**369**
Alanine aminotrans-ferase increased	40	8	1	0	14	0	3	23
Blood bilirubin increased	61	5	2	0	15	1	5	42
Aspartate aminotrans-ferase increased	40	9	1	0	13	0	5	22
Hepatic enzyme increased	56	6	1	0	9	0	2	45
Liver function test increased	51	5	4	0	6	0	0	45
Hepato-toxicity	30	28	2	0	7	0	0	23
Hyper-bilirubinaemia	27	25	4	0	12	0	2	13
Liver disorder	26	4	4	0	1	0	0	25
Hepatic cytolysis	19	18	2	0	12	0	4	3
Drug-induced liver injury	4	4	1	0	1	0	0	3
Liver function test abnormal	16	1	1	0	1	0	0	15

Table 13. Important Identified Risk: Hepatotoxicity

	Hepatic enzyme abnormal	13	0	0	0	2	0	0	11
	Hepatic function abnormal	9	1	1	0	3	0	0	6
	Blood bilirubin abnormal	12	0	0	0	3	0	0	9
	Ascites	8	6	1	0	1	0	0	7
	Hepatic failure	8	8	2	1	2	0	1	4
	Liver injury	6	5	0	0	0	0	0	6
	Hepatitis	10	10	0	0	2	0	0	8
	Transamin-ases increased	8	3	0	0	4	0	1	3
	Hepatic neoplasm	6	5	0	0	0	0	0	6
	Hypertransa minasaemia	6	0	0	0	2	0	0	4
	Hepatic cancer	5	4	0	0	0	0	0	5
	Cholestasis	4	4	1	0	2	0	1	1
	Gamma-glutamyl-transferase increased	4	1	0	0	1	0	1	2
	Hepatic pain	4	1	1	0	1	0	0	3
	Ocular icterus	4	0	0	0	0	0	0	4
	Hepatic cirrhosis	3	2	2	0	0	0	0	3
	Jaundice	3	1	1	0	0	0	0	3
	Liver function test decreased	3	0	0	0	0	0	0	3
	Alanine aminotrans-ferase abnormal	2	0	0	0	0	0	0	2
	Ammonia increased	2	2	2	0	0	0	0	2
	Aspartate aminotransf erase abnormal	2	0	0	0	0	0	0	2
	Gamma-glutamyl-transferase abnormal	2	0	0	0	0	0	0	2
	Hepatic cyst	2	1	0	0	0	0	1	1

Table 13. Important Identified Risk: Hepatotoxicity

	Hepatic lesion	2	0	0	0	0	0	0	2
	Hepatic steatosis	2	0	0	0	0	0	0	2
	Hepato-cellular injury	2	2	2	0	2	0	0	0
	Portal hyper-tension	2	2	1	0	0	0	0	2
	F= Fatal; H=Hospitalization; NR=Not resolved at the time of the last information received; R =Resolving/Resolved; RS=Resolved with sequelae; U= Unknown at the time of last information received								
Risk factors and risk groups	Although no specific risk groups or risk factors have been identified with tucatinib treatment, patients with prior history of hepatic disease, hepatitis, chronic liver conditions, concomitant administration of agents and medications with known adverse hepatic effects, or impaired hepatic function at baseline may be at increased risk.								
Preventability	Although patients likely to develop hepatotoxicity following exposure to tucatinib cannot be identified, the proposed labeling is sufficient and robust for early and adequate management. Per the SmPC, prescribers are advised to monitor ALT, AST, and bilirubin prior to starting tucatinib, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue tucatinib.								
Impact on the risk-benefit balance of the product	Based on available information, the risk of hepatotoxicity with tucatinib treatment does not impact the overall positive benefit-risk balance of the product. More data are being collected regarding this risk and any potential impact to the benefit-risk balance will continue to be evaluated.								
Public health impact	Cases of hepatotoxicity have been reported in participants treated with tucatinib; however, the public health impact is not considered to be high.								

