EU Risk Management Plan (Version 14.2)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

EU Risk Management Plan for selpercatinib (LOXO-292)

RMP version to be assessed as part of the application: 14.2

Data lock point for this RMP: 13 January 2023: Study JZJA (LIBRETTO-001) and Study JZJJ (LIBRETTO-121); 01 May 2023: Study JZJC (LIBRETTO-431); 22 May 2023: Study JZJB (LIBRETTO-531).

Date of final sign off: Approval date on Page 1

Rationale for submitting an updated RMP: This RMP was updated to make corrections in response to a request from EMA and to consolidate the content between EU RMP Version 11.1 and the current EU RMP Version 13.1.

Summary of significant changes in this RMP: Parts I and II were updated with the most up to date data from RMP version 11.1, in order to consolidate the content between EU RMP version 11.1 and the current EU RMP version 13.1.

Other RMP versions under evaluation

None

Details of the currently approved RMP

Version number: 13.1

Approved with procedure: EMEA/H/C/005375/II/0031

Date of approval (opinion date): 27 February 2025

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

Table of Contents

List of Tables

List of Abbreviations

Terms	Definition
ADR	adverse drug reaction
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anaplastic thyroid cancer
AUC	area under the concentration versus time curve
BID	twice daily
C_{max}	maximum observed drug concentration
ECG	Electrocardiogram
EGFR	epidermal growth factor receptor
EMA	Europeans Medicines Agency
EPAR	electronic public assessment report
FTC	follicular thyroid cancer
GGT	gamma-glutamyl transferase
GLOBOCAN	global cancer incidence, mortality, and prevalence
IARC	International Agency for Research on Cancer
MEN	multiple endocrine neoplasia
MET	mesenchymal epithelial transition factor
MKI	multikinase inhibitor
mPFS	median progression-free survival
MTC	medullary thyroid cancer
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
ORR	objective response rate
OS	Overall survival
PD-L1	programmed cell death ligand 1
PDTC	poorly differentiated thyroid carcinoma
PFS	progression-free survival

Terms	Definition
PTC	papillary thyroid cancer
PY	patient-year
QTc	corrected time from the start of the Q wave to the end of the T wave interval
RET	REarranged during Transfection
RMP	risk management plan
ROS1	c-ros oncogene 1
RTK	receptor tyrosine kinase
SAE	serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SmPC	summary of product characteristics
TC	thyroid cancer
TEAE	treatment-emergent adverse event
VEGFR2	vascular endothelial growth factor receptor 2

Part I: Product Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Selpercatinib (LOXO-292; LY3527723)
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical)	L01EX22
Marketing authorisation Applicant	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	1 Selpercatinib
Invented name(s) in the European Economic Area (EEA)	RETSEVMO™
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Selpercatinib is a small molecule competitive inhibitor of RET RTK
	Summary of mode of action: RET is an RTK with critical roles in normal kidney and enteric nervous system development along with roles in maintenance of several adult tissue types. RET receptors are transmembrane glycoproteins which rely on GFR-alpha coreceptors, once bound by ligand, to mitigate *RET* dimerisation and subsequent auto-phosphorylation of intercellular tyrosine residues. Upon auto-phosphorylation, key adaptor proteins are recruited to the RET intracellular domain activating a plethora of signal transduction pathways involved in cellular proliferation. Genetic alterations in the *RET* gene, by either chromosomal rearrangement or point mutation, endow the protein with constitutive active kinase activity giving it oncogenic potential. Furthermore, increased expression of *RET* may also contribute to the growth and survival of some human cancers. Selpercatinib is a small molecule that was designed to block the adenosine triphosphate binding site of the RET RTK competitively, preventing constitutive active or overactive kinase activity.
	Important information about its composition: The synthesis of selpercatinib uses 3 starting materials and consists of 4 steps to produce the crystalline free base form of selpercatinib that will be used for human dosing. Selpercatinib has a molecular weight of approximately 500 g/mol.
Hyperlink to the product information	The proposed PI, • reflecting the results of the 104-week carcinogenicity study, is provided in this submission.

Indications in the EEA	**Current:** RETSEVMO (selpercatinib) as monotherapy is indicated for the treatment of adults with advanced *RET* fusion-positive NSCLC not previously treated with a *RET* inhibitor. RETSEVMO as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with • advanced RET fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate), and • advanced *RET*-mutant MTC. RETSEVMO as monotherapy is indicated for the treatment of adults with advanced *RET* fusion-positive solid tumours, when treatment options not targeting *RET* provide limited clinical benefit or have been exhausted (see Sections 4.4 and 5.1).
Dosage in the EEA	**Current:** Recommended dosage in adults and paediatric patients aged 12 years and older is based on weight: • Less than 50 kg: 120 mg orally twice daily • 50 kg or greater: 160 mg orally twice daily
Pharmaceutical form(s) and strengths	**Current:** Capsules (simple blend): Provided in a simple blend with excipients in a capsule in dose strengths of 40 and 80 mg. Tablet: Provided as round, immediate-release, film-coated tablets in strengths of 40, 80, 120, and 160 mg
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: EEA = European Economic Area; GDNF = glial derived neurotrophic factor; GFR-alpha = GDNF family receptor alpha; INN = International Non-proprietary Name; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PI = package insert; *RET* = REarranged during transfection; RMP = risk management plan; RTK = receptor tyrosine kinase; SOB = Specific Obligation; T = thyroid cancer.

Part II: Safety Specification

Module SI - Epidemiology of the Indications and Target Populations

SI.1 RET Fusion-Positive Solid Tumours

The traditional approval pathway for 1 cancer type has been changing over the past years. In recent years, precision medicine has led to biomarker-based indications and approval based on biomarker status regardless of tumour site or histology (tissue-agnostic). The requirement generally raised for any tumour agnostic drug development is to have a strong biological rationale (Dittrich 2020). Successes of tissue-agnostic approaches are evident, for example, the high objective response rates (ORRs) of 57 to 75% seen for NTRK inhibitors across multiple tumour types. More recently in tissue-agnostic studies targeting RET fusions, ORRs of approximately 70% were reported when RET inhibitors were administered (Adashek et al. 2021). Assuming a poor prognosis in patients with *RET*-altered tumours but promising early results based on the ORR; tissue-agnostic approvals would be beneficial for this sub-type (Pietrantonio et al. 2018; Myer et al. 2022). RET is an RTK critical to development of the enteric nervous system and kidneys. Alterations in *RET* have been implicated in the pathogenesis of several human cancers, including NSCLC, thyroid cancer, and MTC, among other tumour types. *RET* gene fusions occur most commonly in lung cancer (approximately 1% to 2% of NSCLCs), PTC, and PDTC (approximately 5% to 10% of PTCs and PDTCs), and in extremely rare subsets of other cancers, including breast, colon, oesophageal, ovarian, prostate, stomach, pancreatic, salivary gland cancers, and sarcomas (most occurring at rates of less than 1%) (GENIE cBIO Portal, Kato et al. 2017; Davis et al. 2020; Kohno et al. 2020; Santoro et al. 2020).

Multiple lines of evidence suggest that RET fusions are activating genomic events leading to oncogenic addiction regardless of the tumour type in which they arise. RET fusions cause transformation in vitro and in vivo and promote cell proliferation and survival when expressed in human cancer cell lines. They also display the hallmark feature of oncogene addiction and their inhibition in RET fusion patient-derived cancer models leads to tumour cell death. These characteristics and effects have been observed for RET fusions in both in vitro and in vivo models for a range of tumour types, including thyroid, lung, colorectal, pancreatic, and breast cancers, as well as mammary adenocarcinoma and melanoma (Takahashi et al. 1985; Portella et al. 1996; Ohshima et al. 2010; Matsubara et al. 2012; Saito et al. 2014; Stranksy et al. 2014; Drilon et al. 2018; Gozgit et al. 2018; Paratala et al. 2018; Subbiah et al. 2018). Consistent with this observation, RET fusions in tumours identified from patients almost always appear mutually exclusive of other known validated oncogenic drivers, a pattern shared by other bona fide cancer drivers (Farago and Azzoli 2017). The tissue-agnostic indication requires specific diagnostic measures to identify respective RET-fusion alterations, thus achieving the targeted approach for the epidemiology of the population is rather difficult and non-represented in literature.

SI.1.1 Incidence

RET fusions are not extensively studied in solid tumours aside from lung and thyroid cancers (Li et al. 2019). The incidence of the totality of patients with *RET* fusion-positive tumours is poorly described in literature. Limited studies suggest that the incidence of *RET* rearrangements vary widely (2.6% to 70%) (Belli et al. 2021).

SI.1.2 Prevalence

The prevalence of the totality of patients with *RET* fusion-positive tumour is poorly described in literature. Most studies describe the prevalence associated with different indications.
Kato et al. identified *RET* alterations. Among diverse cancer types, *RET* aberrations were identified in 88 cases [1.8% (88/4871)], with mutations being the most common alteration [38.6% (34/88)], followed by fusions [30.7% (27/88), including a novel sequestome1-*RET*] and amplifications [25% (22/88)] (Kato et al. 2017). Ferrara et al. (2017) described an estimated prevalence of *RET* fusion gene between 0.9% to 1.8% in lung adenocarcinoma and 6% to 14% in adenocarcinomas WT (wild type) for other molecular drivers.

Changes in *RET* expression are not common and have been discovered in 30% to 70% of invasive breast cancers and 50% to 60% of pancreatic ductal adenocarcinomas in addition to colorectal adenocarcinoma, melanoma, small-cell lung cancer, neuroblastoma, and small intestine neuroendocrine tumours (Kato et al. 2017; Li et al. 2019b). *RET* did additionally identify RET fusion expression in small cohorts of

- lung carcinosarcoma (16.7%)
- ovarian epithelial carcinoma (1.9%)
- salivary gland adenocarcinoma (3.2%)
- pancreatic ductal adenocarcinoma (0.6%), and
- carcinoma of unknown primary origin (0.7%).

RET aberrations were also identified in 0.2% to 1.6% of all colorectal carcinomas, and *RET* rearrangements were detected in 0.16% of breast cancers (Kato et al. 2017; Li et al. 2019b). Shi et al. (2022) identified that prevalence of functional *RET* fusions was

- 1.05% in lung cancer
- 6.03% in thyroid cancer
- 0.39% in colorectal cancer, and
- less than 0.1% in gastric cancer and hepatocellular carcinoma.

Kato et al. (2017) described the *RET* aberrations and associated cancer diagnosis. Overall, *RET* aberrations were identified in 88 cases [1.8% (88/4,871)].

Limited information from European sources is widely available as follows:

- in 1 Swiss study, Kovac et al. (2021) reported 5 osteosarcomas (5/124, 4%) carried at least 6 additional copies of *RET*, and
- in another large cohort study including Switzerland, the Netherlands and Australia, rearrangement of the *RET* gene was found in 3 cases of pancreatic cancer (7.5%) (Chou et al. 2020).

SI.1.3 Demographics of the Population in the Indication – Age, Gender, Racial and/or Ethnic origin, and Risk Factors for the Disease

The demographics of the totality of patients with *RET* fusion-positive solid tumours are not well-described in literature. Myer et al. (2022) identified frequencies of *RET* fusion and alteration in Africans and Europeans with colorectal cancer.

SI.1.4 Main Existing Treatment Options

Patients with other advanced or metastatic *RET* fusion-positive solid tumour, for example, colon, pancreatic, salivary gland, or breast cancers and soft tissue sarcoma may have established, approved, or both standards of care in early treatment lines. These may vary widely between tumour types and may include surgical resection, radiation therapy, systemic therapy, or combinations of multiple modalities. Systemic therapies can range from oral tyrosine kinase inhibitors or hormone therapy to immunotherapy to multiagent chemotherapy regimens. Differences in standards also exist geographically but recommended or approved regimens are readily available through different treatment guidelines published by relevant medical organisations and cooperative groups, for example, ESMO resources page [WWW] NCCN resources page [WWW]. Alternately, some patients with *RET* fusion-positive solid tumour, for example, cancer of unknown primary origin, certain skin cancers, and histiocytosis may not have established, approved, or both standards of care due to their rarity.

With the emergence of next-generation sequencing tools, cancer genomic data have become more widely available, and cancer therapy has shifted from a purely histology-based approach towards incorporating a precision medicine-based approach. Novel oncogenic drivers and biomarkers have been described across different tumour types, leading to the development of targeted therapies and the design of innovative trials, many of which are evaluating tissue-agnostic therapies (Weis et al. 2021).

SI.1.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

The natural history, including mortality and morbidity of the totality of patients with *RET* fusion-positive tumour is not well-described in literature. However, based on the limited literature available for *RET* fusion-positive solid tumours, including NSCLC, thyroid, pancreatic, and colon cancer, there is no indication that the course of the disease would be meaningfully different to the non-*RET* population.

SI.1.6 Important Co-morbidities

The co-morbidities of the totality of patients with *RET* fusion-positive tumour are not well-described in literature. Information pertaining to NSCLC and thyroid cancer populations is described in the sections below. However, based on the limited literature available for *RET* fusion-positive solid tumours including NSCLC, thyroid, pancreatic, and colon cancer, there is no indication that the important co-morbidities would be meaningfully different to non-RET population.

SI.2 RET Fusion-Positive Non-Small Cell Lung Cancer

Approximately 85% to 90% of lung cancers are NSCLC and include 3 main subtypes: squamous cell carcinoma, adenocarcinoma, and large cell (undifferentiated) carcinoma (Perez-Moreno et al. 2012; ESMO 2019). From all NSCLC cases, approximately 1% to 2% are expected to harbour a chromosomal rearrangement that produces a *RET* gene fusion and subsequently an oncogenically activated *RET* RTK (Kohno et al. 2013; Kato et al. 2017; Ferrara et al. 2018). Patients with *RET* fusion-positive lung cancer have identifiable clinicopathologic characteristics, including

- young age
- females
- have never smoked
- early lymph node metastases
- poorly differentiated cancer, and
- solid predominant cancer subtype.

The *RET* fusions tend to be mutually exclusive to other lung cancer drivers (Planchard et al. 2019), suggesting that it might also be a targetable oncogenic driver (Bronte et al. 2019).

SI.2.1 Incidence

Lung cancer is the most diagnosed cancer worldwide, with approximately 2.5 million diagnoses in 2022, contributing 12.4% of the total cancer cases (IARC 2022a). Lung cancer is responsible for the highest number of deaths due to cancer worldwide (Sung et al. 2021). Globally, the age-standardised incidence rate of lung cancer in 2022 was 23.6 per 100 000. The worldwide age-standardised incidence rate of lung cancer was the highest with 68.0 cases per 100 000 among men in Turkey and 35.0 cases per 100 000 among women in Hungary (IARC 2022a).

In the EU countries, lung cancer is the second most diagnosed cancer among men, and the third most diagnosed cancer among women. In 2022, about 320 000 people in the EU countries were newly diagnosed with lung cancer (OECD 2022). In fact, 319 236 new cases (203 029 in men and 116 207 in women) were reported in 2022, accounting for 14% of all new cancer diagnoses in men and 9% in women (OECD 2022).

The GLOBOCAN reported age-standardised incidence rates for all types of lung cancer per 100 000 cases and the 5-year prevalence number for the year 2022 in the regions shown in Table SI.1 (IARC 2022b).

The age-standardised incidence rate in 2022 for all types of lung cancer was 24.1 (Australia), 32.4 (Canada), 40.8 (China), and 30.5 (Japan) per 100 000 (IARC 2022b).