Table 14. Important Potential Risk: Embryo foetal toxicity

Potential mechanisms	HER2 is essential in embryonic development. Mouse embryos homozygous for the deletion of the Erbb2 gene die on gestational day 10.5 with a lack of trabeculae in the developing heart and defects in the peripheral nervous system.[52] Mouse embryos with a kinase inactivated mutant of Erbb2 have similar findings, demonstrating that the catalytic activity of the HER2 kinase is essential in embryonic development.[53] Tucatinib administered to pregnant dams caused teratogenicity in rabbits and embryo-foetal toxicity in rats. In a preliminary embryo-foetal development study (Study 20144956) in rabbits (6 dams/group), tucatinib caused embryo-foetal toxicity in the absence of significant maternal toxicity. Foetal external and visceral malformations were observed at ≥90 mg/kg/day, including domed heads with severe dilation of the lateral and third ventricles. Other malformations included hyperflexed forepaw, herniated umbilicus, organ malposition, and vascular malformations and variations. The foetal skeletal evaluation showed skeletal malformations. The AUC12h at 90 mg/kg/day in rabbits was approximately the same exposure as participants dosed with the recommended dose of 300 mg

Table 14. Important Potential Risk: Embryo foetal toxicity

	BID. These data indicate that tucatinib is a selective embryo-foetal toxicant in rabbits. In a preliminary embryo-foetal development study in rats (6 dams/group), tucatinib caused embryo-foetal toxicity at a dose that was also toxic to dams. The embryo-foetal toxicity observed in nonclinical species is consistent with the role of HER2 in prenatal development and is similar to toxicity observed with other molecules directed against this target. Based on animal data, embryo-foetal toxicity is an important potential risk for tucatinib treatment. One participant treated in the tucatinib arm of HER2CLIMB reported a pregnancy and underwent elective termination of pregnancy.
Evidence source and strength of evidence	Nonclinical trials and post-marketing data.
Characterisation of the risk	**Clinical Trial Data** The relationship between tucatinib use and embryo-foetal toxicity has not been established in humans. Participants who are pregnant are excluded from all tucatinib clinical trials. Pregnancy testing is required for all women of childbearing potential. Contraception is also mandated for women of childbearing potential and males who have not undergone surgical sterilization and have female partners of childbearing potential. ***Frequency*** On tucatinib arm of HER2CLIMB study, there was one pregnancy reported in a participant who chose to undergo an elective termination of pregnancy. No pregnancies were reported in participants in the MOUNTAINEER (tucatinib in combination with trastuzumab) and HER2CLIMB-02 trial. ***Severity***: Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to be severe. No clinical data are currently available. ***Reversibility***: Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to be irreversible. No clinical data are currently available. ***Long-term outcomes*** Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to have impact on long-term outcomes. No clinical data are currently available. ***Impact on quality of life*** Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to have impact on quality of life. No clinical data are currently available. **Post-marketing data** Cumulatively through 20 December 2024, there were 5 post-marketing cases (all medically confirmed) involving pregnancy. In 2 of the 5 cases the pregnancy/foetal outcome was not reported. The remaining 3 cases reported teratogenicity/congenital anomalies and are described below. In one case a female patient (age unspecified) reported embryo-foetal toxicity (PT Teratogenicity). This case was missing latency, tucatinib dose, details on type of

Table 14. Important Potential Risk: Embryo foetal toxicity

	teratogenicity, information on pregnancy trimester exposure, medical history and concomitant medications which precludes a meaningful assessment of the case. The remaining two cases involved the same pregnancy (mother/foetus cases). The cases involved a 36-year-old female who was receiving tucatinib and co-suspect drugs trastuzumab and capecitabine for breast cancer. The patient had a medical history of prior pregnancy (normal delivery, live child) and spinal metastases. Concomitant medications were not reported. The mother became pregnant during treatment and the foetus was exposed to tucatinib, trastuzumab and capecitabine during the first and second trimesters. The 20-week male foetus experienced hypertelorism, dysmorphism, polydactyly, congenital pulmonary airway malformation, ear malformation and nose deformity. The pregnancy resulted in an elective termination. An autopsy was performed; however, the results were not provided.
Risk factors and risk groups	Risk factors and risk groups include women of childbearing potential, pregnant women, lactating women, and male patients with female partners of childbearing potential.
Preventability	This potential risk is considered preventable with effective contraception measures and avoiding breastfeeding.
Impact on the risk-benefit balance of the product	Impact on the risk-benefit balance is minimal considering the preventability of the risk.
Public health impact	Public health impact is minimal.

SVII.3.2. Presentation of the Missing Information

Table 15. <Missing Information 1> Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin

Evidence source

HER2-directed therapies have the potential to cause cardiotoxicity especially in the elderly when combined with anthracycline-based chemotherapy regimens.

Population in need of further characterisation:

Anticipated risk/consequence of the missing information

Although other HER2-directed therapies, including trastuzumab, have previously demonstrated the potential to cause LVEF decreased, in Study ONT-380-206 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 lowest occurring in the tucatinib monotherapy study.

In participants previously- treated with cumulative dose of doxorubicin >360 mg/m^2 or who have had a previous treatment with another anthracycline with cumulative dose approximately equivalent to >360 mg/m^2 doxorubicin there is a risk for cardiac adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated.

Table 16. <Missing Information 2> Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease

Evidence source

Hepatotoxicity has been evaluated in the tucatinib clinical program with tucatinib monotherapy and in combination with other anti-cancer drugs (trastuzumab, capecitabine, T-DM1).

Anticipated risk/consequence of the missing information

Adverse reactions have been transient, asymptomatic, reversible, and manageable with dose modification. In addition, a study to evaluate the magnitude of any alterations in tucatinib disposition or pharmacokinetics in participants with mild, moderate, and severe hepatic impairment (Study ONT-380-009) was conducted. A total of 3 TEAEs were experienced by 3 of 37 participants in this study; 2 TEAEs were considered Grade 1, and 1 TEAE was considered Grade 2 in severity, and 2 TEAEs were considered related to tucatinib. The Grade 2 TEAE (transaminases increased) was considered related to tucatinib. There was no obvious pattern of association between incidence of TEAEs and hepatic impairment status. Overall, a single oral dose of tucatinib 300 mg was considered to be safe and well tolerated in participants with normal hepatic function or with mild, moderate, or severe hepatic impairment.

Hepatotoxicity is an important identified risk of tucatinib and will be followed up via routine pharmacovigilance activities.

Table 17. <Missing Information 3> Long-term safety

Evidence source

Ongoing clinical trials will provide additional information about the safety with long-term use of the product.

Anticipated risk/consequence of the missing information

The median exposure to tucatinib in the HER2CLIMB trial was 7.4 months (range, <0.1 to 59.4), 29.2% of participants had received at least 12 months of tucatinib treatment, and all participants have had the opportunity to be followed for at least 12 months. Additional pharmacovigilance activities are ongoing for further characterisation.

The median exposure to tucatinib in the MOUNTAINEER trial (tucatinib in combination with trastuzumab) was 7.9 months (range, <0.7 to 64.1). The majority of the participants (55.8%) have received treatment for ≥6 months, including 44.2% who received treatment for ≥9 months, and 38.4% who received treatment for ≥12 months. All participants have had the opportunity to be followed for at least 12 months.

In HER2CLIMB-02, in the tucatinib+T-DM1 arm, the majority of participants (55.4%) received treatment with tucatinib for ≥6 months, including 44.2% who received treatment for ≥9 months, and 31.6% who received treatment for ≥12 months. The median duration of exposure to tucatinib was 7.4 months.

There is no evidence from long-term follow-up in ongoing trials to suggest a different safety profile with long-term use.

Module SVIII. Summary of the Safety Concerns

Table 18. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Diarrhoea Hepatotoxicity
Important potential risks	Embryo-foetal toxicity

Table 18. Summary of Safety Concerns

Summary of Safety Concerns	
Missing information	Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin
	Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease.
	Long-term safety

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADR reporting and signal detection:.

- **Specific adverse reaction follow-up questionnaires for safety concerns:**
  - Tucatinib Hepatoxicity Data Capture Aide
  - Tucatinib Cardiotoxicity Data Capture Aide
- **Other forms of routine pharmacovigilance activities for safety concerns:**

  None.

III.2. Additional Pharmacovigilance Activities

No non-clinical, clinical, epidemiological or post-authorisation safety studies (PASS) are planned at the time of this RMP.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

There are no planned/ongoing additional studies, imposed or required by the competent authority, in the pharmacovigilance plan.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 19. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Diarrhoea	Routine risk communication: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for diagnostic tests to exclude infectious causes are included in SmPC Section 4.4. Other risk minimisation measures beyond the PI: • None
Hepatotoxicity	Routine risk communication: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for liver function monitoring are included in Section 4.4. Other risk minimisation measures beyond the PI: • None
Embryo-foetal toxicity	Routine risk communication: • SmPC Section 4,4, 4.6, and 5.3 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for verification of pregnancy status in females of childbearing potential prior to initiating treatment with tucatinib is included in SmPC Section 4.6 • Recommendation for males and females of reproductive
Missing Information	
Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimization measures beyond the PI: • None

Table 19. Description of Routine Risk Minimisation Measures by Safety Concern

Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	Routine risk communication for hepatotoxicity: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures for hepatotoxicity to address the risk: • Recommendations for liver function monitoring are included in Section 4.4. Other risk minimisation measures beyond the PI: • None
Long-term safety	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the PI: • None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation measures as described in PART V.1 are sufficient to manage the safety concerns of tucatinib.