Table SI.1. Age-standardised Incidence Rates and 5-Year Prevalence of Lung Cancer 2022: GLOBOCAN

Age-standardised Incidence Rates (per 100 000)	5-Year Prevalence number, Both Sexes, N (% Global Distribution among Prevalent Cases)
• World: Male, 31.5; Female, 14.6Polynesia: Male, 54.7; Female, 21.3 • Eastern Asia: Male, 51.4; Female, 28.4 • Eastern Europe: Male, 49.8; Female, 11.9 • Micronesia: Male, 46.1; Female, 19.2 • Southern Europe: Male, 40.8; Female, 16.6 • Western Europe: Male, 39.6; Female, 24.0 • Western Asia: Male, 38.8; Female, 9.3 • Northern America: Male, 33.8; Female, 30.4 • Northern Europe: Male, 30.6; Female, 25.9 • Australia/New Zealand: Male, 28.0; Female, 21.6 • Southern Africa: Male, 25.7; Female, 10.4 • South-Eastern Asia: Male, 26.0; Female, 9.6 • Caribbean: Male, 23.1; Female, 13.5 • Northern Africa: Male, 20.6; Female, 3.8 • South America: Male, 17.9; Female, 10.5 • Melanesia: Male, 15.3; Female, 8.1 • South-Central Asia: Male, 9.9; Female, 3.5 • Central America: Male, 7.3; Female, 3.9 • Eastern Africa: Male, 3.9; Female, 2.7 • Middle Africa: Male, 3.2; Female, 1.6 • Western Africa: Male, 2.6; Female 1.6	• World: 2 480 675 (100) lung 1st • Africa: 49 831 (2.0) • Asia: 1 566 355 (63.1) • Oceania: 17 593 (0.71) • Europe: 484 306 (19.5) • Northern America: 257 284 (10.4) • Latin America and Caribbean: 105 306 (4.2)

Abbreviations: % = percentage; GLOBOCAN = Global Cancer Incidence, Mortality and Prevalence; IARC = International Agency for Research on Cancer; N = number.
Source: IARC 2022.

In NSCLC, the main potentially targetable chromosomal rearrangements involve the *ALK*, *ROS1*, *NTRK*, and *RET* proto-oncogene genes. Although these chromosomal rearrangements are rare and represent a small percentage of patients with lung cancer (1% to 2% for *RET*), considering that approximately 2.2 million new lung cancer cases are reported annually , the implications for treating these patients are far-reaching (IARC 2022a).

With an estimated 226 033 patients having developed lung cancer in the US in 2022 and assuming that 90% of these new cases are NSCLC (203 430), the incidence of new cases of *RET* fusion protein (*RET* approximately1% to 2% of NSCLC) lung cancer was expected to be approximately 2034 to 4069 per year (IARC 2022c; Roskoski and Sadeghi-Nejad 2018). In 2022, approximately 319 236 people in the EU countries were expected to be newly diagnosed with lung cancer (OECD 2022/EU 2022). Assuming 90% of new cases were NSCLC (287 312) and *RET* fusions are present in worldwide 1% to 2% of patients with NSCLC, the incidence of new cases of *RET* fusion-positive lung cancer is expected to be around 2873 to 5746 per year (Nakaoku et al. 2018; ESMO 2019; Belli et al. 2021).

SI.2.2 Prevalence

Lung cancer prevalence has been rising over the past 50 years. This increase is caused mainly by 2 factors that can enhance each other, tobacco smoking prevalence (phases of the tobacco epidemic) and population ageing (Didkowska et al. 2016). In 2022, the IARC published the 5-year prevalence of lung cancer for both sexes presented in Table SI.1 (IARC 2022a).
The 5-year (all ages) prevalence of lung cancer was: 17 112 cases in Australia, 32 961 cases in Canada, 883 100 cases in China, and 216 629 cases in Japan (IARC 2022a).

SI.2.3 Demographics of the Population in the Authorised Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Age, gender, and race

Age, gender, and race are important risk factors for lung cancer, with middle-aged and elderly persons (aged 55 to 84 years) comprising approximately 80% of cases (Howlader et al. 2018). The average age of lung cancer patients at diagnosis in the EU ranged from 69.0 years in Denmark to 71.8 years in the UK (Walters et al. 2013). More than 90% of incident lung cancer patients in the US between 2011 and 2015 were aged 55 years or older (21.7% aged 55 to 64 years; 33.4% aged 65 to 74 years; 26.8% aged 75 to 84 years; and 9.4% older than 84 years), with a median age at diagnosis of 70 years (Noone et al. 2018).

NSCLC is extremely rare in children and adolescents. The number of children and adolescents who have NSCLC is unknown (NORD 2019).

Lung cancer incidence among men generally exceeds that in women, with male/female gender ratios ranging from 2.44 to 1 in Europe, 1.27 to 1 in Denmark, 1.35 to 1 in England, and 4.67 to 1 in the Netherlands (Janssen-Heijnen et al. 1998; Ferlay et al. 2013; Kærgaard Starr et al. 2013; Khakwani et al. 2013). In the US, Hispanics have the lowest annual incidence rates of lung cancer, 34.1 and 23.2 (per 100 000) for men and women, respectively, as compared with Black men (81.1) and White women (50.2) (Noone et al. 2018). In their meta-analysis, Lin C et al. (2015), concluded that the *RET* fusion gene was identified at significant higher frequencies in female (odds ratio: 0.55, 95% confidence interval: 0.35 to 0.85) than male patients.

Risk factors

Smoking is by far the leading risk factor for NSCLC (Alberg and Samet 2003). On average, smokers are at a 5- to 10-fold increased risk of developing lung cancer compared with non-smokers (LCA 2019). Per Ettinger et al. (2010), the risk for lung cancer correlates with

- the number of cigarettes smoked per day
- lifetime duration of smoking
- age at onset of smoking
- degree of inhalation
- tar and nicotine content of the cigarettes, and
- use of unfiltered cigarettes.

In populations with prolonged cigarette use, such as those in Europe and North America, the proportions of lung cancer cases attributable to smoking are high, with 90% to 95% of cases in men and 74% to 85% of cases in women attributed to smoking (Parkin et al. 2005). More than 50 epidemiological studies have also reported a nearly 26% increased risk of lung cancer with exposure to second-hand smoke (Hackshaw et al. 1997; Boffetta 2006).

Other risk factors for NSCLC include exposure to outdoor air pollution (Boffetta 2006), and home and/or occupational exposures to agents, such as arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, and radon progeny (Alberg and Samet 2003). It has been estimated that approximately 1 of 10 lung cancer cases in Europe is attributed to urban air pollution (Boffetta 2006). The mechanism of action of some environmental and occupational carcinogens has been reported to have a synergistic effect with smoking (Alberg and Samet 2003). Excess risk of lung cancer has also been described in relation to family history (Alberg and Samet 2003; Schwartz 2004) and cancer treatment. Individuals with a history of radiation therapy of the chest for Hodgkin's lymphoma and breast cancer have been associated with an increased risk of lung cancer in a dose-dependent manner (Moser et al. 2006; Maddams et al. 2011). While smoking and exposure to outdoor air pollution are known risk factors for NSCLC, they may not predict for *RET* fusion-positive NSCLC, given that patients with *RET* fusion-positive lung cancer have often been associated with never-smoker status.

Among the NSCLC population, Wang et al. (2012) identified 1.4% of patients with *RET* gene fusion. These patients have identifiable clinicopathologic characteristics, including young age, females, have never smoked, early lymph node metastases, poorly differentiated cancer, and a solid predominant cancer subtype (Wang et al. 2012; Kohno et al. 2013; Lin et al. 2015; Ferrara et al. 2018). In their study, Ferrara et al. (2018) reinforce that all patients with *RET* fusion genes had small primary lesions (less than 3 cm) but with significantly more N2 disease (mediastinal lymph node metastases) than patients with other adenocarcinomas with small lesions (54% versus 23%). A significant correlation between *RET* rearrangement and metastatic disease was found in a large retrospective analysis including 165 patients with *RET*-positive NSCLC (Ferrara et al. 2018).

SI.2.4 Main Existing Treatment Options

First-Line Treatment for Patients with Metastatic NSCLC

The shift in treatment approach in NSCLC to identify targetable alterations prior to initiating therapy has been driven by the demonstrated improved outcomes with targeted agents, including those targeting *EGFR*, *ALK*, *ROS1*, and *NTRK*. Thus, targeted therapy has supplanted chemotherapy/immunotherapy as the preferred initial treatment for patients with actionable alterations and approved therapies (Planchard et al. 2020; NCCN 2021). Gavreto® (pralsetinib) has demonstrated promising activity in the treatment of patients with *RET* fusion-positive NSCLC not previously treated with a *RET* inhibitor (Gavreto EMA).

Patients who have an identifiable driver alteration for which there is no approved targeted therapy receive the same treatment as those who do not have an identified driver alteration. Current treatment options for these patients include:

- Platinum-based doublet chemotherapy, alone or in combination with an immune checkpoint inhibitor has demonstrated an ORR of approximately 20% to 30% and an mPFS of approximately 4 to 6 months (Schiller et al. 2002; Socinski et al. 2012, 2018; Patel et al. 2013; Paz-Ares et al. 2013). Response rates of 48% to 58% and a PFS of 6.4 to 9 months are observed in patients receiving platinum-based chemotherapy with an immune checkpoint inhibitor. A response rate of 64% and a PFS of 8.3 months is observed when bevacizumab is added to chemotherapy and an immune checkpoint inhibitor (Paz-Ares et al. 2018; Socinski et al. 2018, West et al. 2019; Rodríguez-Abreu et al. 2021). These benefits have been observed regardless of PD-L1 status (Rodríguez-Abreu et al. 2021).
- Immune checkpoint inhibitor monotherapy for patients with no *ALK* or *EGFR* tumour genomic aberrations, and who express PD-L1, has demonstrated improvements in OS relative to platinum-based chemotherapy. PFS and response rates parallel those of containing platinum with or without immunotherapy (Mok et al. 2019; Herbst et al. 2020; Sezer et al. 2021).

Second or Later Lines of Treatment

Based on available data from first-line platinum-based treatment, approximately 40 to 50% of NSCLC patients receive second-line therapy upon progressive disease (Socinski et al. 2002; Hensing et al. 2005; Sandler et al. 2006; Davies et al. 2017). As with first-line therapy, the preferred treatment approach is with a selective inhibitor that targets the underlying driver of disease (Planchard et al. 2020).

Current treatment options for advanced NSCLC patients who have previously received platinum-based chemotherapy with or without immunotherapy are as follows:

- Chemotherapy such as docetaxel alone or with ramucirumab, or single-agent pemetrexed. Response rates of 8.5% to 23%, mPFS of 2.9 to 4.5 months, and median OS of 8.3 to 10.5 months have been reported (Hanna et al. 2004, Garon et al. 2014).
- Immune checkpoint inhibitors having monotherapy response rates of 14.5% to 22.9%, mPFS of 1.9 to 3.5 months, and median OS of 8.2 to 15.4 months (Borghaei et al. 2015; Garon et al. 2015; Rizvi et al. 2015; Brahmer et al. 2018).
- Multi kinase inhibitors (MKIs) that have modest anti-RET activity in addition to other well-characterised cancer targets, such as *VEGFR2, EGFR, MET*, and *ALK*. Moderate activity, with response rates of 16% to 47% and mPFS of 4.5 to 7.3 months have been reported (Drilon et al. 2016, 2018; Lee et al. 2016; Velcheti et al. 2016; Yoh et al. 2017; Hida et al. 2019).

SI.2.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Approximately 80% to 90% of lung cancers are NSCLCs (ESMO 2020). Most NSCLC patients present with metastatic or advanced stage, unresectable disease; the prognosis for these patients is poor, with a 5-year survival rate of 6% for those diagnosed with distant disease (ESMO 2020; Siegel et al. 2021). In terms of mortality, lung cancer represented 23% of deaths due to cancer among men and 15% among women across the EU countries in 2022 (OECD /EU 2022).

Symptoms associated with lung cancer include

- haemoptysis
- weight loss
- loss of appetite
- dyspnoea
- thoracic pain
- fatigue, and
- cough.

These symptoms may not be present until the disease progresses, and even if symptoms do occur, they are often mistaken for respiratory symptoms due to infection and a history of smoking, causing further delay in diagnosis (Hamilton et al. 2005).

Tumour burden including extensive metastases (30%) was a major cause of death for patients with lung cancer in an autopsy study. Per Nichols et al. 2012, other common immediate causes of death were

- infection including sepsis and pneumonia (20%)
- complications of metastases (18%)
- pulmonary haemorrhage (12%)
- pulmonary thromboembolism (10%), and
- pulmonary diffuse alveolar damage (7%).

Infection is a common complication associated with increased morbidity and mortality among patients with cancer (Akinosoglou et al. 2013).

Because of its high incidence and fatality, lung cancer is the most common cause of death from cancer worldwide, responsible for nearly 1 in 5 deaths due to cancer (1.8 million deaths, 18% of the total) (IARC 2022a). In addition, lung cancer is a leading cause of deaths due to cancer in women in 28 countries (IARC 2022a). Its 5-year survival rate (17.8%) is much lower than that of other leading cancers (Wong et al. 2017). The age-standardised mortality rate for lung cancer in 2020 was 15.8 (Australia), 22.5 (Canada), 30.2 (China), and 14.7 (Japan) per 100 000 in 2020 (IARC 2020a).

The GLOBOCAN reported estimated age-standardised mortality rates of lung cancer per 100 000 in the regions shown in Table SI.2 (IARC 2022b). The world age-standardised mortality rate of lung cancer was 16.8 per 100 000 patients in 2022 (IARC 2022b).

Table SI.2. GLOBOCAN Estimated Age-Standardised Mortality Rates of Lung Cancer for 2022 (per 100 000)

World	**16.8**
Micronesia	30.5
Polynesia	31.7
Eastern Asia	25.1
Western Europe	22.1
Central/Eastern Europe	21.6
Western Asia	21.5
Southern Europe	21.0
Northern Europe	18.7
North America	17.2
Australia/New Zealand	16.2
Caribbean	14.8
Southern Africa	15.7
South-Eastern Asia	15.2
South America	11.7
Northern Africa	10.6
Melanesia	10.2
South-Central Asia	6.1
Central America	4.9
Eastern Africa	3.0
Middle Africa	2.2
Western Africa	2.0

Abbreviation: GLOBOCAN = Global Cancer Incidence, Mortality, and Prevalence .; IARC = International Agency for Research on Cancer.

Source: IARC 2022

SI.2.6 Important Co-morbidities

Co-morbidity burden is high in patients with NSCLC. Combined with the age-related increase in co-morbidities, more than half of patients with NSCLC are estimated to have at least 1 co-morbid condition at the time of diagnosis (Stedman et al. 2019). Co-morbidities and expected co-medications in patients with NSCLC are shown in Table SI.3, and those generally apply to the overall NSCLC population, given that data for *RET* fusion-positive NSCLC are based on a relatively small sample size (Wang et al. 2012).

Table SI.3. Co-morbidities and Expected Co-medications in Lung Cancer

Co-morbidity	Prevalence	Expected Co-medications of Co-morbidity
Chronic obstructive pulmonary disease	• 52% (Wang et al. 2012) in the US Veterans Affair Central Cancer Registry between 2003 and 2008 • 23% of subjects <70 years and 31% of subjects ≥70 years (Janssen-Heijnen et al. 1998) in a Dutch Registry • 14% (Vaslamatzis et al. 2014) in a hospital in Greece	• Bronchodilators • Corticosteroids • Theophylline • Phosphodiesterase-4 inhibitors
Diabetes mellitus	• 26% (Wang et al. 2012) in the US Veterans Affair Central Cancer Registry between 2003 and 2008	• Insulin • Metformin • Sulphonylureas • Meglitinides • Thiazolidinediones • Dipeptidyl peptidase-4 (DPP-4) inhibitors • Glucagon-like peptide-1 (GLP-1) agonists • Sodium-glucose co-transporter-2 inhibitors
Non-lung malignancies	• 21% (Wang et al. 2012) in the US Veterans Affair Central Cancer Registry between 2003 and 2008 • 14% of subjects <70 years and 19% of subjects ≥70 years (Janssen-Heijnen et al. 1998) in a Dutch Registry	• Chemotherapy • Immunotherapy • Targeted therapy • Hormone therapy
Peripheral vascular disease	• 20% (Wang et al. 2012) in the US Veterans Affair Central Cancer Registry between 2003 and 2008	• Antiplatelets • Anticoagulants • Statins • Cilostazol • Pentoxifylline
Congestive heart failure	• 13% (Wang et al. 2012) in US Veterans Affair Central Cancer Registry between 2003 and 2008	• Aspirin • Beta blockers • Diuretics • Digoxin • Angiotensin converting enzyme (ACE) inhibitors • Angiotensin II receptor blockers • Aldosterone antagonists

Co-morbidity	Prevalence	Expected Co-medications of Co-morbidity
Cerebrovascular disease	• 13% (Wang et al. 2012) in US Veterans Affair Central Cancer Registry between 2003 and 2008	• Aspirin • Antiplatelet therapy • Anticoagulants • Statins
Cardiovascular disease	• 20% of subjects <70 years and 30% of subjects ≥70 years (Janssen-Heijnen et al. 1998) in a Dutch registry	• Aspirin • Beta blockers • Calcium channel blockers • Anticoagulants • Antihypertensives • Diuretics • Digoxin • Nitrates • Statins • ACE inhibitors • Angiotensin II receptor blockers • Aldosterone antagonists

Source: JanssenHeijnen et al. 1998; Wang et al. 2012; Vaslamatzis et al. 2014.