V.3. Summary of Risk Minimisation Measures

Table 20. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Diarrhoea	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • Recommendation for diagnostic tests clinically indicated to exclude infections causes are included in SmPC Section 4.4. • PL Section 2 and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Hepatotoxicity	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • Recommendation for liver function monitoring are included in SmPC Section 4.4. • PL Section 2, 3, and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Tucatinib (Tukysa) Hepatotoxicity Data Capture Aide Additional pharmacovigilance activities: • None

Table 20. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Embryo-foetal toxicity	Routine risk minimisation measures: • SmPC Section, 4.4, 4.6, and 5.3 • Recommendation for verification of pregnancy status in women of childbearing potential prior to initiating treatment with tucatinib is included in SmPC Section 4.6. • Recommendation for males and females of reproductive potential to use contraception during and up to at least 1 week after treatment is included in SmPC Section 4.6 • PL Section 2 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Tucatinib (Tukysa) Cardiotoxicity Data Capture Aide Additional pharmacovigilance activities: • None
Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • Recommendation for liver function monitoring are included in Section 4.4. • PL Section 2, 3, and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Tucatinib (Tukysa) Hepatotoxicity Data Capture Aide Additional pharmacovigilance activities: • None
Long-term safety	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for TUKYSA®

This is a summary of the risk management plan (RMP) for TUKYSA. The RMP details important risks of TUKYSA, how these risks can be minimized, and how more information will be obtained about TUKYSA's risks and uncertainties (missing information).

TUKYSA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TUKYSA should be used

This summary of the RMP for TUKYSA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TUKYSA's RMP.

I. The medicine and what it is used for

TUKYSA is authorised in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally-advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens. It contains tucatinib as the active substance and it is given orally.

Further information about the evaluation of TUKYSA's benefits will be found in tucatinib's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage once approved.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TUKYSA, together with measures to minimise such risks and the proposed studies for learning more about TUKYSA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to participants and healthcare professionals, such as warnings, precautions, and advice on correct use;

- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including period safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of tucatinib is not yet available, it is listed under 'missing information' below

II.A List of Important Risks and Missing Information

Important risks of TUKYSA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Important identified risks are concerns for which there is sufficient proof of a link with the use of tucatinib. Important potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Diarrhoea
	Hepatotoxicity
Important potential risks	Embryo-foetal toxicity
Missing information	Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin
	Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease
	Long-term safety

II.B Summary of Important Risks

Table 21. Important identified risk: Diarrhoea

Evidence for linking the risk to the medicine	Tucatinib nonclinical and clinical studies In the clinical development program, participants who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of diarrhoea events than participants who received trastuzumab and capecitabine alone.
Risk factors and risk groups	No specific risk groups at increased risk for diarrhoea have been identified with tucatinib treatment. Risk factors that could potentially be associated with an increased risk of diarrhoea include antibiotic use, side effects of other medications, intestinal abnormalities, food intolerance, and/or general wasting syndromes associated with cancer.

Table 21. Important identified risk: Diarrhoea

Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for diagnostic tests clinically indicated to exclude infectious causes are included in SmPC Section 4.4. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table 22. Important identified risk: Hepatotoxicity

Evidence for linking the risk to the medicine	Tucatinib nonclinical and clinical studies In the clinical development program, participants who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of hepatotoxicity events than participants who received trastuzumab and capecitabine alone.
Risk factors and risk groups	Although no specific risk groups or risk factors have been identified with tucatinib treatment, patients with prior history of hepatic disease, hepatitis, chronic liver conditions, concomitant administration of agents and medications with known adverse hepatic effects, or impaired hepatic function at baseline may be at increased risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for liver function monitoring are included in SmPC Section 4.4. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table 23. Important potential risk: Embryo-foetal toxicity

Evidence for linking the risk to the medicine	Non-clinical trials
Risk factors and risk groups	Risk factors and risk groups include women of childbearing potential, pregnant women, lactating women, and male patients with female partners of childbearing potential.

Table 23. Important potential risk: Embryo-foetal toxicity

Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, 4.6, and 5.3 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for verification of pregnancy status in women of childbearing potential prior to initiating treatment with tucatinib is included in SmPC Section 4.6 • Recommendation for males and females of reproductive potential to use contraception during and up to at least 1 week after treatment is included in SmPC Section 4.6 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table 24. Missing information: Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin

Risk minimisation measures	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the PI: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table 25. Missing information: Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease

Risk minimisation measures	Routine risk communication for hepatotoxicity: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures for hepatotoxicity to address the risk: • Recommendations for liver function monitoring are included in Section 4.4 Other risk minimisation measures beyond the PI: • None

Table 25. Missing information: Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Table 26. Missing information: Long-term safety

Risk minimisation measures	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the PI: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TUKYSA.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for tucatinib.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Table of contents

REFERENCES

[1] Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356-87.

[2] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-49.

[3] Arnold M, Morgan E, Rumgay H et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. The Breast 2022; 66:15-23.

[4] Kim J, Harper A., McCormack V et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries. Nat Med 2025; 31:1154-1162.

[5] Giaquinto AN, Sung H, Miller KD et al. Breast Cancer Statistics, 2022. Ca Cancer J Clin 2022; 72:524-541.

[6] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(1):7-34.

[7] Hurvitz SA, Dalenc F, Campone M, et al. A phase 2 study of everolimus combined with trastuzumab and paclitaxel in patients with HER2-overexpressing advanced breast cancer that progressed during prior trastuzumab and taxane therapy. Breast Cancer Res Treat 2013;141(3):437-46.

[8] Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Cancer Fact Sheets, Breast. Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today, Accessed: 12 Nov, 2019. 2019.

[9] Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177 82.

[10] Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer. 2004;5(1):63-9

[11] Cronin KA, Harlan LC, Dodd KW, Abrams JS, Ballard-Barbash R. Population-based estimate of the prevalence of HER-2 positive breast cancer tumors for early stage patients in the US. Cancer Invest. 2010;28(9):963-8.

[12] Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical

Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med. 2014;138(2):241-56.

[13] Loibl S, Gianni L. HER2-positive breast cancer. Lancet. 2017;389(10087):2415-29.

[14] American Cancer Society. Breast cancer facts & figures (2017-2018). 2018a. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-andstatistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf. Accessed: Dec 12, 2019.

[15] Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. Adolescents and young adults with breast cancer have more aggressive disease and treatment than patients in their forties. Ann Surg Oncol. 2019;26(12):3920-30.

[16] Johansson ALV, Trewin CB, Hjerkind KV et al. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. Int J Cancer. 2019; 144(6):1251-61.

[17] Inwald EC, Koller M, Klinkhammer-Schalke M, et al. 4-IHC classification of breast cancer subtypes in a large cohort of a clinical cancer registry: use in clinical routine for therapeutic decisions and its effect on survival. Breast Cancer Res Treat. 2015;153(3):647-58.

[18] Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst.2014;106(5):dju055.

[19] Ferlay J, Ervik M, Lam F et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed [8 April 2025]

[20] Gathani T, Ali R, Balkwill A, et al. Ethnic differences in breast cancer incidence in England are due to differences in known risk factors for the disease: prospective study. Br J Cancer. 2014;110(1):224-9.

[21] Wu Q, Li J, Zhu S, et al. Breast cancer subtypes predict the preferential site of distant metastases: a SEER based study. Oncotarget. 2017;8(17):27990-6.

[22] Gathani T, Kan SW, Sweetland S et al. Ethnicity and breast cancer incidence in over 329,500 women in England in 2011-2019. Eur J of Surg Oncol. 2025 Jan 6:109585. doi: 10.1016/j.ejso.2025.109585.

[23] National Cancer Institute. Breast cancer risk in American women. 2019. https://www.cancer.gov/types/breast/risk-fact-sheet Accessed: Nov 12, 2019.

[24] American Cancer Society. Breast cancer facts & figures (2022-2024). 2022. https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html Accessed: Nov 8, 2022.

[25] Nelson HD, Zakher B, Cantor A et al. Risk factors for breast cancer in women aged 40 to 49 years. Ann Intern Med. 2012; 156:635-648.

[26] Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2012;379(9816):633-40.

[27] Swain SM, Kim SB, Cortes J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013;14(6):461-71.

[28] Cortes J, Kim SB, Chung SA et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 2022; 386:1143-54.