SI.3 Thyroid Cancer: RET-Mutant Medullary Thyroid Cancer

Thyroid cancer can be split into 4 main types: PTC, FTC, MTC, and ATC. Of these 4, MTC is a rare subtype representing about 3% to 5% of all thyroid cancers (Accardo et al. 2017). MTC can be further broken down into 2 smaller subgroups, sporadic (75%) and familial (25%), which represent 3.7% and 1.3%, respectively, of thyroid cancer as a whole (Moo-Young et al. 2009; Romei et al. 2016; Roskoski and Sadeghi-Nejad 2018).

Robust epidemiology data specific to MTC are sparse, hence, this section will focus primarily on thyroid cancer.

SI.3.1 Incidence

TC is responsible for approximately 821 214 cases worldwide, ranking seventh in incidence in 2022. The global age-standardised incidence rate in women was the highest;51.6 per 100 000 in Cyprus, which is 4-fold higher than that in men, as the highest was 13.3 per 100 000 in China, and the disease represents 1 in every 20 cancers diagnosed among women (Sung et al. 2021; IARC 2022c). Globally, the age-standardised incidence rate of TC in 2022 was 9.1 per 100 000. The age-standardised incidence rate (per 100 000) was the highest in Eastern Asia and the lowest in Western Africa (23.1 versus 0.94). Incidence rates in women varied by region, ranging from 1.4 to 34.3 per 100 000 in Western Africa and Eastern Asia (IARC 2022f). Between 1998 and 2007, the annual incidence of MTC was 0.11 per 100 000 in the Irish population (Lennon et al. 2017). In the US, the mean annual incidence of MTC was 0.21 per 100 000 (Randle et al. 2017).

The age-standardised incidence rate in 2020 of thyroid cancer was 11.4 (Australia), 17.4 (Canada), 11.3 (China), and approximately 8.1 (Japan) per 100 000 (IARC 2020a).

A large European study including 87 population-based cancer registries in 29 countries reported incidence rates ranging from 4 (Wales and the Netherlands) to 22 (Italy) per 100 000 women and from 1.5 (Bulgaria) to 7 (Italy and Iceland) per 100 000 men (Dal Maso et al. 2017). The majority of MTCs are sporadic, with about 25% identified as hereditary due to a germline-activating mutation in the *RET* gene. Approximately, 60% of the sporadic MTCs harbour somatic *RET* mutations (Wirth et al. 2020).

In Europe, 50 229 patients developed TC in 2022 (ECIS 2023). Assuming 5% of those cases were MTC (2511), and assuming *RET* mutations are present in 60% of patients with MTC, the incidence of new cases of *RET*-mutant MTC was approximately 1507 per year (ENCR 2017; Roskoski and Sadeghi-Nejad 2018).

In the US, an estimated 52 169 patients developed thyroid cancer in 2020, and assuming that 5% of those cases were MTC (2608), and assuming *RET*-mutations were present in 60% of MTC patients, the incidence of new cases of *RET*-mutant MTC was approximately 1565 per year (Roskoski and Sadeghi-Nejad 2018; IARC 2022).

TC is a relatively uncommon paediatric diagnosis, yet previous analyses have revealed that the incidence rate is increasing at a rate of approximately 1% annually (Dermody et al. 2016). Overall, paediatric MTC is rare, with an annual incidence ranging from 0.03 to 0.54 cases per 100,000 and constituting 3% to 5% of thyroid cancers in children (Starenki and Park 2015; Hillier et al. 2019). In their study, Vanden Borre et al. (2017) identified that *RET* mutations were detected in 93% (13 of 14 patients) of paediatrics, adolescents, and young adult MTC cases.

SI.3.2 Prevalence

TC prevalence varies by geographic region. As per IARC (2022), there were approximately 652 935 patients with TC worldwide. It reports the highest 1-year prevalence (both sexes, %) in Asia (71.0%), Europe (10.6%), Northern America (8.2%), followed by Latin America and the Caribbean (7.6%), Africa (1.8%), and Oceania (0.67%) (IARC 2022h).

The 5-year (all ages) prevalence of thyroid cancer was: 15 585 cases in Australia, 37 076 cases in Canada, 733 227 cases in China, and 61 142 cases in Japan (IARC 2021).

The *RET* gene is one of the most well-known oncogenes involved in thyroid cancer (Figlioli et al. 2013). The prevalence of *RET* alteration by thyroid tumour type in the US in 2017 is shown in Table SI.4.

Table SI.4. Prevalence of *RET* Mutation or Fusion Protein by Tumour Type in the US in 2017

Type of Tumour	% of Thyroid Cancer Population	% with *RET* Mutation or Fusion Protein
All TC	100	14
Medullary TC:	5	60
Medullary sporadic TC	3.7	50
Medullary familial TC	1.3	100

Abbreviations: % = percentage; *RET* = REarranged during transfection; TC = thyroid cancer.
Source: Roskoski and Sadeghi-Nejad 2018.

SI.3.3 Demographics of the Population in the Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Age, gender, and race

Thyroid cancer varies by both gender and age. Multiple studies reported a preponderance of thyroid cancer cases in females (Dal Maso et al. 2017; SEER). In the US, TC incidence was higher in women than in men (23.3 versus 8.0 per 100 000), regardless of race or ethnicity (SEER). In EUROCARE-5, a study including 87 population-based cancer registries in 29 European countries, women accounted for more than 3 quarters of the patient population (76% of patients with thyroid cancer, that are 65 748 out of 86 690 total cases). Moreover, in both the US and European studies, more than one-third of the cases were diagnosed in patients younger than 45 years and more than half were diagnosed in those younger than 55 years of age (Dal Maso et al. 2017). Notably, in the EUROCARE-5 study, the age distribution of thyroid cancer cases varied significantly with histological type. For example, elderly patients (aged 65 years and older) accounted for approximately one-fifth (17% and 22%) of PTC cases in women and men, respectively, and one-third of MTC cases (34% and 29%) in women and men, respectively. In contrast, female and male patients aged 65 years and older comprised 79% and 64% of the ATC population, respectively (Dal Maso et al. 2017).

In the US, thyroid cancer incidence varies based on race or ethnicity, with Caucasians experiencing the highest incidence (24.5 versus 8.6 per 100 000 in females versus males) and American Indian/Alaskan natives (14.2 versus 4.1 per 100 000 in females versus males) and African Americans (14.3 versus 4.0 per 100 000 in females versus males) experiencing the lowest incidence (SEER).

In paediatrics, MTC is most frequently associated with a family history of multiple endocrine neoplasia type 2 (MEN2)-A, and children typically receive the diagnosis in the pre-symptomatic phase secondary to a family history of a known *RET* mutation transmitted in an autosomal dominant pattern of inheritance (Hanley et al. 2016). Children and adolescents with PTC are more likely to harbour *RET* fusions than older patients with those malignancies (Gerdemann et al. 2019).

Risk factors

Risk factors for thyroid cancer, specifically for PTC vary; however, radiation exposure during childhood is 1 of the main established risk factors (Schneider and Sarne 2005; Colonna et al. 2015). In addition, a positive family history of thyroid disease, for example, thyroid cancer or related syndromes, such as benign nodules/adenomas and goitres, is associated with increased risk of non-MTC (Pal et al. 2001).Specific to MTC, a pooled analysis of studies from Europe, North America, and Asia found significant excess risk of MTC with the following:

- history of thyroid nodules
- hypertension
- gallbladder disease, and
- allergies.

MTC accounts for 5% to 10% of all thyroid cancers, with 70% to 80% occurring as a sporadic entity and 25% as familial MTC. Familial MTC can occur as familial MTC alone or as part of MEN2 (Figlioli et al. 2013).

The typical age of presentation of sporadic MTC is in the fifth or sixth decade, with a slight preponderance in females. In contrast, MEN2A and familial MTC typically present in the third decade of life, and MEN2B usually presents in those younger than 20 years (Roy et al. 2013). At presentation, 35% to 50% of patients with MTC have regional metastasis, while 13% to 15% have distant metastasis mainly to the lung, bone, and liver (Priya et al. 2017).

SI.3.4 Main Existing Treatment Options

Introduction

The clinical course of MTC is highly heterogeneous, varying from indolent tumours that remain unchanged for many years to aggressive cancers associated with high mortality. Surgery can be curative for approximately 85% of patients who present with localised disease. However, approximately 50% of all patients, independent of whether they present with localised or metastatic disease, develop recurrent disease (Wells et al. 2015). Recurrent disease may be indicated by a rising level of serum tumour markers calcitonin and/or carcinoembryonic antigen, which can predate the development of radiographically measurable metastases. Locally, recurrent disease is treated with re-operation and/or external beam radiation therapy. However, these treatments are associated with significant morbidity and are often not curative.

First-Line treatment for patients with metastatic MTC

Metastatic MTC is incurable (ACS 2019). Two MKIs, cabozantinib and vandetanib, have received regulatory approval for advanced MTC, irrespective of the presence or absence of *RET* mutation. However, many patients treated with these agents experience significant toxicities requiring dose interruptions, reductions, and/or treatment cessation.

Second or later lines of treatment

There is no approved systemic therapy with proven efficacy after the failure of a prior MKI.

SI.3.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Approximately, 1% to 5% of thyroid cancers are MTC. Worldwide, MTC represents 3% to 5% of thyroid cancers, while in the US, MTC accounts for a lower proportion (1% to 2%) primarily due to the increased incidence of PTC in the US (Wells et al. 2015).

An individual with a positive family history of germline mutation of the *RET* gene has a 50% chance of inheriting the same mutation. Once identified as a genetic carrier, there is a nearly 100% lifetime risk of developing malignancy, as it is transmitted in an autosomal-dominant fashion (Roy et al. 2013). Activating mutations in the *RET* proto-oncogene, which encodes RTK, is the main driver mutation in MTC. A germline *RET* mutation is reported in almost all familial forms of MTC, and a somatic *RET* mutation is reported in about 50% of sporadic MTC tumours. Of these, 85% are mutations at Codon 918, which are associated with a poor outcome. RAS

mutations have been noted in up to 68% of MTC tumours without *RET* mutation, but are rarely noted concurrently with a *RET* mutation (Hadoux et al. 2016).

Approximately half of the patients with metastatic MTC in an international study (48.2%; n=159) were *RET*-mutation positive, 12% (n=41) were *RET*-mutation negative, and 39% (n=130) had unknown *RET* mutation status. M918T was the predominant *RET* mutation (74%; 118 of 159 patients with documented mutations) (Elisei et al. 2013). A more recent international study found the prevalence of *RET*-mutation positive status was 51.2% and the prevalence of *RET* M918T was 38.2% in patients with metastatic MTC (Schlumberger et al. 2017).

In general, patients with tumours confined to the thyroid gland have a 10-year survival rate greater than 95%, whereas patients with regional stage disease had an OS rate of 75%. Patients with distant metastases at diagnosis have a poor prognosis, with only 40% surviving 10 years (Figlioli et al. 2013).

MTC accounts for 13.4% of all thyroid cancer-related deaths (Figlioli et al. 2013). Prognosis is favourable for PTC and FTC, but MTC may have a more intermediate or severe prognosis accounting for a larger proportion of deaths attributed to thyroid cancer (Dal Maso et al. 2017). MTC can present at late stages and does not respond to thyroid-stimulating hormone suppression or iodine, conferring reduced survival compared with thyroid cancer overall (Machens et al. 2014). A US based study using SEER data reported reduced survival in patients with MTC compared with other thyroid cancer histologies. The 10-year survival was lowest among patients with MTC (73.7%) and FTC (80.2%) versus PTC (87.7%) (Bhattacharyya 2003).

In Europe, the 5-year relative survival for patients with MTC was 88% (women) and 85% (men) (Dal Maso et al. 2017). Survival in patients with MTC in the US is strongly influenced by age and stage at diagnosis, with reported overall 5-year survival rates ranging from 56% to 87% based on the results of several studies. Patients younger than 40 years at the time of diagnosis had a significantly higher adjusted survival rate than older patients (Ernani et al. 2016).

As reported by Adam et al. (2017), survival by stage using a US based SEER national cancer database found that the 5-year OS rates for MTC decreased with increasing stage at diagnosis as follows:

- Stage I 95%
- Stage II 91%
- Stage III 89%, and
- Stage IV 68%.

The age-standardised mortality rate for thyroid cancer in 2020 was 0.27 (Australia), 0.28 (Canada), and 0.40 (China) per 100 000 in 2020 (IARC 2020a).

The 10-year OS rate of patients with localised disease is approximately 95%, while that of patients with regional stage disease is about 75%. Only 20% of patients with distant metastases (13% to 15% of the MTC population) at diagnosis survive 10 years after diagnosis (Priya et al. 2017).

SI.3.6 Important Co-morbidities

Co-morbidity in patients with cancer is of increasing interest because of ageing of the population and increased incidence of cancer in elderly people (Kuijpens et al. 2006). Several co-morbidities are commonly diagnosed among patients with thyroid cancer (Table SI.5).

Table SI.5. Co-morbidities and Expected Co-medications in Patients with Thyroid Cancer

Co-morbidity	Prevalence/Incidence	Expected Co-medications of Co-morbidity
Hypertension	18% (the Netherlands; all ages; Kuijpens et al. 2006)	Angiotensin converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Calcium channel blockers Diuretics
Cardiovascular disease	6% (the Netherlands; all ages; Kuijpens et al. 2006)	Aspirin Beta blockers Calcium channel blockers Anticoagulants Antihypertensives Diuretics Digoxin Nitrates
Diabetes mellitus	6% (the Netherlands; all ages; Kuijpens et al. 2006)	Insulin Metformin Sulphonylureas Meglitinides Thiazolidinediones Dipeptidyl peptidase-4 inhibitors Glucagon-like peptide-1 agonists Sodium-glucose co-transporter-2 inhibitors
Previous malignancies (except basal skin carcinoma and carcinoma in situ of the cervix)	7% (the Netherlands; all ages; Kuijpens et al. 2006)	
Venous thrombotic events (VTE)	3.1/1000 PY (UK Clinical Practice Research Datalink; Walker et al. 2013)	Anticoagulants Low molecular weight heparin Rivaroxaban Fondaparinux Unfractionated heparin

Abbreviations: PY = patient-years; UK = United Kingdom.
Source: Kuijpens et al. 2006; Walker et al. 2013.

SI.4 Thyroid Cancer: RET Fusion-Positive Thyroid Cancer

The thyroid follicle-derived, differentiated cancers (PTC and FTC) are the most common thyroid cancers, accounting for 80% to 85% and 10% to 15% of all thyroid cancer cases, respectively (Aboelnaga and Ahmed 2015). Poorly differentiated subtypes (PDTC) and ATC account for 5% to 10% of thyroid cancers and are characterised by less differentiated histologic features and more aggressive clinical behaviour than the differentiated subtypes (Landa et al. 2016).

RET gene fusions have been identified in approximately 6% to 9% of PTCs and approximately 6% of PDTCs (Fusco et al. 1987; Agrawal et al. 2013; CGAR 2014; Landa et al. 2016; Kato et al. 2017). In contrast to PTC and PDTC, neither FTC nor ATC are frequently associated with *RET* gene fusions. Most differentiated thyroid cancers, including PTC, are largely asymptomatic, treatable tumours with an excellent prognosis after surgical resection and radioiodine therapy (Pacini et al. 2012).

SI.4.1 Incidence

Please consult Section SI.3.1.

In France, the age-adjusted (world) incidence rate of PTC was 3.5 per 100 000 in men and 12.6 per 100 000 in women from 2006 to 2010. Similar to that of thyroid cancer overall, the incidence rate of PTC increased significantly over time, with an approximately 6-fold difference from the period of 1982 to 1985 to the period of 2006 to 2010 (Colonna et al. 2015).

PTC can occur at any age, and its incidence has been increasing over the last few decades. There are about 65 000 new cases of PTC in the US each year. It is now ranked as the fifth most common cancer in women in the US, and the most common cancer in women aged 15 to 34 years, and the second most common cancer for age 35 to 49 years (AAES 2021).

In Europe, an estimated 50 229 patients developed TC in 2020 . Assuming 84% of those cases were PTC (42 192), and assuming *RET* fusion gene alterations are present in 11% of the patients with PTC, the incidence of new cases of *RET* fusion-positive PTC was approximately 4641 per year (ENCR 2017; Roskoski and Sadeghi-Nejad 2018).

In the US, an estimated 52 169 patients developed thyroid cancer in 2020. Assuming 84% of those cases were PTC (43 822), and assuming *RET*-fusion gene alterations are present in 11% of PTC patients, the incidence of new cases of *RET*-fusion positive PTC was approximately 4820 patients per year (Roskoski and Sadeghi-Nejad 2018; IARC 2020b).

In a study, the frequency of oncogenic fusions was further enriched in paediatric patients with PTC, with 60% of the paediatric PTCs harboured an *RET* or *ALK* fusion (Vanden Borre et al. 2017).

SI.4.2 Prevalence

Please consult Section SI.3.2.

RET is 1 of the most well-known oncogenes involved in thyroid cancer (Figlioli et al. 2013,). The prevalence of *RET* alterations by thyroid tumour type in the US in 2017 is shown in Table SI.6.

Table SI.6. Prevalence of *RET* Fusion Protein Tumour Type in the US in 2017

Type of Tumour	% of Thyroid Cancer Population	% with *RET* Mutation or Fusion Protein
All TCs	100	14
Papillary TC	84	11

Abbreviations: % = percentage; *RET* = REarranged during transfection; TC = thyroid cancer.
Source: Roskoski and Sadeghi-Nejad et al. 2018

SI.4.3 Demographics of the Population in the Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Age, gender, and race

Please consult Section SI.3.3.

Although extremely rare, the most common form of thyroid cancer in children is PTC. In addition, children with differentiated thyroid cancer have a higher prevalence of gene rearrangements (Segni 2017). These RET rearrangements were especially identified in subjects with previous exposure to ionising radiation. 50% to 90% of children show RET rearrangements in post-Chernobyl PTC as their follicular cells are susceptible to undergo genetic mutations due to high proliferation rate. CCDC6 and NCOA4 are the two most frequent (more than 90% of cases) RET fusion partners in PTC, with the latter usually associated with bigger tumour size, aggressive behaviour, and advanced stage at diagnosis (Belli et al. 2020).

Risk factors

In the US SEER Medicare dataset, PTC was the most common type of thyroid cancer (82.1%) and most patients had localised disease (61.8%) (Choksi et al. 2017).

Risk factors for PTC are radiation exposure (childhood exposure, medical therapy, or environmental exposure) or genetics. PTC can be hereditary and may be associated with genetic syndromes. Patients with a positive family history are at greater risk , for thyroid cancer than those with no family history (AAES 2021).).

SI.4.4 Main Existing Treatment Options

The clinical course of *RET* fusion-positive PTC is heterogeneous, varying from some tumours being cured by surgical resection to aggressive cancers associated with metastases and high mortality. Recurrent disease is treated with re-operation and/or radioactive iodine therapy. However, these treatments are associated with significant morbidity and are often not curative.

MKIs, lenvatinib and sorafenib, have received regulatory approval for advanced PTC (irrespective of the presence or absence of an *RET* mutation). However, most patients treated with these agents experience significant toxicities requiring dose interruptions, reductions, and/or treatment cessation. There are no other approved systemic therapies with proven efficacy after failure of these MKIs (Ancker et al. 2010).

SI.4.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

In the EU, 71% of thyroid cancer cases were PTCs; however, this varied significantly by region and country. For example, 74% and 79% of thyroid cancers were PTC in Northern and Southern Europe, respectively, compared with 58% in the UK and Ireland where the proportion of FTC was highest (23%) (Dal Maso et al. 2017).

The prognosis is favourable for PTC and FTC, as they are slower-growing, indolent and rarely fatal cancers, as evidenced by the high 5-year relative survival in the EUROCARE-5 study (greater than 95% in PTC and 87% in FTC; Dal Maso et al. 2017). In the US, the 5-year survival rate for metastatic PTC is 78% compared to 99% for localised cancer (ASCO 2021).

SI.4.6 Important Co-morbidities

Please consult Section SI.3.6.

Module SII – Non-clinical Part of the Safety Specification

SII.1 Toxicity

Target organ toxicity:

- In repeat-dose studies in minipigs, mucosal atrophy was observed in tissues in the gastrointestinal tract, whereas in rats, mucosal atrophy was observed only in the tongue. In a 91-day study in minipigs, lesions in the non-glandular stomach were considered the cause of moribund condition leading to early unscheduled euthanasia of the high-dose group animals. In the 91-day study, adverse oesophageal and gastric lesions were not fully reversible.
- In repeat-dose studies in rats and minipigs, bone marrow hypocellularity with correlative haematology changes (decreases in platelet counts, reticulocyte, and/or red cell mass) were observed.
- In repeat-dose studies, depletion of lymphocytes was observed in multiple lymphoid tissues in minipigs and decreases in circulating lymphocytes were observed in rats.
- In repeat-dose studies in rats, minimal increases in ALT, AST, ALP, GGT activities, and cholesterol were observed with no correlating microscopic hepatic lesions.
- In repeat-dose studies in rats and minipigs, physeal dysplasia of the epiphyseal growth plate of the femur or sternum was observed. This finding was not fully reversible.
- In repeat-dose studies in rats, white discoloration and/or malocclusions in incisor teeth were observed. This finding was not fully reversible.
- In repeat-dose studies in rats, mineralisation was observed in multiple tissues and correlated with increased inorganic phosphorus observed by clinical chemistry. This finding was not fully reversible.

Reproductive/developmental toxicity:

- In a fertility study in male rats, germ cell depletion and spermatid retention in the testes and increased cellular debris in the epididymis were observed in dose-dependent manner. These effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm at the highest dose.
- In a fertility and early embryonic study in female rats, at the high dose only, a reduction in the number of oestrous cycles with an increase in the precoital interval was observed, and there was an increase in the number of dead embryos, increased post-implantation loss, and a reduction in the number of live embryos.
- In repeat-dose studies in male rats and minipigs, testicular degeneration with correlative luminal debris in the epididymis was observed. This finding persisted after a 28-day recovery period.
- In repeat-dose studies in female rats, vaginal mucification was observed. In repeat-dose studies in female minipigs, decreased corpora lutea were observed in the ovaries.
- In an embryo-foetal development study in rats, embryo-lethality was observed at all doses with foetal loss near 100%. External malformations were observed in viable foetuses.

Juvenile toxicity:

In a study, juvenile rats were administered selpercatinib from post-natal Day 21 through up to post-natal Day 70 (depending on survival). Effects were generally consistent with those observed in adolescent or young adult rats, with the following key exceptions:

- skeletal changes:
  - irreversible physeal dysplasia at bone growth plates
  - decreased bone size or geometry, mass, and/or density at both the distal femur metaphysis and femur diaphysis (some findings not reversible), and
  - decreased femur length (observed at recovery necropsy)
- large intestine: enteropathy
- effects on male reproductive performance (based on mating treated males with naïve females):
  - lower male fertility and copulation indices
  - increased pre-implantation loss
  - increased post-implantation loss, and
  - lower mean number and proportion of viable embryos, and
- delayed attainment of vaginal patency in female rats.

The skeletal changes were observed at exposures approximately 1 to 4 times the exposure in adults at the efficacious dose of 160 mg BID and are, therefore, considered potentially relevant to the paediatric patient population.

Genotoxicity:

- Selpercatinib was not mutagenic or clastogenic in vitro.
- Selpercatinib was genotoxic in an in vivo micronucleus assay in rats at an exposure that also resulted in bone marrow toxicity, and that resulted in C_{max} approximately 7-fold above the C_{max} in patients.

Carcinogenicity:

Selpercatinib caused no neoplasms in a 6-month carcinogenicity study in rasH2 hemizygous mice.

In a 2-year carcinogenicity study in rats, vaginal squamous cell carcinoma and vaginal carcinoma were observed in 2 and 1 female rats, respectively, which were administered high dose of 40 mg/kg selpercatinib, and considered possibly related to selpercatinib. No selpercatinib-related increased incidences of epithelial hyperplasia or other possible pre-neoplastic changes were noted in the reproductive tract of females at any dose level. No selpercatinib-related increased incidences of neoplasms were noted in females administered 4 or 15 mg/kg, or in males administered up to 20 mg/kg, the highest dose level evaluated in male rats.

SII.2 Safety Pharmacology

In a repeat-dose study in minipigs, non-adverse, reversible, 7% to 12% prolongation of QTc was observed at approximately 0.2 times the human C_{max} at the clinical dose of 160 mg BID.

SII.3 Other Toxicity-Related Information or Data

Table SII.1. Key Safety Findings for Non-clinical Studies and Relevance to Humans

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Liver toxicity: In rats, increases in ALT, AST, ALP, GGT activities, and cholesterol were observed with no correlating microscopic hepatic lesions.	Grade ≥3 increased ALT and Grade ≥3 increased AST were reported in patients. Patients should be advised of this risk. Monitor ALT and AST prior to the start of selpercatinib therapy, every 2 weeks during the first 3 months of treatment, then monthly thereafter, and as clinically indicated.
QTc prolongation: In minipigs, 7% to 12% prolongation of the QTc interval was observed at approximately 0.2 times the human C_{max} at the clinical dose of 160 mg BID.	Treatment-emergent QTc prolongation (all grades) has been reported in 71 (13.4% drug-related) patients receiving selpercatinib, of whom 3.6% were Grade 3. Use with caution in patients with conditions, such as congenital long QT syndrome, acquired long QT syndrome, or other clinical conditions that predispose to arrhythmias. Patients must have a QTcF interval of ≤470 msec and serum electrolytes within normal range before starting selpercatinib treatment. Monitor electrocardiograms and serum electrolytes in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months of selpercatinib treatment, and otherwise as clinically indicated. The effect of selpercatinib on the QTc interval was evaluated in a thorough QT study in healthy subjects. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90% CI: 12.1 msec) at the mean steady-state C_{max} observed in patients after administration of 160 mg BID. The increase in QTc was concentration dependent.
Gastrointestinal toxicity: In minipigs, mucosal atrophy was observed in tissues in the upper and lower gastrointestinal tract, whereas in rats, mucosal atrophy was observed only in the tongue. Enteropathy was observed in the large intestine of juvenile rats.	In patients, treatment-related AEs including but not limited to dry mouth, diarrhoea, constipation, nausea, abdominal pain, and vomiting have been observed. Patients should be advised of this risk and be treated symptomatically.
Bone marrow suppression: In rats and minipigs, bone marrow hypocellularity with correlative haematology changes (decreases in platelet counts, reticulocyte, and/or red cell mass) were observed.	Treatment-related thrombocytopaenia, anaemia, leukopenia, and neutropenia have been observed in patients. Patients should be advised of this risk and be monitored for decreases in circulating blood cell populations.
Growth plate abnormalities: In adolescent/young adult rats and minipigs, physeal dysplasia of the epiphyseal growth plate of sternum and/or femur were observed in animals with a patent (open) growth plate. In juvenile rats, physeal dysplasia was irreversible, and associated with decreased bone density and decreased femur length.	The non-clinical data indicate that there is a risk for growth plate abnormalities that could possibly impact adolescent and younger patients. Monitor for epiphyseal plate changes in any patient suspected to have not yet obtained full adult height.

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Male reproductive tissue injury: In male rats and minipigs, testicular degeneration with correlative luminal debris in the epididymis were observed. Reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm were observed in a rat fertility study. Impaired reproductive performance was observed in male rats administered selpercatinib as juveniles.	The non-clinical data indicate that there is a risk for reproductive organ injury and impaired fertility in men. Men should be advised of this risk. Monitor pubertal development in patients who have not reached sexual maturity.
Female reproductive tissue injury: In female rats, vaginal mucification was observed. In female minipigs, decreased corpora lutea were observed in ovaries. In a fertility study in rats, a reduction in the number of oestrous cycles with an increase in the precoital interval was observed, and there was an increase in the number of dead embryos, increased post-implantation loss, and a reduction in the number of live embryos. Selpercatinib treatment resulted in delayed attainment of vaginal patency in female juvenile rats.	The non-clinical data indicate that there is a risk of reproductive organ injury and impaired fertility in women. Women should be advised of this risk. Monitor pubertal development in patients who have not reached sexual maturity.
Reproductive and developmental toxicity: In an embryo-foetal development study in rats, embryo-lethality was observed at all doses and foetal loss was near 100%. External malformations were observed in viable foetuses. Foetal loss occurred at maternal exposures that were approximately 1.4 times the exposure of the recommended human dose (AUC).	The non-clinical data indicate a potential for severe developmental toxicities in women exposed to selpercatinib during pregnancy. Advise women with reproductive potential to use highly effective contraception during treatment and for at least 1 week after the last dose of selpercatinib. Advise men with female partners with reproductive potential to use highly effective contraception during treatment and for at least 1 week after the last dose of selpercatinib. Selpercatinib should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Carcinogenicity: vaginal squamous cell carcinoma and vaginal carcinoma were observed in 2 and 1 female rats, respectively, at the highest dose evaluated in a 2-year study. No selpercatinib-related increased incidences of epithelial hyperplasia or other possible pre-neoplastic changes were noted in the reproductive tract of females at any dose level.	The nonclinical data indicate a possible risk for human carcinogenicity. Vaginal tumours were observed at exposures similar to exposure in adults at the efficacious dose of 160 mg BID. The clinical relevance of the vaginal neoplasms observed in rats is uncertain due to • the incidence in only 3 rats • the absence of preneoplastic changes in the reproductive tract of female rats • the absence of neoplasms and preneoplastic changes in mice • being considered non-genotoxic at clinically relevant doses • not being a hormonal disruptor, and • absence of published literature suggesting that inhibition of RET activity increases carcinogenicity.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the concentration versus time curve; BID = twice daily; CI = confidence interval; C_{max} = maximum observed drug concentration; GGT = gamma-glutamyl transferase; QTc = corrected time from the start of the Q wave to the end of the T wave interval; QTcF = corrected time from the start of the Q wave to the end of the T wave interval - Fridericia formula.

A paediatric study is still ongoing; therefore, safety and efficacy of selpercatinib have not been established in this population. It is currently unclear if selpercatinib has any impact on child development including growth, sexual maturity, and cognitive development. As agreed in the Paediatric Investigation Plan, the impact of selpercatinib on child development will be monitored through routine physical examinations and clinical assessments in accordance with the Schedule of Assessments through safety follow-up visit.