[29] National Comprehensive Cancer Network Guidelines in Oncology: Breast Cancer Version 1.2025- January 31, 2025. Accessed in April 2025.

[30] ESMO Metastatic breast cancer living guide. Ann Oncol 2021; 32(12):1475-1495.

[31] Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.

[32] Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(6):732-42.

[33] Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355(26):2733-43.

[34] Blackwell KL, Miles D, Gianni L, et al. Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2- positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and taxane. J Clin Oncol. 2012;30(18 Suppl 1):Abstract LBA1.

[35] Giordano SH, Elias AD, Gradishar WJ. NCCN Guidelines updates: breast cancer. J Natl Compr Canc Netw. 2018;16(5s):605-10.

[36] American Cancer Society. Global cancer facts & figures 4th edition. 2018b. https://www.cancer.org/research/cancer-facts-statistics/global.html Accessed: Nov 12, 2019.

[37] Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000- 14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391(10125):1023-75.

[38] De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014;15(1):23-34.

[39] Christiansen P, Bjerre K, Ejlertsen B et al. Mortality rates among early-stage hormone receptor-positive breast cancer patients: A population-based cohort study in Denmark. J Natl Cancer Inst 2011;103:1363-1372.

[40] Ess SM, Herrmann C, Bouchardy C, et al. Impact of subtypes and comorbidities on breast cancer relapse and survival in population-based studies. Breast. 2018;41:151-8.

[41] Ewertz M, Land LH, Dalton SO, Cronin-Fenton D, Jensen MB. Influence of specific comorbidities on survival after early-stage breast cancer. Acta Oncol. 2018;57(1):129-34.

[42] Dumas E. Grandal Rejo B, Gougis P et al. Concomitant medication, comorbidity and survival in patients with breast cancer. Nat Comm. 2024 Apr 5;15(1):2966. doi: 10.1038/s41467-024-47002-3.

[43] Connor AE, Schmaltz Cl, Jackson-Thompson J et al. Comorbidities and the risk of cardiovascular disease mortality among racially diverse patients with breast cancer. Cancer. 2021 Aug 1;127(15):2614-2622. doi: 10.1002/cncr.33530.

[44] Nyrop KA, Damone EM, Deal AM et al. Obesity, comorbidities, and treatment selection in Black and White women with early breast cancer. Cancer. 2021 Mar 15;127(6):922-930. doi: 10.1002/cncr.33288.

[45] Ng HS, Vitry A, Koczwara B et al. Patterns of comorbidities in women with breast cancer: a Canadian population-based study. Cancer Causes & Control. 2019: 30:931-941.

[46] Ng HS, Koczwara B, Roder DM et al. Comorbidities in Australian women with hormone-dependent breast cancer: a population-based analysis. Med J Aust. 2018 Jan 15;208(1):24-28.

[47] Duan T, Cil O, Thiagarajah JR, Verkman AS. Intestinal epithelial potassium channels and CFTR chloride channels activated in ErbB tyrosine kinase inhibitor diarrhea. JCI Insight. 2019;4(4):126444.

[48] Rugo HS, Di Palma JA, Tripathy D, et al. The characterization, management, and future considerations for ErbB-family TKI-associated diarrhea. Breast Cancer Res Treat. 2019;175(1):5-15.

[49] Van Sebille YZA, Gibson RJ, Wardill HR, Bowen JM. ErbB small molecule tyrosine kinase inhibitor (TKI) induced diarrhoea: chloride secretion as a mechanistic hypothesis. Cancer Treat Rev. 2015;41(7):646-52.

[50] Yan H, Endo Y, Shen Y, et al. Ado-trastuzumab emtansine targets hepatocytes via human epidermal growth factor receptor 2 to induce hepatotoxicity. Mol Cancer Ther. 2016;15(3):480-90.

[51] Hall AP, Elcombe CR, Foster JR, et al. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes--conclusions from the 3rd International ESTP Expert Workshop. Toxicol Pathol. 2012;40(7):971-94.

[52] Lee KF, Simon H, Chen H, et al. Requirement for neuregulin receptor erbB2 in neural and cardiac development. Nature. 1995;378(6555):394-8.

[53] Chan R, Hardy WR, Laing MA, Hardy SE, Muller WJ. The catalytic activity of the ErbB-2 receptor tyrosine kinase is essential for embryonic development. Mol Cell Biol. 2002;22(4):1073-8.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Follow-up forms

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.