Module SIII - Clinical Trial Exposure

Table SIII.1. Duration of Exposure

Duration of Selpercatinib Exposure (at least)	Persons	Person-Time (months)
Cumulative for All Tumour Types		
Selpercatinib single agent		
1 month (≥1 to ≤30 days)	40	23.99
3 months (≥31 to ≤90 days)	72	149.19
6 months (≥91 to ≤180 days)	79	356.11
>6 months (≥181 days)	1024	29 493.54
Total	1215	30 022.83
Tumour Type: *RET* Fusion-Positive NSCLC		
Selpercatinib single agent		
1 month (≥1 to ≤30 days)	18	10.09
3 months (≥31 to ≤90 days)	31	59.93
6 months (≥91 to ≤180 days)	31	142.72
>6 months (≥181 days)	440	11 828.17
Total	520	12 040.91
Tumour Type: *RET*-Mutant MTC		
Selpercatinib single agent		
1 month (≥1 to ≤30 days)	13	8.02
3 months (≥31 to ≤90 days)	22	51.84
6 months (≥91 to ≤180 days)	31	138.57
>6 months (≥181 days)	465	14 527.67
Total	531	14 726.10
Tumour Type: *RET* Fusion-Positive Thyroid Cancer		
Selpercatinib single agent		
1 month (≥1 to ≤30 days)	0	0
3 months (≥31 to ≤90 days)	0	0
6 months (≥91 to ≤180 days)	5	21.59
>6 months (≥181 days)	71	2006.51
Total	76	2028.10
Tumour Type: *RET* fusion-positive Non-lung/Thyroid Solid Tumours		
Selpercatinib single agent		
1 month (≥1 to ≤30 days)	5	3.52
3 months (≥31 to ≤90 days)	11	23.29
6 months (≥91 to ≤180 days)	10	44.88
>6 months (≥181 days)	30	712.02
Total	56	783.71

Abbreviations: MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; *RET* = REarranged during transfection; Study JZJA = J2G-MC-JZJA; Study JZJB = J2G-MC-JZJB; Study JZJC = J2G-MC-JZJC; Study JZJJ = J2G-OX-JZJJ.

Cut-off Date: 13 January 2023: Study JZJA (LIBRETTO-001) and Study JZJJ (LIBRETTO-121); 01 May 2023: Study JZJC (LIBRETTO-431); 22 May 2023: Study JZJB (LIBRETTO-531).

Source: /lillyce/prd/ly3527723/integration/adr/output/restricted/rmp/abcj//t_rmp_expo_dur.rtf

Table SIII.2. Age Group and Gender

Age Group (year)	Persons		Person-Time (months)	
	Male	Female	Male	Female
Cumulative for All Tumour Types				
Selpercatinib single agent				
<12 years	4	2	89.66	38.24
≥12 and <18 years	10	9	206.07	209.38
≥18 and <65 years	418	377	10 935.82	9350.41
≥65 and <75 years	146	142	3667.39	3203.12
≥75 and <85 years	49	48	981.98	1196.68
≥85 years	3	7	18.76	125.34
Total	630	585	15 899.68	14 123.17
Tumour Type: *RET* Fusion-Positive NSCLC				
Selpercatinib single agent				
≥18 and <65 years	147	181	3386.25	4302.06
≥65 and <75 years	63	84	1422.09	1993.03
≥75 and <85 years	17	23	289.78	545.34
≥85 years	0	5	NA	102.34
Total	227	293	5098.12	6942.77
Tumour Type: *RET*-Mutant MTC				
Selpercatinib single agent				
<12 years	4	1	89.66	37.82
≥12 and <18 years	4	5	116.21	153.07
≥18 and <65 years	223	145	6547.25	3967.98
≥65 and <75 years	64	41	1851.14	936.42
≥75 and <85 years	24	17	555.10	460
≥85 years	2	1	3.45	8.05
Total	321	210	9162.81	5563.34
Tumour Type: *RET* Fusion-Positive Thyroid Cancer				
Selpercatinib single agent				
≥12 years and <18 years	5	3	86.18	55.39
≥18 and <65 years	20	20	599.26	580.24
≥65 and <75 years	9	7	279.49	170.02
≥75 and <85 years	4	7	57.46	185.10
≥85 years	0	1	NA	14.95
Total	38	38	1022.39	1005.70
Tumour Type: *RET* fusion-positive Non-lung/Thyroid Solid Tumours				
Selpercatinib single agent				
≥12 years and <18 years	1	0	3.68	NA
≥18 and <65 years	17	22	233.07	383.21
≥65 and <75 years	6	6	51.02	37.42
≥75 and <85 years	3	0	59.99	NA
≥85 years	1	0	15.31	NA
Total	28	28	363.07	420.63

Abbreviations: MTC = medullary thyroid cancer; NA = not applicable; NSCLC = non-small cell lung cancer; *RET* = REarranged during transfection; Study JZJA = J2G-MC-JZJA; Study JZJB = J2G-MC-JZJB; Study JZJC = J2G-MC-JZJC; Study JZJJ = J2G-OX-JZJJ.

Cut-off Date: 13 January 2023: Study JZJA (LIBRETTO-001) and Study JZJJ (LIBRETTO-121); 01 May 2023: Study JZJC (LIBRETTO-431); 22 May 2023: Study JZJB (LIBRETTO-531).

Source: /lillyce/prd/ly3527723/integration/adr/output/restricted/rmp/abcj/t_rmp_expo_age_gender.rtf

Table SIII.3. Dose

	Persons	Person-Time (months)
Cumulative for All Tumour Types		
Total	**1215**	**30 022.83**
Phase 1 dose escalation	117	3694.16
Phase 1 dose expansion/Phase 2	747	20 652.94
Phase 3	351	5675.73
Tumour Type: *RET* Fusion-Positive NSCLC		
Total	**520**	**12 040.90**
Phase 1 dose escalation	58	1622.28
Phase 1 dose expansion/Phase 2	304	7790.09
Phase 3	158	2628.53
Tumour Type: *RET*-Mutant MTC		
Total	**531**	**14 726.11**
Phase 1 dose escalation	41	1611.07
Phase 1 dose expansion/Phase 2	297	10 067.84
Phase 3	193	3047.2
Tumour Type: *RET* Fusion-Positive Thyroid Cancer		
Total	**76**	**2028.09**
Phase 1 dose escalation	9	330.81
Phase 1 dose expansion/Phase 2	67	1697.28
Tumour Type: *RET* fusion-positive Non-lung/Thyroid Solid Tumours		
Total	**56**	**783.71**
Phase 1 dose escalation	3	66.17
Phase 1 dose expansion/Phase 2	53	717.54

Abbreviations: MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; *RET* = REarranged during transfection; Study JZJA = J2G-MC-JZJA; Study JZJB = J2G-MC-JZJB; Study JZJC = J2G-MC-JZJC; Study JZJJ = J2G-OX-JZJJ.

Cut-off Date: 13 January 2023: Study JZJA (LIBRETTO-001) and Study JZJJ (LIBRETTO-121); 01 May 2023: Study JZJC (LIBRETTO-431); 22 May 2023: Study JZJB (LIBRETTO-531).

Source: /lillyce/prd/ly3527723/integration/adr/output/restricted/rmp/abcj/jzja_jzjb_jzjc_jzjj_RMP_Table_SIII_3

Table SIII.4. Patients Treated at 160 mg BID (RP2D)

Cumulative for All Tumour Types			
Dose of Exposure	**Total No. of Patients**	**Intra-Patient Dose Escalated to 160 mg BID**	**Dose Reduced to 160 mg BID**
20 mg QD	6	4	0
20 mg BID	10	6	0
40 mg BID	16	11	0
60 mg BID	12	8	0
160 mg QD	1	1	0
80 mg BID	20	17	0
110 mg BID	1	1	0
120 mg BID	22	13	0
140 mg BID	1	1	0
160 mg BID	1102	0	0
200 mg BID	3	0	1
240 mg BID	6	0	4
Total	1200	62	5

Tumour Type	**RET Fusion-Positive NSCLC**	**RET-Mutant MTC**	**RET Fusion-Positive Thyroid Cancer**	**RET fusion-positive Non-lung/Thyroid Solid Tumours**
Total Treated				
Subjects who received at least 1 dose of 160 mg BID	505	513	69	55
Starting dose of 160 mg BID	475	487	60	54
Intra-patient dose escalated to 160 mg BID	27	22	6	1
Dose reduced to 160 mg BID	3	1	1	NA

Abbreviations: BID = twice daily; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; QD = once daily; *RET* = REarranged during transfection; RP2D = recommended phase 2 dose; Study JZJA = J2G-MC-JZJA; Study JZJB = J2G-MC-JZJB; Study JZJC = J2G-MC-JZJC; Study JZJJ = J2G-OX-JZJJ.

Cut-off Date: 13 January 2023: Study JZJA (LIBRETTO-001) and Study JZJJ (LIBRETTO-121); 01 May 2023: Study JZJC (LIBRETTO-431); 22 May 2023: Study JZJB (LIBRETTO-531).

Note 1: In Study JZJC, 2 patients started off at doses lower than 160 mg BID. JZJC Protocol requires all patients to start at 160 mg BID, therefore these 2 patients are summarised under the category “Starting dose of 160 mg BID”.

Note 2: In Study JZJB, 2 patients started off at doses lower than 160 mg BID. JZJB Protocol requires all adult patients to start at 160 mg BID, therefore these 2 patients are summarised under the category “Starting dose of 160 mg BID”.

Note 3: Patients receiving 110 mg and 140 mg BID are from Study JZJJ. The study includes absolute doses for patients in Study JZJJ, not dose level doses.

Source: /lillyce/prd/ly3527723/integration/adr/output/restricted/rmp/abcj/jzja_jzjb_jzjc_jzjj_RMP_Table_SIII_4

Table SIII.5. Ethnic Origin

Ethnic/Racial Origin	Persons	Person-Time (months)
Cumulative for All Tumour Types		
Selpercatinib single agent		
White	759	19 820.11
Black or African American	37	811.43
Asian	337	7394.82
American Indian or Alaska Native	4	77.37
Native Hawaiian or other Pacific Islander	2	64.72
Other	36	1174.86
Missing	40	679.49
Total	1215	30 022.80
Tumour Type: RET Fusion-Positive NSCLC		
Selpercatinib single agent		
White	236	5463.72
Black or African American	18	444.71
Asian	245	5692.48
American Indian or Alaska Native	3	66.26
Other	12	231.88
Missing	6	141.83
Total	520	12 040.88
Tumour Type: *RET*-Mutant MTC		
Selpercatinib single agent		
White	412	12 029.20
Black or African American	11	216.31
Asian	56	1182.91
American Indian or Alaska Native	1	11.10
Native Hawaiian or other Pacific Islander	1	50.86
Other	18	722.99
Missing	32	512.72
Total	531	14 726.09
Tumour Type: *RET* Fusion-Positive Thyroid Cancer		
Selpercatinib single agent		
White	47	1423.61
Black or African American	3	61.90
Asian	18	297.66
Other	6	219.99
Missing	2	24.94
Total	76	2028.10
Tumour Type: RET fusion-positive Non-Lung/Thyroid Solid Tumours		
Selpercatinib single agent		
White	37	529.91
Black or African American	3	31.21

Asian	15	208.72
Native Hawaiian or other Pacific Islander	1	13.86
Total	56	780.82

Abbreviations: MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; *RET* = REarranged during transfection; Study JZJA = J2G-MC-JZJA; Study JZJB = J2G-MC-JZJB; Study JZJC = J2G-MC-JZJC; Study JZJJ = J2G-OX-JZJJ.

Cut-off Date: 13 January 2023: Study JZJA (LIBRETTO-001) and Study JZJJ (LIBRETTO-121); 01 May 2023: Study JZJC (LIBRETTO-431); 22 May 2023: Study JZJB (LIBRETTO-531).

Source: /lillyce/prd/ly3527723/integration/adr/output/restricted/rmp/ abcj/t_rmp_expo_race.rtf

Module SIV - Populations Not Studied in Clinical Trials

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

In selpercatinib clinical development programme, the primary population studied comprised of patients with *RET* fusion-positive NSCLC, *RET*-mutant MTC, and *RET* fusion-positive thyroid cancer. Key exclusion criteria were consistent among all protocols, most of which were intended to ensure safety and minimise risk in a research setting.

Specific and relevant exclusion criteria that are important to selpercatinib are addressed in this section.

Criterion: Patient is pregnant or a lactating woman.

Reason for exclusion: Studies in animals have shown reproductive toxicity (Module SII).

Selpercatinib should not be used during pregnancy and in women of childbearing potential who are not using contraception. It is unknown whether selpercatinib is excreted in human milk. A risk to newborns/infants cannot be excluded. Patients receiving selpercatinib should not breast-feed.

Is it considered to be included as missing information? No

Rationale: Labelling information will clearly indicate that selpercatinib should not be used in women who are pregnant or breastfeeding and that women of childbearing potential should use highly effective contraception.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged and/or cumulative exposure.

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

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	
Patients with relevant co-morbidities: Patients with hepatic impairment Patients with renal impairment	Patients with severe hepatic impairment were excluded from entering the clinical trials. However, selpercatinib is not contraindicated in this population. Patients with severe renal impairment and patients on dialysis were excluded from entering the clinical trials. Selpercatinib has not been studied in patients with severe renal impairment (eGFR <15 ml/min) or on dialysis.
Patients with relevant co-morbidities: Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Population with relevant different ethnic origin	The clinical trial enrolled patients of various racial and/or ethnic origins and there were no restrictions outlined in clinical protocol. Approximately 68.5% of the population were White; the largest minority was Asian, which constituted 23.2% of the population. The toxicity pattern was in general consistent with the overall population. There were slight differences in the interval incidence and frequency of certain AEs between racial groups. For White versus Asian patients, AEs with a frequency of 20% or higher were • diarrhoea (49.5% vs. 52.3%) • dry mouth (45.3% vs. 42.1%) • fatigue (45.1% vs. 22.6%) • hypertension (41.6% vs. 43.6%) • nausea (38.5% vs. 20.0%) • constipation (37.8% vs. 24.6%) • AST increase (35.8% vs. 46.7%) • oedema peripheral (34.6% vs. 41.5%) • ALT increase (33.0% vs. 48.7%) • abdominal pain (32.0% vs. 12.3%) • headache (30.8% vs. 22.1%)

Type of Special Population	Exposure
	• vomiting (29.4% vs. 17.9%) • blood creatinine increased (27.6% vs. 25.1%) • arthralgia (26.7% vs. 9.7%) • dyspnoea (25.3% vs. 14.4%) • cough (24.7% vs. 17.4%) • back pain (24.0% vs. 11.8%) • rash (21.9% vs. 28.7%) • decreased appetite (21.3% vs. 23.6%) • urinary tract infection (20.8% vs. 10.3%) • electrocardiogram QT prolonged (20.5% vs. 23.6%) • pyrexia (18.0% vs. 24.1%) • thrombocytopenia (15.0% vs. 26.2%), and • face oedema (7.7% vs. 21.0%).
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Children and adolescents (<18 years)	There are limited safety and efficacy data of selpercatinib in children and adolescents (<18 years). The paediatric investigation plan for selpercatinib has been agreed with the European Medicines Agency's Paediatric Committee to explore the safety and efficacy of selpercatinib in paediatric patients with *RET*-mutant medullary thyroid cancer and *RET*-altered cancers.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; *RET* = REarranged during transfection.

Module SV - Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Worldwide sales of selpercatinib have been collected cumulatively through 31 October 2023.

Patient exposure estimates for selpercatinib are provided in terms of estimated patients exposed and estimated patient-years of exposure. The estimates were calculated as follows:

- **Patient-Years:** Calculated by dividing the total number of milligrams sold by the recommended daily dose of 320 mg (160 mg BID) to determine the total days' supply on the market. Total days' supply was then divided by 365 days to estimate patient-years of therapy.
- **Patients:** Calculated by dividing the total number of milligrams sold by the estimated total dose per patient. The estimated total dose per patient was determined by dividing total sales in the US by the estimated number of patients who have received selpercatinib in the US based upon the IQVIA's National Prescription Audit database. The US total dose per patient was then used as a proxy for other geographic regions because anonymised patient-level data are not available in other regions.
    - total dose per patient (cumulative) = 81 369 mg

SV.1.2 Exposure

As of 31 October 2023, a total of 441 012 310 milligrams of selpercatinib were sold worldwide. This resulted in an estimated 5420 patients exposed to selpercatinib and 3770 PYs of exposure in the post-marketing environment. Table SV.1 provides a summary of cumulative worldwide sales and estimated patient exposure.

Table SV.1. Estimated Cumulative Patient Exposure for Selpercatinib as of 31 October 2023

Region	Sales (mg)	Estimated Patient Exposure (patients)	Estimated Patient-Years of Exposure
Europe	142 329 120	1740	1210
Japan	41 888 000	510	350
United States	207 393 600	2540	1770
Other Countries	49 401 590	600	420
Global Totals[a]	441 012 310	5420	3770

[a] Global totals may not sum for patient exposure estimates due to independent rounding.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Selpercatinib has not been studied systematically in humans for its potential for abuse, tolerance, or physical dependence. While the current clinical trial programme did not reveal any tendency for any drug seeking behaviour, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which an anticancer drug will be misused, diverted, and/or abused once marketed. If stolen, like any drug, selpercatinib has a potential for misuse.

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

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- dry mouth
- diarrhoea
- fatigue
- constipation
- headache
- nausea
- oedema peripheral, and
- blood creatinine increased.

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:

- Not applicable

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 product information are adhered by prescribers:

- Not applicable

Known risks that do not impact the risk-benefit profile:

- Not applicable

Other reasons for considering the risks not important:

- Hypertension: Hypertension is considered an ADR for selpercatinib and is included in Sections 4.2, 4.4, and 4.8 of the SmPC. The majority of events were non-serious, monitorable, and treatable. There are no fatal outcomes reported. The management of the event is well known. Treating physicians can identify the patients at higher risk and monitor these patients. The severity of the outcomes of hypertension do not have a significant enough impact on risk-benefit balance to consider it as important.
- Hypersensitivity reactions: Hypersensitivity reactions are considered an ADR for selpercatinib and are included in Section 4.2, 4.4, and 4.8 of the SmPC. Hypersensitivity reactions were easily recognised and manageable by routine medical intervention. No fatal outcomes were reported. The severity of the outcomes of these events do not have a significant enough impact on risk-benefit balance to consider them as important.
- Thrombocytopaenia: Thrombocytopaenia is considered an ADR for selpercatinib and is included in Section 4.8 of the SmPC. The majority of the events were non-serious,

monitorable, and treatable. There are no fatal cases reported. The management of these events is well known by physicians who treat patients with cancer. The severity of the outcomes of thrombocytopaenia does not have a significant enough impact on risk-benefit balance to consider it as important.

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

Important Identified Risk 1: None

Risk-Benefit Impact:

Not applicable

Important Potential Risk 1: Liver injury

Risk-Benefit Impact:

Liver injury, as indicated by increases of aminotransferases, may be considered to have an impact on the risk-benefit balance of selpercatinib. Liver injury is the severe clinical outcome, which may be associated with the ADRs of increased aminotransferases (ALT and AST). Cases of increased ALT and AST were very commonly observed (more than 10%) by both TEAEs and by laboratory analysis in the clinical Study JZJA (LIBRETTO-001). These events were predominantly Grade 1 or Grade 2. Generally, ALT and AST increases were manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment.

Based on the frequency of reported events of aminotransferase increased, and their potential to indicate liver injury, liver injury is considered an important potential risk. Only few cases of severe increases of aminotransferases and serious hepatic events were reported, and no Grade 5 liver-related events were reported. Therefore, liver injury is considered an important potential risk and will be further evaluated in the planned Phase 3 clinical trials.

Important Potential Risk 2: Cardiac arrhythmia due to QT prolongation

Risk-Benefit Impact:

Cardiac arrhythmia due to QT prolongation, such as *torsades de pointes* can have a substantial impact on individual patients, as the outcome can be severe and, in some cases, fatal if severe events are not treated. The TEAE of ECG QT prolonged is considered an ADR for selpercatinib and is included in Sections 4.2 and 4.4 of the SmPC. In pre-clinical studies, low magnitude of QTc increase was noted and potentially related to selpercatinib. In the clinical Study JZJA (LIBRETTO-001), ECG QT prolonged was observed very commonly (more than 10%). The majority of events were low grade. The severe clinical outcome that may be associated with this ADR is cardiac arrhythmia; however, to date, no clinically significant treatment-emergent arrhythmias or *torsades de pointes* have been observed. Moreover, no patients administered selpercatinib were discontinued due to QT prolongation in study JZJA (LIBRETTO-001).

Due to the potentially severe clinical consequence, cardiac arrhythmia due to QT prolongation is considered an important potential risk and will be further evaluated in the planned Phase 3 clinical trials.

Important Potential Risk 3: Reproductive and developmental toxicities

Selpercatinib was found to be embryo-lethal at all doses in an embryo-foetal development study in rats. External malformations were observed in viable foetuses. Decreased testicular weights, decreased sperm motility, and increase in the number of abnormal sperm were observed in a fertility study in male rats and vaginal mucification with a reduction in the number of oestrous cycles with an increase in the precoital interval were observed in a fertility study in female rats.

Pregnant and lactating women were excluded from the clinical trials for selpercatinib, and therefore, this effect has not been observed in humans; however, non-clinical data indicate that there is a risk for reproductive and developmental toxicities in women exposed to selpercatinib during pregnancy and a risk for reproductive organ injury and fertility effects in men during and after exposure to selpercatinib.

Risk-benefit impact:

Animal studies indicate the potential of selpercatinib to harm the offspring when administered to humans at recommended doses. This important risk has been addressed in the clinical development programme of selpercatinib by ensuring that pregnant women are not exposed to selpercatinib by excluding them from the Phase 3 clinical trials. Furthermore, the Phase 3 protocols are designed to prevent exposure of selpercatinib to women who become pregnant by requiring women of childbearing potential and men with partners of childbearing potential to agree to use highly effective contraceptive methods during treatment and 6 months following the last dose of study drug. In the event of a pregnancy, appropriate information will be collected, and the impact to the reproductive and developmental toxicities risk will be assessed.

Consequently, this is addressed in clear language incorporated in the labelling to direct the treating physician’s attention to this risk. Any report of exposure of selpercatinib to pregnant women or women who are breastfeeding will undergo detailed follow-up activities, including targeted follow-up questionnaires.

Missing Information 1: Exposure and Safety in Patients with Severe Hepatic Impairment

Selpercatinib is metabolised by microsomal fractions and hepatocytes in mice, rats, dogs, minipigs, and humans. In the clinical pharmacology study, mild and moderate Child-Pugh groups were similar to normal in clearance; although, in severe disease, exposure was increased with AUC being 77% higher in the severe Child-Pugh group. There were no safety concerns in this single-dose study. Hence, safety data on effects in patients with severe hepatic impairment are limited.

Risk-Benefit Impact:

Patients with severe hepatic impairment have been excluded from participation in the selpercatinib clinical development programme; therefore, no data in humans are available. Incidences of increased ALT and AST, both from reported TEAEs and on laboratory analysis, were observed. These were predominantly Grade 1 or Grade 2. There were no reported cases of hepatic failure or fatal hepatic events.

Use of selpercatinib in patients with hepatic impairment is not contraindicated.

Selpercatinib should be administered with caution in patients with hepatic impairment (Child-Pugh Class C).

Missing Information 2: Exposure and safety in patients with cardiac impairment

Patients with clinically significant cardiac disease prior to planned start of study treatment have been excluded from participation in the selpercatinib clinical development programme. Hence, safety data on effects in patients with a history of cardiac disease are limited. There is no evidence to suggest that treatment with selpercatinib leads to clinically significant cardiac impairment, however, TEAEs cardiac arrythmia and cardiac failure were observed. These were predominantly Grade 1 or Grade 2. As no controlled data are available in the study, the role of selpercatinib in the onset of cardiac disorders cannot be definitively ruled out.

Use of selpercatinib in patients with cardiac impairment is not contraindicated.

Risk-Benefit Impact:

The population of patients eligible for treatment with selpercatinib, who also have cardiac impairment, is anticipated to be small.

If data for the role of selpercatinib in the onset of cardiac disorders in patients become available, the effect on the risk-benefit profile will be assessed.

SVII.2 New Safety Concerns and Re-classification with a Submission of an Updated RMP

Not applicable.

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

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

Important Identified Risk: None

Important Potential Risk 1: Liver Injury

Potential mechanisms:

The pathogenesis of transaminase increased in patients receiving selpercatinib is not well understood. Selpercatinib is metabolised by microsomal fractions and hepatocytes. In animal studies, liver effects that include higher ALT, ALP, AST, and cholesterol levels were observed. Other MKIs, such as cabozantinib, that inhibit *RET* have included transaminase increased as an ADR (Cabometyx package insert, 2019). Increases of aminotransferases, notably ALT, can indicate liver injury.

Evidence source(s) and strength of evidence:

In the Study LIBRETTO-001, increases of aminotransferases, including ALT and AST, have been very commonly observed (more than 10%) as both TEAEs and by laboratory analysis in patients treated with selpercatinib. These events were mostly Grade 1 or Grade 2.

There were no reports of liver failure assessed as related to selpercatinib. Generally, increases of aminotransferases were of low severity and manageable by dose reduction or dose omission and/or resolved upon discontinuation of study treatment. Therefore, based on the frequency of reported events of aminotransferase increased, and their potential to indicate liver injury, liver injury is considered an important potential risk.

Characterisation of the risk

Based on pooled data from the Phase 1/2 Study JZJA (LIBRETTO-001), Phase 3 Study JZJC (LIBRETTO-431), and Phase 3 Study JZJB (LIBRETTO-531), the incidence of all grade and Grade ≥3 events from the Drug-related hepatic disorders Standardised Medical Dictionary for Regulatory Activities Query were 718 (60.4%) and 239 (20.1%), respectively.

Table SVII.2.1. A Breakdown of Hepatic Events by Study

Clinical Trial	ALT Increased n (%)	AST Increased n (%)	Liver Injuries (Drug related hepatic disorders SMQ) n (%)
LIBRETTO-001			
All Grades	316(37.8)	305(36.4)	511(61.1)
Grade 3/4	73(8.7)	99(11.8)	164(19.6)
LIBRETTO-431			
All Grades	95(60.1)	97(61.4)	123(77.8)
Grade 3/4	35(22.2)	20(12.7)	49(31.0)
LIBRETTO-121			
All Grades	7(25.9)	7(25.9)	14(51.9)
Grade 3/4	1(3.7)	1(3.7)	1(3.7)
LIBRETTO-531			
All Grades	51(26.4)	46(23.8)	84(43.5)
Grade 3/4	20(10.4)	9(4.7)	26(13.5)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; n = number of events; SMQ = standardised MedDRA query; Study JZJA = J2G-MC-JZJA; Study JZJB = J2G-MC-JZJB; Study JZJC = J2G-MC-JZJC; Study JZJJ = J2G-OX-JZJJ.

Cut-off Date: 13 January 2023: Study JZJA (LIBRETTO-001) and Study JZJJ (LIBRETTO-121); 01 May 2023: Study JZJC (LIBRETTO-431); 22 May 2023: Study JZJB (LIBRETTO-531).

Data source: prd\ly3527723\j2g_ox_jzja\csr5\output\restricted\overall\T14.3.2.10
prd/ly3527723/j2g_ox_jzja/csr5/output/restricted/overall/taesi_liver_injury_acn.rtf
Liver Injury: ly3527723/j2g_mc_jzjc/csr1/output/restricted/t_14_3_2_6_14_1.rtf
AST incr: ly3527723/j2g_mc_jzjc/csr1/output/restricted/topline/t_14_3_2_6_5_1.rtf
ALT incr: ly3527723/j2g_mc_jzjc/csr1/output/restricted/topline/t_14_3_2_6_6_1.rtf
AST: prd/ly3527723/j2g_mc_jzjb/csr1/output/restricted/for_safety/t_14_3_2_6_5_1.rtf
ALT: prd/ly3527723/j2g_mc_jzjb/csr1/output/restricted/for_safety/t_14_3_2_6_6_1.rtf
prd/ly3527723/j2g_mc_jzjb/csr1/output/restricted/non-topline/for_safety/t_14_3_2_6_14.rtf

prd\ly3527723\j2g_ox_jzjj\intrm1\output\shared\JZJJ_FinalTFLs_HeaderUpdate_All_20230516\T14.3.1.10.1.

Risk factors and risk groups:

There are a number of risk factors associated with liver injury, including advancing age, female gender, nutritional deficiencies, alcohol consumption, chronic hepatitis B and C, and genetic risk factors (Ingawale et al. 2014). Liver function abnormalities are commonly observed in cancer patient populations, and identifying their aetiology is often difficult (Floyd et al. 2006). Potential causes of abnormal liver function in patients with cancer include pre-existing medical problems such as hepatic metastases, alcoholism, hepatitis viruses, use of immunosuppressive drugs, malnutrition, paraneoplastic syndromes, portal vein thrombosis, infections, hepatic metastasectomy, and blood transfusion (Rodriguez-Frias and Lee 2007). Concomitant medications, including nonsteroidal anti-inflammatory drugs, antiemetic drugs, analgesics, or antibiotics may also be associated with hepatotoxicity due to interaction effects (Rodriguez-Frias and Lee 2007; Ingawale et al. 2014). Idiosyncratic drug-induced liver injury

can arise due to the complex interaction between genetic and non-genetic risk factors, which can be further subdivided into host susceptibility and environmental factors and include age, sex, and other diseases, such as chronic liver disease or human immunodeficiency virus infection (Chalasani et al. 2014). Compound-specific risk factors include daily dose, metabolic characteristics, and the propensity for drug interactions (Chalasani and Björnsson 2010).

Preventability:

Generally, in the clinical development programme of selpercatinib, ALT and AST increases were manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment.

Accordingly, this risk is addressed in the proposed labelling, including information for monitoring and management in case of increases in aminotransaminases.

Impact on the risk-benefit balance of the product:

Liver injury, as indicated by increases of aminotransferases, may be considered to have an impact on the risk-benefit balance of selpercatinib. Incidence of increased ALT and AST, both from reported TEAEs and on laboratory analysis, were observed in the Study (LIBRETTO-001). These were mostly Grade 1 or Grade 2. A majority of patients with Grade 3 to Grade 4 events of ALT or AST increased were able to continue in the study following dose interruption, decreased dose, or both. Generally, ALT and AST increases were manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment.

Based on the frequency of reported events of aminotransferase increased, and their potential to indicate liver injury, this is considered an important potential risk.

Public health impact:

A low incidence of severe increases of aminotransferases and serious hepatic events suggests that this risk is appropriately addressed by clinical management. As selpercatinib is used in a small population of patients with advanced cancer, the public health impact is low.

Important Potential Risk 2: Cardiac arrhythmia due to QT prolongation

Potential mechanisms:

The pathogenesis of QT prolongation associated with the use of selpercatinib is not well understood. In the 3-month repeated-dose study, an increase in QTc interval was noted in female minipigs administered 5 mg/kg/day of selpercatinib, but the degree of increase was small (approximately 7% to 12%). This low magnitude of QTc increase was noted and considered potentially related to selpercatinib but was not considered adverse. Some MKIs that can inhibit *RET*, such as vandetanib, were reported to be associated with prolongation of the QTc interval, *torsade de pointes*, and sudden death (Zang et al. 2012; Shah et al. 2013; Caprelsa package insert, 2019). However, not all MKIs are associated with clinically significant QT prolongation (Ghatalia et al. 2015).

Evidence source(s) and strength of evidence:

In LOXO-RET-18032, a single-dose pharmacokinetic/pharmacodynamic study of the effects of selpercatinib on cardiac repolarisation in healthy volunteer subjects, the results showed that selpercatinib had a positive signal as per the International Council for Harmonisation E14 criteria for QTc prolongation. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90% CI: 12.1 msec) at the mean steady-state C_{max} observed in patients after administration of 160 mg BID. The increase in QTc was concentration dependent.

Characterisation of the risk:

In the ongoing Phase 1/2 clinical study, TEAEs of QT prolongation were observed in 21.1of patients treated with selpercatinib. A majority of events were Grade 1 (8.2%) or Grade 2 (8.0%). Grade 3 events were observed in 4.9% of patients.

Two patients discontinued selpercatinib treatment due to QT prolongation.

Table SVII.2.2. A Breakdown of QT Prolongation Events by Study

Clinical Trial	ECG QT Prolongation (TEAEs) n (%)
LIBRETTO-001	
All Grades	177(21.1)
Grade 3/4	41(4.9)
LIBRETTO-431	
All Grades	32(20.3)
Grade 3/4	14(8.9)
LIBRETTO-121	
All Grades	2(7.4)
Grade 3/4	0(0.0)
LIBRETTO-531	
All Grades	26(13.5)
Grade 3/4	9(4.7)

Abbreviations: ECG = electrocardiogram; n = number of events; QT = time from the start of the Q wave to the end of the T wave; TEAE = treatment-emergent adverse event.

Data source: prd\ly3527723\j2g_ox_jzja\csr5\output\restricted\overall\taesi_qtcomp_acn

QT prolongation: j2g_mc_jzjc/csr1/output/restricted/topline/t_14_3_2_6_4_1.rtf

JZJB: prd/ly3527723/j2g_mc_jzjb/csr1/output/restricted/for_safety/t_14_3_2_6_4_1.rtf

JJ prd/ly3527723/j2g_ox_jzjj/intrm1/output/shared/regulatory/taesi_ecg_qt_prolongation.rtf

There were no reports of *torsades de pointes*, ventricular tachycardia, ventricular fibrillation, or ventricular flutter There was 1 report of sudden death (assessed as unrelated to selpercatinib) in a patient with significant cardiac history who experienced episodes of prolonged QT during the course of the study. One patient discontinued treatment due to QT prolongation.

Risk factors and risk groups:

Patients at higher risk of QT prolongation include those with occult congenital long QT syndrome, genetic polymorphisms (reduced repolarised reserve), underlying heart conditions, such as bradycardia, myocardial infarction, congenital heart failure or cardiac hypertrophy, female sex, and advanced age (Makkar et al. 1993; Roden 1998; Zeltser et al. 2003; Curigliano et al. 2009; Drew et al. 2010). Certain medications are a common cause of QT prolongation and include diuretics, antiarrhythmic drugs, certain antimicrobials, such as macrolide and fluoroquinolone antibiotics, and certain gastric motility agents, such as cisapride (Viskin et al. 2003; Roden 2004; Curigliano et al. 2009).

Preventability:

Cardiac arrhythmia due to QT prolongation is potentially preventable and reversible if recognised promptly and treated appropriately. Selpercatinib should be used with caution in patients at risk of QT prolongation. As part of routine practice, oncology physicians monitor patients during treatment with selpercatinib to detect changes in ECGs and associated symptoms, enabling early detection and management of QT prolongation, thus, minimising serious outcomes.

Accordingly, this risk is addressed in the current labelling, including information for monitoring and management of cardiac arrythmia due to QT prolongation.

Impact on the risk-benefit balance of the product:

The potential for severe consequences indicates QT prolongation is an important risk. Arrhythmia due to QT prolongation is potentially preventable and reversible if recognised promptly and treated appropriately. Cardiac arrhythmia due to QT prolongation such as *torsades de pointes* can have a substantial impact on individual patients, as outcome can be severe and, in some cases, fatal. The TEAE of ECG QT prolonged is considered an ADR for selpercatinib. In preclinical studies, low magnitude of QTc increase was noted and was potentially related to selpercatinib. In the clinical study, ECG QT prolonged was observed (21.1%). A majority of events were low grade. To date, no clinically significant or fatal treatment-emergent arrhythmias or *torsades de pointes* have been observed. Therefore, this risk is considered to have a low impact on the risk-benefit balance for selpercatinib.

Public health impact:

Administration of selpercatinib is limited to the small number of patients with advanced *RET*-altered cancer. Therefore, the impact on public health is considered minimal.

Important Potential Risk 3: Reproductive and developmental toxicities

Potential mechanisms:

The signalling of *RET* has critical roles in development of the enteric nervous system and kidney (Arighi et al. 2005). Though the mechanism is not clear, selpercatinib was shown to be a developmental toxicant and embryo-lethal in an animal study. Decreased testicular weights and vaginal mucification with altered oestrous cycle were also observed in animal studies.

Evidence source(s) and strength of evidence:

Non-clinical data suggest that there is a risk for reproductive and developmental toxicities in women exposed to selpercatinib during pregnancy and a risk for reproductive organ injury and fertility effects in men. Accordingly, this has been determined to be a key safety finding from the non-clinical development programme of selpercatinib.

Pregnant women are excluded from participation in the clinical development programme for selpercatinib. Women of childbearing potential and men were required to use highly effective contraception during participation in any clinical trial. Therefore, no human data are available.

Characterisation of the risk:
Non-clinical data suggest that this safety concern is a key safety finding. No human data are available.

Risk factors and risk groups:

Known risk factor associated with reproductive and developmental toxicities may include malnutrition, hypoxia, chronic inflammation, toxic or teratogenic effects of cancer treatment (Lu et al. 2017), decreased fertility due to chemotherapy in women, and gonadal dysfunction due to neoplastic agents, such as cisplatin (Ruddy and Partridge 2012). Furthermore, maternal pre-existing conditions that are risk factors associated with reproductive and developmental toxicities include smoking, diabetes, obesity (Gardosi et al. 2013), alcohol consumption, and maternal advanced age (Harris et al. 2017). Higher maternal or paternal age (Maconochie et al. 2007) may also increase risk. Certain medications can increase risk including those for cancer treatment, for example, cytarabine, 5-fluorouracil, cyclophosphamide, tamoxifen, and imatinib, (Voulgaris et al. 2011) or for other medical conditions, for example, antiepileptic drugs, folic acid antagonists (Harris et al. 2017; Sabers et al. 2017).

Preventability:

There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to the foetus. Women of childbearing potential have to use highly effective contraception during treatment and for at least 1 week after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least 1 week after the last dose of selpercatinib. Selpercatinib is not recommended during pregnancy, in women of childbearing potential, or in men not using contraception.

Impact on the risk-benefit balance of the product:

Based on findings from non-clinical studies, any exposure of selpercatinib during pregnancy may have severe consequences on the foetus. This risk and appropriate risk minimisation measures are clearly addressed in respective sections of the current labelling.

Public health impact:

The public health impact is considered minimal, as the use of selpercatinib should be avoided during pregnancy and due to the low pregnancy rates expected in the indicated population.

Important Potential Risk 4: Growth plate abnormalities in paediatric patients

Potential mechanisms:

The pathogenesis of growth plate abnormalities associated with the use of selpercatinib is not well understood. RET is an RTK with critical roles in normal kidney and enteric nervous system development along with roles in maintenance of several adult tissue types. Effects on growth plates in rats have been reported for RTK inhibitors, including sunitinib and lenvatinib and are related to the pharmacological activity of these compounds on growth plates of the long bones and periosteal cartilage development.

Evidence source(s) and strength of evidence:

Juvenile and adolescent rats and adolescent minipigs with open growth plates administered selpercatinib exhibited microscopic changes of hypertrophy, hyperplasia, and dysplasia of growth-plate cartilage (physis). In the juvenile rat study, the skeletal changes were

- irreversible physeal dysplasia at bone growth plates
- decreased bone size or geometry, mass, and/or density at both the distal femur metaphysis and femur diaphysis (some findings not reversible), and
- decreased femur length (observed at recovery necropsy).

The skeletal changes were observed at exposures approximately 1 to 4 times the exposure in adults at the efficacious dose of 160 mg BID and are, therefore, considered potentially relevant to the paediatric patient population.

Characterisation of the risk:

The non-clinical bone-related findings suggest a risk for growth plate abnormalities in patients with open growth plates, the potential impact of which could include decreased longitudinal bone growth or epiphysiolysis (slipped capital femoral epiphysis/slipped upper femoral epiphysis).

Very limited data are available in the paediatric and adolescent population. Therefore, there is insufficient human data informing the drug-associated risk. In Clinical Study LIBRETTO-001, no TEAEs related to growth disorders have been identified.

Risk factors and risk groups:

Paediatric and adolescent patients with open growth plates who have not yet obtained full adult height may be at risk for growth plate abnormalities, the potential impact of which could include decreased longitudinal bone growth.

Patients with childhood cancer may have impaired growth before, during, or after treatment for their cancer. A number of factors are responsible for this, including

- the disease process itself
- complications of treatment (infection)

- direct effects during treatment (anorexia, vomiting), and
- direct and indirect late effects attributable to therapy.

The particular risks of growth impairment for any individual survivor depend upon the cancer type, the treatment given, and the age at presentation.

Preventability:

Based on the non-clinical findings, this risk is addressed in the product labelling, including information for monitoring of open growth plates in adolescent patients.

Impact on the risk-benefit balance of the product:

Based on findings in animals, selpercatinib has the potential to impact the development of the epiphyseal plate. Very limited data are available in the paediatric and adolescent population, therefore, there are insufficient human data informing the drug-associated risk. In the context of the target population, which includes adolescent patients with advanced *RET*-altered cancer with limited life expectancy, the clinical significance of any effect on the growth plates is unclear and is not expected to have a significant impact on the risk-benefit profile of selpercatinib.

Public health impact:

Administration of selpercatinib is limited to the small number of adolescent patients aged 12 years and older with advanced *RET*-mutant MTC. Therefore, the impact on public health is considered very minimal.

SVII.3.2 Presentation of the Missing Information

Missing Information 1: Exposure and safety in patients with severe hepatic impairment

Patients with severe hepatic impairment were excluded from the clinical trials. In the clinical pharmacology study, mild and moderate Child-Pugh groups were similar to normal in clearance, although in severe disease, exposure was increased with AUC being 77% higher in the severe Child-Pugh group. There were no safety concerns in this single-dose study. Hence, safety data on effects in patients with severe hepatic impairment are limited.

Evidence source:

Pharmacological properties indicate that selpercatinib is metabolised by microsomal fractions and hepatocytes from mice, rats, dogs, minipigs, and humans. In the clinical study, increases of aminotransferases, including ALT and AST, have been observed in patients treated with selpercatinib. Liver injury is considered an important potential risk.

Anticipated risk/consequence of the missing information:

Use of selpercatinib in patients with severe hepatic impairment is not contraindicated. Selpercatinib 80 mg BID should be administered with caution to patients with severe hepatic impairment.

If exposure data for selpercatinib in patients with severe hepatic impairment becomes available, the effect on the risk-benefit profile will be assessed.

Missing Information 2: Exposure and safety in patients with cardiac impairment

Patients with clinically significant active cardiac disease prior to planned start of study treatment have been excluded from participation in the selpercatinib clinical development programme. Hence, safety data on effects in patients with clinically significant active cardiac disease are limited.

Evidence source:

Incidences of cardiac arrythmia and cardiac failure from reported TEAEs were observed in the clinical study LIBRETTO-001. These were predominantly Grade 1 or Grade 2. There is no evidence to suggest that treatment with selpercatinib leads to clinically significant cardiac impairment. However, as no controlled data are available in the study, the role of selpercatinib in the onset of cardiac disorders cannot be definitively ruled out.

Anticipated risk/consequence of the missing information:

Use of selpercatinib in patients with clinically significant active cardiac disease is not contraindicated. The population of patients eligible for treatment with selpercatinib, who also have cardiac impairment, is anticipated to be small.

If data for the potential role of selpercatinib in the onset of cardiac disorders or in patients with cardiac impairment become available, the effect on the risk-benefit profile will be assessed.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Liver injury Cardiac arrhythmia due to QT prolongation Reproductive and developmental toxicities Growth plate abnormalities in paediatric patients
Missing information	Exposure and safety in patients with severe hepatic impairment Exposure and safety in patients with cardiac impairment

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

As part of routine pharmacovigilance activities, specific follow-up forms are used to collect additional scientific or medical data to facilitate evaluation of cases. The follow-up forms listed here are only related to the currently listed safety concerns that are liver injury, cardiac arrhythmia due to QT prolongation, and reproductive and developmental toxicities.

Follow-up forms:

- Pregnancy data collection form–maternal
- Pregnancy outcome form–maternal
- Pregnancy data collection form–paternal
- Pregnancy outcome form–paternal

Other forms of routine pharmacovigilance activities for safety concerns:

The safety of selpercatinib in paediatric patients, including the potential risk of growth disorders, will be further characterised in the Study LIBRETTO-121 (LOXO-RET-18036/J2G-OX-JZJJ).

Routine safety evaluations will include growth as measured by height and weight. In addition, patients, who have not yet obtained full adult height, will undergo either X-ray or magnetic resonance imaging of the right knee at baseline and every 6 months during participation in the study while the growth plate remains open. Relevant findings will be presented in the Periodic Safety Update Report as they emerge. Monitoring and data collection are ongoing across these studies until the end of data collection.

III.2 Additional Pharmacovigilance Activities

None

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable

Part IV: Plans for Post-authorisation Efficacy Studies

Table Part IV.1. Planned and Ongoing Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

	Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation	None				
Efficacy studies that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances	**Protocol Number:** **J2G-OX-JZJJ/LOXO-RET-18036/LIBRETTO-121** A Phase 1/2 Study of the Oral *RET* Inhibitor LOXO-292 in Pediatric Patients with Advanced *RET*-Altered Solid or Primary Central Nervous System Tumors **Status:** Ongoing	To determine the objective response rate, other efficacy outcomes, and safety in paediatric patients with advanced cancer harbouring an activating *RET* alteration following initiation of selpercatinib	Long-term efficacy in paediatric patients	First patient visit	July 2019
				Final study report	Estimated 30 June 2025

Abbreviations: MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PFS = progression-free survival; *RET* = REarranged during transfection TFFS = treatment failure-free survival.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important potential risks	
Liver injury	**Routine risk communication:** SmPC Sections 4.2 and 4.4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for liver function monitoring are included in SmPC Section 4.4. • Recommendations for management of increased transaminases are included in SmPC Section 4.2. **Pack size:** Not applicable **Legal status**: Not applicable
Cardiac arrhythmia due to QT prolongation	**Routine risk communication:** SmPC Sections 4.2 and 4.4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for ECG monitoring are included in SmPC Section 4.4. • Recommendations for management of QT interval prolongation are included in SmPC Section 4.2. **Pack size:** Not applicable **Legal status:** Not applicable
Reproductive and developmental toxicity	**Routine risk communication**: SmPC Sections 4.4 and 4.6. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for women and men of childbearing potential are included in SmPC Section 4.6. **Pack size:** Not applicable **Legal status:** Not applicable
Growth plate abnormalities in paediatric patients	**Routine risk communication**: SmPC Sections 4.2 and 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for monitoring of open growth plates in adolescent patients and for the management of growth plate abnormalities are included in SmPC Section 4.2.

	Pack size: Not applicable **Legal status:** Not applicable
Missing information	
Exposure and safety in patients with severe hepatic impairment	**Routine risk communication:** SmPC Sections 4.2 and 4.4. A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is completed. The respective safety and pharmacokinetics data are described in the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Not applicable **Pack size:** Not applicable **Legal status:** Not applicable
Exposure and safety in patients with cardiac impairment	**Routine risk communication:** • Not applicable **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Not applicable **Pack size:** Not applicable **Legal status:** Not applicable

Abbreviations: ECG = electrocardiogram; SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.2. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Cardiac arrhythmia due to QT prolongation	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Pregnancy and Breastfeeding follow-up forms **Additional pharmacovigilance activities:** Study: None
Growth plate abnormalities in paediatric patients	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.3 **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Exposure and safety in patients with severe hepatic impairment	**Routine risk minimisation measures:** A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is completed. SmPC is updated based on the safety and pharmacokinetic data. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None
Exposure and safety in patients with cardiac impairment	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study: None

Abbreviation: SmPC = Summary of Product Characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Selpercatinib

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

Selpercatinib's SmPC and its package leaflet give essential information to healthcare professionals and patients on how selpercatinib should be used.

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

I – RETSEVMO and What it is Used for

See SmPC for full indication information. RETSEVMO contains selpercatinib as the active substance, given orally, in the form of a simple blend with excipient capsule in dose strengths of 40 or 80 mg or in the form of round, immediate-release, film-coated tablets in strengths of 40, 80, 120, and 160 mg.

RETSEVMO (selpercatinib) as monotherapy is indicated for the treatment of adults with

- advanced *RET* fusion-positive NSCLC not previously treated with a *RET* inhibitor, and
- advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit or have been exhausted (see Sections 4.4 and 5.1).

RETSEVMO as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with

- advanced RET fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate), and
- advanced *RET*-mutant MTC.

Further information about the evaluation of RETSEVMO's benefits can be found in RETSEVMO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo

II – Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of selpercatinib, together with measures to minimise such risks and the proposed studies for learning more about selpercatinib's risks, are outlined in this section.

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 patients and healthcare professionals
- 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, and
- the medicine's legal status — the way a medicine is supplied to the patient, for example, with or without prescription can help to minimise its risks.

Together, these constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 selpercatinib is not yet available, it is listed under 'missing information' as follows.

II.A List of Important Risks and Missing Information

Important risks of selpercatinib are those that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of selpercatinib. 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, for example, on the long-term use of the medicine.

List of important risks and missing information	
Important identified risks	None
Important potential risks	Liver injury Cardiac arrhythmia due to QT prolongation Reproductive and developmental toxicities Growth plate abnormalities in paediatric patients
Missing information	Exposure and safety in patients with severe hepatic impairment Exposure and safety in patients with cardiac impairment

II.B Summary of Important Risks

Important Potential Risk 1: Liver injury	
Evidence for linking the risk to the medicine	In the Study LIBRETTO-001, increases in aminotransferases, including ALT and AST, have been observed in patients treated with selpercatinib. Based on the frequency of reported events of aminotransferase increased, and their potential to indicate liver injury, liver injury is considered an important potential risk. Generally, increases of aminotransferases were of low severity and manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment.
Risk factors and risk groups	There are a number of risk factors associated with liver injury, including advancing age, female gender, nutritional deficiencies, alcohol consumption, chronic hepatitis B and C, and genetic risk factors (Ingawale et al. 2014). Liver function abnormalities are commonly observed in cancer patient populations and identifying their aetiology is often difficult (Floyd et al. 2006). Potential causes of abnormal liver function in patients with cancer include pre-existing medical problems such as hepatic metastases, alcoholism, hepatitis viruses, use of immunosuppression drugs, malnutrition, paraneoplastic syndromes, portal vein thrombosis, infections, hepatic metastasectomy, and blood transfusion (Rodriguez-Frias and Lee 2007). Concomitant medications including nonsteroidal anti-inflammatory drugs, antiemetic drugs, analgesics, or antibiotics may also be associated with hepatotoxicity due to interaction effects (Rodriguez-Frias and Lee 2007; Ingawale et al. 2014). Idiosyncratic drug-induced liver injury can arise due to the complex interaction between genetic and non-genetic risk factors which can be further subdivided into host susceptibility and environmental factors and include age, sex and other diseases such as chronic liver disease or human immunodeficiency virus infection (Chalasani 2014). Compound-specific risk factors include daily dose, metabolic characteristics, and the propensity for drug interactions (Chalasani and Björnsson, 2010).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; SmPC = Summary of Product Characteristics.

Important Potential Risk 2: Cardiac arrhythmias due to QT	
Evidence for linking the risk to the medicine	In the ongoing Phase 1/2 clinical study clinical, TEAE of QT prolongation was observed in 21.1% of patients treated with selpercatinib. A majority of the events has been Grade 1 (8.2%) or Grade 2 (8.0%) in severity. Grade 3 events were observed in 4.9% of patients. Fatal events such as sudden death and cardiac arrest were reported in patients with significant cardiac history. The effect of selpercatinib on the QTc interval was evaluated in a thorough QT study in healthy subjects. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90% CI: 12.1 msec) at the mean steady-state C_{max} observed in patients after administration of selpercatinib 160 mg twice daily. The increase in QTc was concentration-dependent.
Risk factors and risk groups	Patients at higher risk of QT prolongation include occult congenital long QT syndrome, genetic polymorphisms (reduced repolarised reserve), underlying heart conditions such as bradycardia, myocardial infarction, congenital heart failure or cardiac hypertrophy, female sex, and advanced age (Makkar et al. 1993; Roden 1998; Zeltser et al. 2003; Curigliano et al. 2009; Drew et al. 2010). Certain medications are a common cause of QT prolongation including diuretics, antiarrhythmic drugs, certain antimicrobials, such as macrolide and fluoroquinolone antibiotics, and certain gastric motility agents such as cisapride (Viskin et al. 2003; Roden 2004; Curigliano et al. 2009).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: CI = confidence interval; C_{max} = maximum observed drug concentration; QTc = corrected time from the start of the Q wave to the end of the T wave interval; SmPC = summary of product characteristics; TEAE = treatment-emergent adverse event.

Important Potential Risk 3: Reproductive and developmental toxicities	
Evidence for linking the risk to the medicine	Non-clinical data suggest that there is a potential risk for reproductive and developmental toxicities in women exposed to selpercatinib during pregnancy, and a potential risk for reproductive organ injury and fertility effects in men. Accordingly, this has been determined a key safety finding from the non-clinical development programme of selpercatinib.
Risk factors and risk groups	Known risk factor on maternal cancer on foetal and infant health may include malnutrition, hypoxia, chronic inflammation, and toxic or teratogenic effects of cancer treatment (Lu et al. 2017). Other risk factors associated with reproductive and developmental outcomes are listed as follows: • For maternal and paternal infertility: temporary or permanent amenorrhea and decreased fertility due to chemotherapy in women and gonadal dysfunction due to neoplastic agents such as cisplatin (Ruddy and Partridge 2012). • For spontaneous abortion (miscarriage): for example, previous miscarriage, termination and infertility, assisted conception, regular/high alcohol consumption, feeling stressed, higher maternal and paternal age (Maconochie et al. 2007). • For stillbirth: parity, ethnicity, maternal obesity, smoking, pre-existing diabetes, history of mental health problems, antepartum haemorrhage, and foetal growth restriction (Gardosi et al. 2013). • For congenital anomalies and teratogenicity: certain maternal factors, such as alcohol consumption, folic acid deficiency, uncontrolled maternal diabetes, or phenylketonuria, obesity, advanced maternal age (Harris et al. 2017); certain medications used to treat cancer (for example, cytarabine, 5-fluorouracil, cyclophosphamide, tamoxifen, and imatinib) (Voulgaris et al. 2011); or other medical conditions (for example, antiepileptic drugs, folic acid antagonists) (Harris et al. 2017; Sabers et al. 2017).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** Not applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: SmPC = summary of product characteristics.

Important Potential Risk 4: Growth plate abnormalities in paediatric patients	
Evidence for linking the risk to the medicine	Juvenile and adolescent rats and adolescent minipigs with open growth plates administered selpercatinib, exhibited microscopic changes of hypertrophy, hyperplasia, and dysplasia of growth-plate cartilage (physis). In the juvenile rat study, the skeletal changes were • irreversible physeal dysplasia at bone growth plates • decreased bone size or geometry, mass, and/or density at both the distal femur metaphysis and femur diaphysis (some findings not reversible), and • decreased femur length (observed at recovery necropsy). The skeletal changes were observed at exposures approximately 1 to 4 times the exposure in adults at the efficacious dose of 160 mg twice daily and are, therefore, considered potentially relevant to the paediatric patient population.
Risk factors and risk groups	Paediatric and adolescent patients with open growth plates, who have not yet obtained full adult height, may be at risk for growth plate abnormalities. The potential impact of which could include decreased longitudinal bone growth. Patients with cancer since childhood may have impaired growth before, during, or after treatment for their cancer. A number of factors are responsible for this, including the disease process itself, complications of treatment (infection), direct effects during treatment (anorexia, vomiting), and direct and indirect late effects attributable to therapy. The particular risks of growth impairment for any individual survivor depend upon the cancer type, the treatment given, and the age at presentation.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 **Additional risk minimisation measures:** Not applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: SmPC = summary of product characteristics.

Important Missing Information 1: Exposure and safety in patients with severe hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures:** A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is complete. The respective safety and pharmacokinetic data are described in the SmPC. **Additional risk minimisation measures:** Not applicable.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Missing Information 2: Exposure and safety in patients with cardiac impairment	
Risk minimisation measures	**Routine risk minimisation measures:** None. **Additional risk minimisation measures:** Not applicable.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: SmPC = summary of product characteristics.

II.C Post-authorisation Development Plan

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

The following studies are conditions of the marketing authorisation:

Study short name: **LOXO-RET-18036/J2G-OX-JZJJ**

Purpose of the study: To determine the ORR and other efficacy outcomes in paediatric patients with advanced cancer harbouring an activating *RET* alteration following initiation of selpercatinib.

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

Study short name: **LOXO-RET-18036/J2G-OX-JZJJ**

Purpose of the study: To determine the ORR and other efficacy outcomes in paediatric patients with advanced cancer harbouring an activating *RET* alteration following initiation of selpercatinib.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the Form
Form 1: Pregnancy Data Collection – Maternal	Example: *Pregnancy*
Form 2: Pregnancy Outcome – Maternal	Example: *Pregnancy Outcome*
Form 3: Pregnancy Data Collection – Paternal	Example: *Pregnancy*
Form 4: Pregnancy Outcome – Paternal	Example: *Pregnancy Outcome*

Form 1: Pregnancy Data Collection – Maternal

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Birth Date or Age:

Patient Name or Initials: _____ _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: _____

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Pregnancy Data Collection - Maternal

Pregnancy Details

Name or initials: _____ Date of Birth or Age: _____

Due Date: _____ Last menstrual period: _____

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	○ M ○ F				

Maternal medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Contraceptive method:

_____

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:

Eli Lilly and Company - Global Patient Safety **Case Number:**

○ 0-12 weeks/1st trimester ○ 13-24 weeks/2nd trimester ○ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance(please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ○ No ○ Yes

Define complications:

Treatment:

Continuing: ○ No ○ Yes

Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)

Additional Contact Information

Medical professional responsible for monitoring patient's pregnancy:

Name:

Address:

Phone:

Fax:

Medical professional responsible for monitoring the infant:

Name:

Address:

Phone:

Fax:

Was this event related to a Lilly drug?

☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Form 2: Pregnancy Outcome – Maternal

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____
Patient Birth Date or Age:
Patient Name or Initials: _____ _____

Gender: ◯ F ◯ M ◯ Unknown	**Race:** ◯ Caucasian ◯ Asian ◯ Black ◯ Other	**Weight:** _____ ◯ lb ◯ kg	**Height:** _____ ◯ in ◯ cm

Reported Drug: _____
Lot/Control Number (if available): _____ **Indication:** _____
Dose: _____ **Frequency:** _____ **Formulation:** _____
Start Date: _____ **Dose when event occurred:** _____ **Route:** _____
Drug D/C? ◯ No ◯ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ◯ Yes ◯ No
Drug Restarted? ◯ No ◯ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ◯ Yes ◯ No

Pregnancy Outcome Maternal

Pregnancy Details

Name or initials: _____ Date of Birth or Age: _____

Due Date: _____ Last menstrual period: _____

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	◯ M ◯ F				

Maternal medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Contraceptive method:
_____

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:

Eli Lilly and Company - Global Patient Safety **Case Number:**

○ 0-12 weeks/1st trimester ○ 13-24 weeks/2nd trimester ○ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance(please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ○ No ○ Yes

Define complications:

Treatment:

Continuing: ○ No ○ Yes

Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)

Pregnancy/Fetal Outcome

○ Live birth/full term
○ Premature birth (less than 37 weeks)
○ Spontaneous/missed abortion
○ Fetal death in utero/stillbirth
○ Live birth with neonatal death
○ Post natal death

Were congenital or chromosomal abnormalities detected? ○ No ○ Yes

Please define:

Neonatal/Infant Data

Infant name or initials: _____ EDC (Due Date): _____ Date of Delivery: _____

Gestational age: _____ Gender: ○ Undetermined/unknown ○ Male ○ Female

Apgar scores: at 1 minute _____ at 5 minutes _____

Weight: _____ ○ grams ○ pounds Length: _____ ○ cm ○ inches

Infant's overall healthy status?

Infant Adverse Events/Complications

Did the infant experience any problems while breast feeding? ○ No ○ Yes

Please describe:

Treatment:

Continuing: ◯ No ◯ Yes

Infant's overall health status:

_____

Additional Contact Information

Medical professional responsible for monitoring patient's pregnancy:
Name:

_____

Address:

Phone:

_____

Fax:

_____

Medical professional responsible for monitoring the infant:

Name:

_____

Address:

Phone: _____

Fax:_____

Was this event related to a Lilly drug?

☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Form 3: Pregnancy Data Collection – Paternal

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____
Patient Birth Date or Age: _____
Patient Name or Initials: _____

Gender: ◯ F ◯ M ◯ Unknown	**Race:** ◯ Caucasian ◯ Asian ◯ Black ◯ Other	**Weight:** _____ ◯ lb ◯ kg	**Height:** _____ ◯ in ◯ cm

Reported Drug: _____
Lot/Control Number (if available): _____ **Indication:** _____
Dose: _____ **Frequency:** _____ **Formulation:** _____
Start Date: _____ **Dose when event occurred:** _____ **Route:** _____
Drug D/C? ◯ No ◯ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ◯ Yes ◯ No
Drug Restarted? ◯ No ◯ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ◯ Yes ◯ No

Pregnancy Data Collection - Paternal

Patient (Father) Details
Name or initials: _____ Date of Birth or Age: _____

Father's medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Pregnancy Details

Name or initials: _____ Date of Birth or Age: _____

Due Date: _____ Last menstrual period: _____

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	◯ M ◯ F				

Maternal medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:

○ 0-12 weeks/1st trimester ○ 13-24 weeks/2nd trimester ○ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC and herbal)

Maternal Concomitant Medications/Substance(please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ○ No ○ Yes

Define complications:

Treatment:

Continuing: ○ No ○ Yes

Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)

Additional Contact Information

Medical professional responsible for monitoring the father:
Name:

Address:

Phone:

Fax:

Medical professional responsible for monitoring the mother:
Name:

Address:

Phone:

Fax:

Was this event related to a Lilly drug?

☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety Case Number:

Form 4: Pregnancy Outcome – Paternal

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____
Patient Birth Date or Age:
Patient Name or Initials: _____ _____

Gender: ◯ F ◯ M ◯ Unknown	**Race:** ◯ Caucasian ◯ Asian ◯ Black ◯ Other	**Weight:** _____ ◯ lb ◯ kg	**Height:** _____ ◯ in ◯ cm

Reported Drug: _____
Lot/Control Number (if available): _____ **Indication:** _____
Dose: _____ **Frequency:** _____ **Formulation:** _____
Start Date: _____ **Dose when event occurred:** _____ **Route:** _____
Drug D/C? ◯ No ◯ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ◯ Yes ◯ No
Drug Restarted? ◯ No ◯ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ◯ Yes ◯ No

Pregnancy Outcome Paternal

Patient (Father) Details
Name or initials: _____ Date of Birth or Age: _____

Father's medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Pregnancy Details

Name or initials: _____ Date of Birth or Age: _____

Due Date: _____ Last menstrual period: _____

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	◯ M ◯ F				

Maternal medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Contraceptive method:

_____

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:

○ 0-12 weeks/1st trimester ○ 13-24 weeks/2nd trimester ○ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC and herbal)

Maternal Concomitant Medications/Substance(please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ○ No ○ Yes

Define complications:

Treatment:

Continuing: ○ No ○ Yes

Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)

Pregnancy/Fetal Outcome

○ Live birth/full term
○ Premature birth (less than 37 weeks)
○ Spontaneous/missed abortion
○ Fetal death in utero/stillbirth
○ Live birth with neonatal death
○ Post natal death

Were congenital or chromosomal abnormalities detected? ○ No ○ Yes

Please define:

Neonatal/Infant Data

Infant name or initials: _____ EDC (Due Date): _____ Date of Delivery: _____

Gestational age: _____ Gender: ○ Undetermined/unknown ○ Male ○ Female

Apgar scores: at 1 minute _____ at 5 minutes _____

Weight: _____ ○ grams ○ pounds Length: _____ ○ cm ○ inches

Infant's overall healthy status?

Infant Adverse Events/Complications

Did the infant experience any problems while breast feeding? ○ No ○ Yes

Please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment:

Continuing: ◯ No ◯ Yes

Infant's overall health status:

Additional Contact Information

Medical professional responsible for monitoring the father:
Name:

Address:

Phone:

Fax:

Medical professional responsible for monitoring the mother:
Name:

Address:

Phone:

Fax:

Was this event related to a Lilly drug?

☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable