EU Risk Management Plan
for
KRAZATI
(adagrasib)

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EU QPPV name: Marcella Coyne

EU QPPV oversight declaration:

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

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LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ALT	Alanine aminotransferase
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BID	Twice daily
CI	Confidence interval
CIT	Checkpoint inhibitor therapy
Cmax	Maximum concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CSR	Clinical study report
CVD	Cardiovascular disease
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECIS	European cancer information system
EFD	Embryofoetal development
EU	European Union
FDA	Food and Drug Administration
GDP	Guanosine diphosphate
GLP	Good laboratory practice
HIV	human immunodeficiency virus
HR	Hazard ratio
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ILD	Interstitial lung disease
ISS	Integrated safety summary
MATE	Multidrug and toxin extrusion
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency

NCCN	National comprehensive cancer network
NOAEL	No-observed-adverse-effect-level
NSCLC	Non-small cell lung cancer
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OS	Overall survival
ORR	Objective response rate
PBPK	Physiologically based pharmacokinetic
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PY	Patient years
QD	Once daily
QTc	Corrected QT
QTcF	Corrected QT interval based on Fridericia's formula
RMP	Risk management plan
SOC	System organ class
SmPC	Summary of product characteristics
SMQ	Standardise MedDRA query
TEAE	Treatment-emergent adverse event
TNM	tumour, node and metastasis
ULN	Upper limit of normal
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States
yr	Year

PART I: PRODUCT(S) OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Adagrasib
Pharmacotherapeutic group(s) (ATC Code)	Other antineoplastic agents, ATC Code L01XX77
Marketing Authorisation Applicant	Mirati Therapeutics B.V.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	KRAZATI®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: KRAS G12C inhibitor
	Summary of mode of action: Adagrasib is a selective, irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive, GDP-bound conformation, which prevents KRAS-dependent downstream signalling without affecting wild-type KRAS protein. Adagrasib inhibits tumour cell growth and viability in cells harbouring *KRAS* G12C mutations and results in regression in *KRAS* G12C-positive nonclinical tumour models with minimal off-target activity.
	Important information about its composition: Krazati is formulated as a film-coated tablet. Each tablet contains, in addition to adagrasib, microcrystalline cellulose (E 460), mannitol (E 421), crospovidone, silica, colloidal anhydrous (E 551), and magnesium stearate (vegetable). The film-coating is comprised of hypromellose, titanium dioxide (E 171), polydextrose (E 1200), talc (E 553b), maltodextrin, and medium chain triglycerides (vegetable). Each film-coated tablet contains up to 0.25 mg glucose and up to 0.12 mg sorbitol.
Hyperlink to the Product Information	Krazati Product Information (Module 1.3.1)
Indication(s) in the EEA	Current: Krazati as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation and disease progression after at least one prior systemic therapy.
	Proposed: Not applicable

Dosage in the EEA	Current: The recommended dose of Krazati is 600 mg (three 200 mg tablets) twice daily.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: White to off-white, oval shaped, film-coated tablets, each containing 200 mg adagrasib
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication

Krazati as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation and disease progression after at least one prior systemic therapy.

Incidence and prevalence

Worldwide, lung cancer (11.4% of total cases) is the second most commonly diagnosed cancer and is the most frequently occurring cancer in men (14.3%) and third most common in women (8.4%). An estimated 2.2 million (2,206,771) new lung cancer cases occurred worldwide in 2020, with Europe accounting for 22.8% (4.4 million) of the worldwide total cancer cases (19.3 million) (Sung 2021). There were an estimated half million (477,534) new lung cancer cases across Europe in 2020 according to the European Cancer Information System (ECIS 2021), with 318,327 incident cases across 27 countries comprising the European Union (EU-27). In 2020, lung cancer incidence (age standardised rate) was estimated to vary 2-fold ranging from 43.9–55.7 cases per 100,000 people (eg, Sweden, Bulgaria) to 90.1-101.7 cases (eg, Ireland, Hungary) across the EU-27 (ECIS 2021).

The RAS family of genes comprises 3 members, *KRAS*, *NRAS*, and *HRAS*, which are mutated in nearly 25% of all human cancers. The majority of RAS family mutations are missense mutations that result in changes at residues (codons) 12, 13, and 61. Among the RAS isoforms, missense mutations are found most commonly in *KRAS* (85%) and much less in *NRAS* (12%) and *HRAS* (3%) (Simanshu 2017). *KRAS* is the most frequently mutated gene of the RAS family and accounts for approximately 30% of lung adenocarcinomas with the *KRAS* G12C mutation prevalent in 13% of total lung adenocarcinomas (Uras 2020). Based on this, and with NSCLC comprising 85% of lung cancer cases (https://www.drugs.com/cancer-lung.html; Duma 2019), the annual incidence of patients with *KRAS* G12C-mutated NSCLC in EU-27 in 2020 is estimated to be 35,175.

The survival of patients with lung cancer at 5 years after diagnosis is only 10% to 20% (Sung 2021). The number of 5-year prevalent cases of lung cancer in EU-27 in 2020 is estimated between 0.16 and 0.32 million. With NSCLC comprising 85% of lung cancer cases and assuming 13% of these are patients with *KRAS* G12C mutation, the 5-year prevalence of *KRAS* G12C-mutated NSCLC in the EU-27 is estimated at 17,680 to 35,360.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

In Europe (EU-27), lung cancer is the second most diagnosed cancer in men, after prostate cancer, and the third most diagnosed in women, after breast and colorectal cancers with 205,253 and 113,074 new cases occurring in 2020 in males and females, respectively. The lifetime risk (ages 0-74) of developing lung cancer in men (1:19) is approximately

double that in women (1:37) (ECIS 2021). The incidence of lung cancer remains low in patients younger than 40 years, peaking between ages 65 and 84 years (Duma 2019).

Tobacco smoking is the largest preventable cause of lung cancer and is estimated to account for 85% to 90% of lung cancers (Duma 2019). Mutation of glycine specifically to cysteine occurs in approximately 13% of lung adenocarcinomas, and results from a deoxyribonucleic acid (DNA) transversion mutation (guanine to thymine in *KRAS* gene) that has been attributed to carcinogens in tobacco smoke, particularly polycyclic aromatic hydrocarbons (Pfeifer 2002, Riely 2008). Despite recent declines in smoking prevalence, Europe as a region has the highest prevalence of tobacco smoking among adults (aged 15 years or greater) in the world with an estimated 36% of men and 20% of women smoking tobacco in 2020. In 2017, overall age-standardised prevalence of current tobacco smoking in the European population aged 35 years and older was 27.4% and 20.2% in men and women, respectively (Gredner 2021).

Whilst the risk of developing cancer is associated with the extent of smoking (ie, number of cigarettes smoked each day, the age at which smoking began, and the length of time over which smoking has continued) it is also associated with exposure to other carcinogenic factors, such as asbestos. Other risk factors include ionising radiation (as found in patients with a history of Hodgkin lymphoma or breast cancer); environmental toxins, such as second-hand smoke, radon, and metals (arsenic, chromium, and nickel); and polycyclic aromatic hydrocarbons. History of pulmonary fibrosis, human immunodeficiency virus (HIV) infection, and alcohol consumption have also been defined as risk factors for lung cancer (Gredner 2021, Duma 2019) as well as tuberculosis (https://www.drugs.com/cancer-lung.html).

The main existing treatment options

Treatment of NSCLC depends on the stage, histology, genetic alterations, and patient's condition. Treatment approaches include surgery, radiotherapy, chemotherapy, immunotherapy, and molecularly targeted therapy either alone or in combined modality (Alexander 2020).

In the absence of a targeted treatment option, initial treatment of advanced/metastatic NSCLC includes platinum-based chemotherapy and immune checkpoint (programmed death-1 [PD-1] or programmed death-ligand 1 [PD-L1]) inhibitor therapy administered concurrently or sequentially. Until recently, platinum-based chemotherapy doublets, with or without bevacizumab in selected patients, had been the standard of care for most patients with advanced NSCLC in the first-line treatment setting (Schiller 2002, Sandler 2006, Scagliotti 2009). Subsequently, checkpoint inhibitor therapies (CITs), including nivolumab, pembrolizumab, and atezolizumab, were proven to be effective in the treatment of advanced NSCLC in the second-line setting (Borghaei 2015, Garon 2015, Herbst 2016, Rittmeyer 2017), followed by studies in the first-line setting demonstrating a survival advantage as monotherapy in patients with untreated, advanced NSCLC characterised by ≥ 50% PD-L1 expression (Reck 2016, Herbst 2020), and in combination with a platinum-based chemotherapy regimen in the first-line, advanced disease treatment setting for patients with NSCLC regardless of PD-L1 status (Gandhi 2018, Socinski 2018).

Second-line chemotherapy remains a standard after failure of a platinum-based chemotherapy and CIT. Docetaxel, alone or in combination with ramucirumab or nintedanib, and pemetrexed remain approved chemotherapy options in patients previously treated with platinum-based chemotherapy and a checkpoint inhibitor. Median overall survival (OS) reported in randomised

clinical trials using these regimens as experimental or comparator therapies has varied between approximately 5.7 and 9.5 months, while median progression-free survival (PFS) and objective response rate (ORR) have ranged from 2.3 to 4.5 months and 5.5% to 12%, respectively (Shepherd 2000, Fossella 2000, Hanna 2004, Cohen 2005, Cohen 2009, Krzakowski 2010, Scagliotti 2009, Al-Saleh 2012, Tomasini 2016). With combination therapy, an ORR of 23% (95% confidence interval [CI]: 20% to 26%) has been observed in patients receiving docetaxel with ramucirumab or nintedanib (Garon, 2014). These regimens are associated with significant myelosuppression and consequent risk of infection as well as other adverse events that could limit their use (TAXOTERE SmPC, 2005), (CYRAMZA SmPC, 2019).

The European Commission granted a conditional marketing authorisation on 10 January 2022 for sotorasib for the treatment of adult patients with advanced NSCLC with the *KRAS* G12C mutation who have progressed beyond one prior line of therapy. The Medicines and Healthcare products Regulatory Agency (MHRA) had similarly granted a conditional marketing authorisation for sotorasib in Great Britain on 08 September 2021, based on an ORR of 37.1% (95% CI, 28.6-46.2) and a median duration of response of 10.0 months (95% CI, 6.9-11.1) (MHRA Public Assessment Report LUMYKRAS, 2021). The United States (US) Food and Drug Administration (FDA) previously granted accelerated approval of sotorasib on 28 May 2021, for *KRAS* G12C mutated NSCLC after at least one prior systemic therapy. Regulatory approvals were granted during 2021 in Switzerland and Canada (under the FDA's Project Orbis), and registration continues worldwide.

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

The natural history of lung cancer is one of progressive disease that is rapidly fatal (Detterbeck, 2008), and despite the significant advances of chemotherapy and immunotherapy for NSCLC, patients ultimately develop progressive disease.

NSCLC is often not diagnosed until advanced-stage unresectable disease is present (Planchard 2018). Cough, seen in 50% to 75% of patients, is the most common symptom, followed by haemoptysis, chest pain, and dyspnoea. Other less common symptoms include laboratory abnormalities or paraneoplastic syndromes (Duma 2019). Weight loss is another symptom, and patients with symptoms are more likely to have chronic obstructive pulmonary disease (COPD) (NCCN 2022). Diagnosis requires biopsy for histologic confirmation, with computed tomography (CT) being another initial modality of choice for diagnosis and staging of suspected lung cancer (Lang-Lazdunski 2013). The most common diagnostic procedure for lung cancer is bronchoscopic lung biopsy, often extended with evaluation of regional lymph nodes by endobronchial ultrasound and/or endoscopic ultrasound. In most cases this will be sufficient to diagnose NSCLC, although quite often the amount of obtained material is not sufficient to sub-classify the tumour in more detail (Postmus 2017). Evaluation also requires determination of the extent of the tumour to define the tumour, node and metastasis (TNM) stage (Brierley 2017). While adjuvant platinum-based chemotherapy is recommended for stages II-IIIA disease with an absolute decreased risk of death of 5.4% at 5 years, the relapse rates are high with a relatively high rate of toxicity (Alexander 2020). Approximately 30% of patients with NSCLC will have locally advanced disease (T3-T4, N2-N3, stage IIIA-C). Most of the patients with stage III NSCLC are non-surgical candidates for whom the current standard of care is concurrent chemoradiotherapy followed by immunotherapy (Alexander 2020). The 5-year overall survival

rate for NSCLC remains poor, from 68% in patients with stage IB disease to less than 10% in patients with stage IVA-IVB disease (Duma 2019). From 2009 to 2015, the overall 5-year survival rate for all NSCLC was 25% in the United States (US); patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer with 5-year survival rates ranging from 15% to 50%. However, despite this decline in death rates, there are still more deaths from lung cancer than from breast, prostate, colorectal, and brain cancers combined (NCCN 2022), and the 5-year survival of metastatic NSCLC remains at approximately 6% in the US (Howlader 2019).

Important co-morbidities

Lung cancer is associated with age and smoking, and both age and smoking are strongly associated with comorbidity. Comorbidity, such as diseases of cardiovascular and pulmonary systems, may influence prognosis in lung cancer as well as complicate its treatment. Indeed, the co-existence of pulmonary diseases before the diagnosis of lung tumour, may delay the diagnosis itself, with the most common respiratory co-morbidities being COPD (36%), pneumonia (3%), residual tuberculosis (3%), and silicosis (1%) (Dutkowska 2016). Assessment of prevalence and severity of comorbidities conducted in the UK showed that most patients (87.3%) had at least one comorbidity, the most common being weight loss (53%), COPD (43%), renal impairment (28%) and ischaemic heart disease (27%). A composite score was produced that included both number and severity of comorbidities. One in seven patients (15.3%) had severe comorbidity scores; disease stage was not associated with comorbidity score (Grose 2014).

A non-interventional cohort study comparing adult patients newly diagnosed with advanced NSCLC during 2006–2013 with the general population showed that the prevalence of analysed comorbidities was significantly higher for NSCLC patients compared with the general population, with an odds ratio of 2.44 (95% CI: 2.27–2.63). Overall, most incidence rates were higher for NSCLC patients, compared to the general population, and the all-cause mortality rate for the NSCLC cohort was significantly higher leading to an incidence rate ratio of 32.5 (95% CI: 31.0-34.2) (Linden 2020).

Patients with NSCLC and COPD comorbidity have a 20% excess mortality than patients without this comorbidity (Dutkowska 2016; Iachina 2015). However, more recently, findings from a study in Denmark investigating the influence of COPD and other common comorbidities on NSCLC mortality suggested that neither COPD nor other common comorbidities (ie, ischaemic heart disease, hypertension, diabetes mellitus, cerebrovascular accident, previous malignancy, interstitial lung disease [ILD] and psychiatric comorbidity) have any impact on survival among patients with NSCLC in all disease stages and should therefore not restrict treatment strategies (Media 2019).

Cardiovascular comorbidity includes hypertension, coronary artery disease, peripheral vascular disease, arrhythmia, and abdominal aortic aneurysm. Cardiovascular diseases (CVDs) are another common comorbidity in lung cancer with prevalence from 12.9% to 43% according to different studies, but the influence of cardiovascular comorbidity on the prognosis of lung cancer patients remains controversial (Dutkowska 2016). Patients with cardiovascular comorbidity were reported to have a 30% higher death rate (hazard ratio [HR] 1.30 with 95% CI,1.13-1.49) than patients without comorbidity (Iachina 2015). Whilst some studies indicate cardiovascular comorbidity as an unfavourable survival marker for patients with Stage I/II NSCLC undergoing surgery, cardiac comorbidity has also been reported as having little or no risk (Dutkowska 2016).

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Adagrasib is a covalent, mutant-selective inhibitor of *KRAS* G12C being developed (Fell 2020; Goebel 2020, Hallin 2020) for the treatment of various cancers containing this specific genetic mutation, including NSCLC.

Key safety findings from nonclinical studies and relevance to human usage (as derived from safety analysis of the 188 NSCLC patients, in general) are presented in Table 2. It is noteworthy that as of 15 October 2021, 265 subjects in Study 849-001 have received adagrasib monotherapy across 5 specific patient cohorts and include 188 NSCLC patients treated with 600 mg BID. Overall, 260 patients were treated with adagrasib 600 mg BID irrespective of indication (PART II: MODULE SIII).

Table 2: Key safety findings from nonclinical studies and relevance to human usage:

Key safety findings from toxicity studies	Relevance to human usage
Acute or repeat-dose toxicity studies Single dose toxicity studies with MRTX849 have not been conducted. Exploratory and definitive repeat-dose toxicity studies were conducted with MRTX849 in rats and dogs (2.4 Nonclinical Overview: Studies TX-MRTX849-002, TX-MRTX849-003, TX-MRTX849-004, TX-MRTX849-005, TX-MRTX849-012, TX-MRTX849-013). Early treatment related deaths associated with adagrasib was observed in the 14-day and 28-day toxicity study in rats at doses ≥ 300 mg/kg/day (TX-MRT849-001 and TX-MRTX849-004). A dose of 300 mg/kg/day converts to a human equivalent dose of over 2900 mg for a 60 kg human, which is well above the human dose of 1200 mg. In the 28-day repeat dose toxicity study, the exposures in rats treated with 300 mg/kg/day were below the human exposure after administration of 1200 mg, but the rat exposure at this dose level was also below the exposures from the mid-dose group animals. The lower exposures at a higher dose suggest an issue with the oral formulation at this higher dose. Given that rats lack the ability to vomit, the suspension interfered with the ability of the animal to eat given their low food consumption leading to decreased body weight and normal organ function. In the 13-week toxicology study in rats, a dose of 150 mg/kg/day was the no-observed-adverse-effect-level (NOAEL) with a systemic exposure that was 2.4 times the human efficacious exposure. Therefore, the early deaths in the 28-day toxicity study are due to the local effect of the suspension and not due to systemic effects. In the 13-week dog study (TX-MRTX849-013), one dog at 25 mg/kg/day was euthanized on Day 11 due to clinicals signs of abnormal gait, incoordination, and decreased activity. The cause of death of this animal was undetermined and likely not related to adagrasib given that this was not seen at the same dose level in the 28-day toxicity study and was not seen in other dogs at this dose level in the 13-week toxicity study. In repeat dose toxicology studies, the primary target organ effects were caused by phospholipidosis in multiple tissues in both rats and dogs.	In Study 849-001 laboratory parameters were collected to monitor for potential effects of phospholipidosis in a broad range of organ systems including those identified in the nonclinical studies. The key risks were identified based on adverse event frequency and severity and included QT prolongation and increased transaminases. QT prolongation treatment-emergent adverse events (TEAEs) occurred in 19.1% (36/188) NSCLC patients treated with 600 mg twice daily (BID) adagrasib. Ten (5.3%) patients experienced Grade 3 QT prolongation and no patients had a Grade 4 event, with 1.1% of patients having a serious QT event. QT prolongation resolved in 66.7% (24/36) of those patients experiencing such a TEAE (Table 11, Module SVII.1.1). No ventricular arrhythmias associated with QT prolongation were reported, and QT prolongation was manageable with dose interruption and reduction. QT prolongation is not an important risk (Module SVII.1.1). Hepatotoxicity TEAEs occurred in 43.1% (81/188) NSCLC patients treated with 600 mg BID adagrasib, which were treatment-related according to the investigator in 37.2% (70/188) of patients. Sixteen (8.5%) patients experienced Grade 3 hepatotoxicity and only 1 (0.5%) patient had a Grade 4 event, with 1.1% of patients having a serious event. Hepatotoxicity resolved in 59.3% (48/81) of those patients experiencing hepatotoxicity events, with 40.7% cases remaining unresolved (Table 13, Module SVII.1.1). Hepatotoxicity is not an important risk (Module SVII.1.1). Increased amylase/lipase TEAEs were reported in 21.3% (40/188) NSCLC patients treated with 600 mg BID adagrasib. Twelve (6.4%) patients experienced Grade 3 increased amylase/lipase, 1 (0.5%) patient experienced Grade 4 increased amylase/lipase, and there were no Grade 5 events reported. Only 1.1% (2) patients

Key safety findings from toxicity studies	Relevance to human usage
Similar to other cationic amphiphilic drugs, MRTX849 treatment was associated with phospholipidosis based on the presence of foamy macrophages and vacuolated epithelium. These changes occurred in multiple tissues and were prominent in rats treated with the non-tolerated dose level of MRTX849 (≥ 300 mg/kg/day) in the 28-day study. In the dog, vacuolated tissues were present, but the effect appeared to be less severe. In the rat 28-day study, target organs associated with adverse findings included lung, trachea, heart, skeletal muscle, spleen, ovaries, uterus, and vagina. In the dog 28-day study, target organs associated with adverse findings included the lung, heart, and bone marrow. In the 13-week rat study, microscopic findings were noted in multiple tissues that were consistent with phospholipidosis; however, these findings were not considered adverse. At the end of the recovery periods in the repeat dose rat and dog studies, all toxicological effects demonstrated either complete or partial reversibility. Although the pathophysiological consequence of phospholipidosis is not well described, vacuolated changes in the absence of degenerative effects are not considered adverse and these changes are reversible (2.4 Nonclinical Overview). Additionally, in the 28-day rat study, decreased erythrocytic precursors not associated with clinical pathology changes were observed and considered not adverse. In the 28-day dog study, inhibition of erythropoiesis leading to decreased red blood cell parameters and reticulocytes was observed, although these changes were not noted in the 13-week dog study at lower doses (2.4 Nonclinical Overview).	had serious events. Increased amylase/lipase resolved in 67.5% (27/40) of those patients (Table 16, Module SVII.1.1). While phospholipidosis was observed in many tissues in the nonclinical setting, there are no data indicating whether this phenomenon occurs in patients treated with adagrasib nor whether occurrence would manifest as the adverse events that have been assessed as risks associated with adagrasib treatment (2.5 Clinical Overview). Nonclinical data suggest that treatment with MRTX849 may result in anaemia characterised by low reticulocyte count. Among the 183 NSCLC patients with baseline and postbaseline laboratory results, 16 (8.7%) patients experienced ≥ Grade 3 anaemia postbaseline (based on the clinical laboratory data). The median haemoglobin decreased from baseline to Cycle 2 Day 1 or 15, then generally increased afterwards, reaching baseline values by Cycle 6 Day 1, then typically increasing over subsequent cycles. The changes in the mean and median over time are consistent with a limited effect in humans (2.7.4 Summary of Clinical Safety).
Reproductive/developmental toxicity Dedicated fertility studies with adagrasib have not been conducted in animals, in line with ICH S9 guidance. In the general toxicology studies orally administered adagrasib resulted in adverse effects on female reproductive organs in rats but not in dogs. Evidence of vacuolation in female sex organs (ovaries and uterus) was considered adverse due to the expected effect on reproduction and was suggestive of phospholipidosis but reversed after cessation of dosing. A definitive embryofoetal development (EFD) rat study was initiated at doses of 30, 90, and 270 mg/kg/day with 22 pregnant rats per group	There are no data from the use of adagrasib in pregnant women. Based on the findings from animal studies, there are no direct effects of adagrasib on EFD at non-maternally toxic doses. Whilst embryofoetal toxicity is not considered a risk, adagrasib is not recommended for use in women during pregnancy or in women of childbearing potential not using contraception.

Key safety findings from toxicity studies	Relevance to human usage
(TX-MRTX849-001). MRTX849 and vehicle control were administered once daily during Gestation Days 6-17. In the presence of maternal toxicity, mean foetal body weights in the 270 mg/kg/day group were approximately 19.3% to 20.0% lower than the control group. This finding was considered adverse and corresponded to lower mean gravid uterine weight. Intrauterine growth in the 30 and 90 mg/kg/day groups and intrauterine survival at 30, 90, and 270 mg/kg/day were unaffected by MRTX849 administration. Higher mean litter proportions of skeletal malformations (bent limb bones) and developmental variations (bent scapula in conjunction with bent limb bones, wavy ribs, and supernumerary short cervical ribs) were observed in the 270 mg/kg/day group. These findings were noted in the presence of test article-related maternal toxicity. Based on maternal body weight loss, lower mean body weight gain and food consumption at 270 mg/kg/day, a dose level of 90 mg/kg/day was considered to be NOAEL for maternal and developmental toxicity for MRTX849 in this study. No test article-related foetal malformations or developmental variations were noted at 30 and 90 mg/kg/day. In the definitive EFD rabbit study (TX-MRTX849-021), pregnant New Zealand White rabbits (22/group) were dosed via oral gavage once daily during Gestation Days 7–20, the critical period of organogenesis. There were decreases in body weight gain and food consumption in rabbits administered 30 mg/kg/day; however, the mean adjusted body weight and gravid uterine weight in this group were generally comparable to the control group. Mean body weights, body weight gains, adjusted body weights, adjusted body weight changes, gravid uterine weights, and food consumption in the 6 and 15 mg/kg/day groups were similar to the control group throughout the study. Mean foetal body weights in the 30 mg/kg/day group were 5.48% to 7.04% lower than the concurrent control group and were considered test article-related but not adverse because of the small magnitude of difference. Intrauterine growth in the 6 and 15 mg/kg/day groups and survival in the 6, 15, and 30 mg/kg/day groups were comparable to the control group. Based on the lack of adverse effects on dams and foetuses, a dose level of	

Key safety findings from toxicity studies	Relevance to human usage
30 mg/kg/day was considered the NOAEL for maternal toxicity and developmental toxicity. There was no evidence of embryo-toxicity or teratogenic effects of MRTX849 in rats or rabbits at non-maternally toxic doses.	
Genotoxicity The genotoxicity of MRTX849 was assessed in a screening bacterial mutation assay (TX MRTX849-006), a screening in vitro chromosomal aberration assay (TX-MRTX849-007), a definitive bacterial mutation assay (TX-MRTX849-010), and a chromosomal aberration assay (TX-MRTX849-011). The in vitro assays were conducted with and without exogenous Aroclor-induced rat liver S9 and MRTX849 concentrations up to those limited by cytotoxicity or solubility. In vivo, the clastogenic effects of MRTX849 were evaluated in rats by measuring micronuclei present in peripheral blood reticulocytes after oral dosing at 250, 500, and 1000 mg/kg/day for two days (TX-MRTX849-016). The 1000 mg/kg/day dose was selected as the maximum tolerated dose based on lack of tolerability at 2000 mg/kg/day in an initial range-finding study. In summary, MRTX849 was negative in all the genotoxicity studies.	There is no evidence that adagrasib might be genotoxic.
Carcinogenicity In accordance with ICH S9, carcinogenicity studies with MRTX849 have not been performed given the intended treatment of patients with advanced cancer.	Not applicable.

Key safety findings from safety pharmacology studies	Relevance to human usage
Cardiovascular system, including potential effect on the QT interval Based on an in vitro hERG binding study (PH-MRTX849-025), an in vitro Guinea pig Langendorff study (PH-MRTX849-010), and ECG parameters collected in the repeat dose dog toxicology studies (TX-MRTX849-005, TX-MRTX849-013), MRTX849 poses minimal risk for QT prolongation. In addition, there were no changes in heart rate, blood pressure, or changes in ECG parameters in dogs with telemetry implants treated at doses up to 25 mg/kg/day (TX-MRTX849-009) (2.4 Nonclinical Overview).	In the clinical development programme, in Study 849-001, there did not appear to be any clinically significant mean or median change from baseline for heart rate among the NSCLC patients who initiated treatment at 600 mg BID (n=188) nor in the 600 mg Twice Daily Total group (n=260, all indications). QTc interval prolongation can occur in patients treated with MRTX849. In the NSCLC patient group 13 patients (7.0% of 185 patients with nonmissing QTc results) had QTcF > 500 msec, and 22 patients (11.9%) had a maximum change from baseline in QTcF of > 60 msec. In the 600 mg Twice Daily Total group, 17 patients (6.6% of 257 patients with nonmissing QTc results) had QTcF > 500 msec, and 34 patients (13.2%) had an increase from baseline QTcF > 60 msec. No Torsade de Pointes was associated with this QT prolongation (2.7.4 Summary of Clinical Safety).
Nervous system A separate study to assess the central nervous system (CNS) effects of MRTX849 was not conducted. Nevertheless, CNS effects were monitored during the conduct of the rat and dog 28-day (TX-MRTX849-004, TX-MRTX849-005) and 13-week (TX-MRTX849-012, TX-MRTX849-013) repeat dose toxicology studies. There were no remarkable clinical signs suggestive of CNS effects, nor were there microscopic changes in neuronal tissues. In addition, based on the absorption, distribution, metabolism, excretion (ADME) properties of MRTX849, appreciable brain exposure to MRTX849 is not expected (2.4 Nonclinical Overview).	In the clinical development programme, in Study 849-001, TEAEs in the System Organ Class (SOC) of nervous system disorders occurred in 98/188 patients (52.1%) in the NSCLC group. The most common TEAEs (≥ 10% patients) included dizziness, headache, and dysgeusia reported in 22.3%, 14.4% and 13.8%, respectively; adagrasib-related TEAEs included dysgeusia (11.7%) and dizziness (8.5%) but not headache. There were no Grade ≥ 3 TEAEs reported in ≥ 2% patients in the NSCLC group. TEAEs leading to a dose modification (dose reduction or treatment interruption) for more than 1 patient in the NSCLC group included 5 (2.7%) cases of dizziness (4 Grade 1/2 [2 treatment-related], 1 Grade ≥ 3 [treatment-related]) and 4 (2.1%) cases of dysgeusia (all Grade 1/2 and unrelated to treatment). There was a single TEAE with outcome of death in the nervous system disorders SOC (cerebrovascular accident), which was considered unrelated to treatment (2.7.4 Summary of Clinical Safety).

Key safety findings from studies investigating mechanisms for drug interactions	Relevance to human usage
Drug-drug interactions In vitro evaluations of MRTX849 as a potential substrate of drug transporters indicate that MRTX849 is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) (PK-MRTX849-012, PK-MRTX849-040, and PK-MRTX849-015). The percent contribution of CYP3A4 and CYP2C8 to the in vivo clearance of MRTX849 was calculated to be 72% and 28%, respectively (PK-MRTX849-008). MRTX849 clinical dose of 600 mg BID has the potential to inhibit cytochrome P450(CYP)2B6, CYP2C9, CYP2D6, and CYP3A4 and to induce CYP3A4 (PK-MRTX849-013 and PK-MRTX849-014). MRTX849 is also a time dependent inhibitor of CYP3A4 (PK-MRTX849-013). MRTX849 also inhibits drug transporters P-gp, BCRP, organic anion transporting polypeptide (OATP)1B1, multidrug toxin extrusion (MATE)1 and organic cation transporter (OCT)1 (PK-MRTX849-012, PK-MRTX849-035, PK-MRTX849-021, and PK-MRTX849-030) (2.4 Nonclinical Overview).	Clinical pharmacology Study 849-006 and physiologically based pharmacokinetic (PBPK) modelling (2.7.4, Summary of Clinical Safety, Section 2.1.10.4) were conducted in healthy subjects to investigate the drug-drug interactions with MRTX849 as a potential "victim" of CYP3A/P-gp inhibition and induction and gastric acid-reducing agent or as a potential "perpetrator" of CYP2C9, CYP2D6, CYP3A4, P-gp, or BCRP inhibition or induction. Results from the drug interaction evaluations based on the clinical study and PBPK modelling support the following recommendations: • Co-administration of MRTX849 with strong CYP3A inducers should be avoided • Co-administration of MRTX849 with strong CYP3A inhibitors should be avoided • Co-administration of medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration of MRTX849 with other sensitive CYP3A substrates should be avoided unless otherwise recommended in the SmPC for these substrates • Co-administration of MRTX849 with sensitive CYP2C9 or CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions should be avoided unless otherwise recommended in the SmPC for these substrates • Co-administration of MRTX849 with P-gp substrates where minimal concentration changes may lead to serious adverse reactions should be avoided unless otherwise recommended in the SmPC for these substrates • No clinically significant differences in the pharmacokinetics of rosuvastatin (a BCRP/OATP1B1 substrate) were observed when coadministered with MRTX849

Key safety findings from studies investigating mechanisms for drug interactions	Relevance to human usage

Key safety findings from other toxicity-related information or data	Relevance to human usage
MRTX849 metabolites The two human MRTX849 metabolites, M11 (also known as WX-41090 or MRTX2359) and M68 (also known as WX-42050 or MRTX4928), were negative in the bacterial mutagenicity assay conducted using *Salmonella typhimurium* strains TA 98 and TA 100 with and without metabolic activation at concentrations up to the limit of solubility or cytotoxicity (TX-MRTX849-025). M11 and M68 were also negative in a screening in vitro micronucleus assay using TK6 cells with and without metabolic activation (TX-MRTX849-026).	Not applicable.
Phototoxicity The phototoxic potential of MRTX849 was assessed in a Good Laboratory Practice (GLP) in vitro phototoxicity study using 3T3 mouse fibroblasts (TX-MRTX849-014). At concentrations up to 100 µg/mL, MRTX849 did not produce any evidence of phototoxicity in the 3T3 neutral red uptake assay.	Not applicable.
Local tolerance Specific or specialised local toleration studies have not been conducted with MRTX849.	Not applicable.

Conclusions from the nonclinical development programme

There are no nonclinical findings relevant to human usage or suggestive of a significant hazard to human health. Clinical data (Module SVII.1) confirm this absence of safety concerns with adagrasib use in humans.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The safety data associated with oral administration of adagrasib monotherapy were generated primarily in the ongoing Study 849-001, a multicentre, Phase 1/2, multiple expansion cohort study evaluating the safety, pharmacokinetics (PK), and clinical activity/efficacy of MRTX849 as monotherapy in patients with advanced solid tumours with *KRAS* G12C mutation. The Phase 1/1b dose finding component established the recommended starting dose of 600 mg BID, with Phase 2 assessing ORR.

Safety data are summarised using a data lock point of 15 October 2021 for 265 subjects treated in Study 849-001 across 5 specific patient cohorts:

- Phase 1/1b dose finding cohort includes 25 patients with solid tumours with *KRAS* G12C mutation treated with escalating doses of MRTX849
- Phase 2 Cohort A (the pivotal efficacy study) includes 116 patients with NSCLC with *KRAS* G12C mutation detected in tumour tissue
- Phase 2 Cohort B includes 56 patients with NSCLC with *KRAS* G12C mutation detected in blood (ie, circulating tumour DNA [ctDNA])
- Phase 2 Cohort C includes 44 patients with colorectal cancer with *KRAS* G12C mutation detected in tumour tissue and/or blood
- Phase 2 Cohort D includes 24 patients with other solid tumours with *KRAS* G12C mutation detected in tumour tissue and/or blood

The total 265 subjects who received adagrasib monotherapy can be subdivided into 3 groups depending on indication and treatment dose:

- All NSCLC patients treated with 600 mg BID = 188
  - (Cohort A = 116; Cohort B =56; Phase 1/1b = 16)
- Patients with Other Indications treated with 600mg BID = 72
  - (Cohort C = 44; Cohort D = 24; Phase 1/1b = 4)
- Other Dosing Regimens = 5
  - (Initiating treatment at different dose levels in the dose-escalation [Phase 1] portion of the study)

The safety analysis was conducted for the 188 NSCLC patients enrolled and treated up to 15 June 2021. Four additional patients (enrolled in Cohort B; all male aged < 65 years [2 patients] and ≥ 65 years [2 patients]), who received treatment between the previous data cut of 29 January 2021 and that of 15 June 2021, were deliberately excluded to keep the populations aligned across analyses and considering the anticipated minimal contribution from these 4 patients to the overall safety analysis.

Table 3: Duration of exposure

All indications

Duration of exposure	Patients	Person time (yr)
< 1 m	27	1.04
1 to <3 m	51	8.31
3 to < 6 m	54	20.61
6 to < 9 m	41	25.73
9 to < 12 m	39	34.36
≥ 12 m	53	70.93
Total person time	**265**	**160.99**

NSCLC

Duration of exposure	Patients	Person time (yr)
< 1 m	23	0.84
1 to < 3 m	37	5.97
3 to < 6 m	33	12.85
6 to < 9 m	28	17.88
9 to < 12 m	25	22.20
≥ 12 m	42	54.47
Total person time	**188**	**114.21**

Source: RMP Table SIII.1
m=month; yr=year

Table 4: Age group and gender

All indications

Age group	Patients		Person time (yr)	
	M	**F**	**M**	**F**
Adults (18-64 years)	55	92	34.17	56.31
Elderly people				
65-74 years	44	42	25.62	25.91
≥ 75 years	15	17	8.60	10.38
Total	**114**	**151**	**68.39**	**92.61**

NSCLC

Age group	Patients		Person time (yr)	
	M	**F**	**M**	**F**
Adults (18-64 years)	31	65	21.85	42.94
Elderly people				
65-74 years	33	34	19.55	17.39
≥ 75 years	11	14	5.88	6.60
Total	**75**	**113**	**47.28**	**66.93**

Source: RMP Table SIII.2
F=female; M=male; yr=year

Table 5: Dose of exposure

All indications

Dose of exposure	Patients	Person time (yr)
150 mg QD*	1	2.74
300 mg QD*	1	0.56
600 mg QD*	2	0.39
1200 mg QD*	1	0.03
600 mg BID	260	157.28
Total	**265**	**160.99**

NSCLC

Dose of exposure	Patients	Person time (yr)
150 mg QD*	0	0
300 mg QD*	0	0
600 mg QD*	0	0
1200 mg QD*	0	0
600 mg BID	188	114.21
Total	**188**	**114.21**

Source: RMP Table SIII.3
BID=twice daily; QD=once daily; yr=year
*Dose escalation

Table 6: Race

All indications

Race	Patients	Person time (yr)
White	221	135.63
Black or African American	21	9.53
Asian	11	8.10
American Indian or Alaska Native	2	1.93
Native Hawaiian or other Pacific Islander	0	0
Other	10	5.80
Total	**265**	**160.99**

NSCLC

Race	Patients	Person time (yr)
White	164	99.34
Black or African American	12	6.25
Asian	6	4.45
American Indian or Alaska Native	1	1.28
Native Hawaiian or other Pacific Islander	0	0
Other	5	2.89
Total	**188**	**114.21**

Source: RMP Table SIII.4
yr=year

For all indications and NSCLC, the majority of patients were not of Hispanic or Latino ethnicity (91.2% and 92.0%, respectively; ISS table 14.1.3).

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria from Study 849-001 are detailed below:

Exclusion criteria whose purpose is to ensure standardisation of the trial population that are common to most clinical trials are not discussed in this section, including:

- Pregnancy: women of childbearing potential must have a negative serum or urine pregnancy test documented within the screening period prior start of study drug.
- Breast-feeding or planning to breast feed during the study or within 6 months after study treatment.
- Age <18 years.
- Life expectancy <3 months.

Exclusion criteria related to ongoing or recent conditions or treatments that may confound the interpretation of study results and impact the safety and efficacy assessment of MRTX849 are similarly not discussed, including:

- Prior treatment with a therapy targeting *KRAS* G12C mutation (Phase 2 cohorts only).
- History of intestinal disease or major gastric surgery likely to alter absorption of study treatment or inability to swallow oral medications.
- Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments.
- Any serious illness, uncontrolled intercurrent illness, psychiatric illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results.
- Undergone major surgery within 4 weeks of first dose date.
- Known HIV seropositivity or active Hepatitis B or C. Patients treated for hepatitis C with no detectable viral load are permitted.
- Patients with carcinomatous meningitis. Patients with focal leptomeningeal disease are allowed in the Phase 1b cohort for patients with brain metastases.
- History of significant haemoptysis or haemorrhage within 4 weeks of the first dose date.
- History of stroke or transient ischaemic attack within the previous 6 months.
- Active brain metastases, unless adequately treated and patients are neurologically stable for at least 2 weeks prior to enrolment without the use of corticosteroids or are on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).

Exclusion criteria identified for discussion are presented below:

Ongoing need for a medication with any of the following characteristics that cannot be switched to alternative treatment prior to study entry: known risk of Torsades de Pointes; substrate of CYP3A with narrow therapeutic index; strong inducer of CYP3A and/or P-gp; strong inhibitor of BCRP; and proton pump inhibitors.

Reason for exclusion: Adagrasib has been shown to increase QTc in patients (Module SVII.1.1), but the effect of coadministration of medicinal products known to prolong the QTc interval with adagrasib is unknown. Clinical drug-drug interaction studies showed that adagrasib is a strong inhibitor of CYP3A4. In addition, strong inducers of CYP3A4/P-gp reduced the exposure of adagrasib, which may decrease its efficacy. The clinical significance of PPIs on adagrasib exposure is unknown. In vitro, adagrasib is a substrate of BCRP and inhibitors of BCRP may increase adagrasib exposure (PART II: MODULE SIII). Patients with the above specified ongoing medications were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of adagrasib.

Is it considered to be included as missing information? No

Rationale: The potential for drug interactions with adagrasib has been adequately characterised.

Section 4.5 of the Krazati SmPC describes the interactions of adagrasib with other medicinal products including strong CYP3A inducers or inhibitors, CYP3A, CYP2C9 or CYP2D6 substrates, P-gp or BCRP/ OATP1B1 substrates, and medicinal products that prolong the QTc interval.

Concomitant use of strong CYP3A inducers with adagrasib should be avoided. Adagrasib is highly dependent on CYP3A for clearance, and strong CYP3A inducers will reduce drug levels of adagrasib.

Adagrasib is a strong CYP3A4 inhibitor. Co-administration of medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil for treatment of pulmonary arterial hypertension, oral midazolam, triazolam). Krazati may be administered only after switching to acceptable alternative medicinal products.

When adagrasib is co-administered with other medicinal products that are sensitive CYP3A substrates without a narrow therapeutic index, the SmPC for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant use of adagrasib with sensitive CYP2C9 substrates, sensitive CYP2D6 substrates, or P-gp substrates where minimal concentration changes may lead to serious adverse reactions should also be avoided unless otherwise recommended in the Prescribing Information for these substrates. The use of medicinal products known to prolong the QTc interval should be avoided. If concomitant administration of such medicinal products cannot be avoided, periodic ECG monitoring should be conducted.

Any of the following cardiac abnormalities within the last 6 months:

- **Unstable angina pectoris**

- **Congestive heart failure ≥ NYHA Class 3**
- **QTc > 480 milliseconds or family history or medical history of Long QT Syndrome**

Reason for exclusion: Comorbidities associated with NSCLC, including CVD, have the potential to confound study results and were excluded. Although nonclinical data (Part II: MODULE SII) suggest a minimal risk for QT prolongation, with no remarkable ECG changes in the 28-day (TX-MRTX849-005) or the 13-week (TX-MRTX849-013) repeat dose toxicology studies in dogs, patients with the above cardiac abnormalities were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of adagrasib.

Is it considered to be included as missing information? No

Rationale: The risk of QT prolongation with adagrasib has been adequately characterised. QT prolongation is included in the special warnings and precautions section of the Krazati SmPC. QTc interval prolongation can occur in patients treated with adagrasib. It is recommended that a baseline ECG prior to treatment initiation be performed in all patients and repeated during treatment.

When possible, the use of Krazati should be avoided in patients with congenital long QT syndrome, in patients with concurrent QTc prolongation and in patients who have experienced *torsades de pointes* arrhythmia in the past. Periodic monitoring with ECGs and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Based on the severity of the adverse reaction, and after correction of any possible electrolyte disturbances, treatment with Krazati can be continued with a reduced dose or temporarily discontinued followed by resumption at a reduced dose after recovery to ≤ Grade 1 or return to baseline. In patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia, Krazati should be permanently discontinued. The use of medicinal products known to prolong the QTc interval should be avoided.

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 or cumulative exposure.

For those NSCLC patients who initiated treatment at 600 mg BID (n=188) adverse reactions with a frequency greater than 1 in 63 could be detected if there was no background incidence, rising to a frequency of 1 in 88 if considering all 265 adagrasib-treated patients regardless of indication and/or dose.

The duration of treatment in subjects with NSCLC treated with adagrasib (n=188) is limited beyond 12 months of treatment (≥ 6 months: 95/188 [50.5%]; ≥ 9 months: 67/188 [35.6%]; ≥ 12 months: 42/188 [22.3%]) (Table 3). Adverse reactions with a long latency or cumulative effects are not expected due to the limited life-expectancy of patients with NSCLC.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7: 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 comorbidities:	
Patients with hepatic impairment	Whilst patients with hepatic impairment were not specifically excluded from participation, patients with any serious illness, uncontrolled intercurrent illness, active or uncontrolled infection, or other medical history, including laboratory results (eg, high transaminases or alkaline phosphatase), which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results, were excluded. Furthermore, patients with active Hepatitis B or C were also excluded (Module SIV.1). Study 849-003 was conducted in 39 subjects with mild (Child-Pugh class A, score 5 or 6; n=8), moderate (Child-Pugh class B, score 7 to 9; n=12), or severe (Child-Pugh class C, score 10-15; n=8) hepatic impairment or with normal (n=11) hepatic function. Subjects were administered a single oral dose of 600mg adagrasib following an overnight fast. Adagrasib unbound exposures (C_{max} and AUC_{∞}) in subjects with mild or moderate hepatic impairment were comparable to those in subjects with normal hepatic function. Subjects with severe hepatic impairment showed a similar unbound C_{max} and 66% higher unbound AUC∞ compared with subjects with normal hepatic function. All TEAEs reported were either Grade 1 (mild) or Grade 2 (moderate) in severity and all recovered/resolved. The most common treatment-related TEAEs were gastrointestinal disorders, including diarrhoea (reported in 3 of 11 [27.3%] subjects with normal hepatic function, 2 of 8 [25.0%] subjects with mild hepatic impairment, 3 of 12 [25.0%] subjects with moderate hepatic impairment, and 1 of 8 [12.5%] subjects with severe hepatic impairment); nausea (reported in 2 [18.2%] subjects with normal hepatic function, 2 [25.0%] subjects with mild hepatic impairment, and 5 [41.7%] subjects with moderate hepatic impairment); and vomiting (reported in 1 [12.5%] subject with mild hepatic impairment and 3 [25.0%] subjects with moderate hepatic impairment). No other treatment-related TEAEs were reported in more than 1 subject in the study (Study 849-003 CSR).

Type of special population	Exposure
Patients with renal impairment	Whilst patients with renal impairment were not specifically excluded from participation the study included an entry criterion for CrCl (≥ 60 mL/min). Patients with any serious illness, uncontrolled inter-current illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results, were excluded (Module SIV.1). Study 849-004 was conducted in 31 subjects with mild (CrCl of ≥ 60 to <90; n=8), moderate (≥ 30 to <60; n=7), or severe (≥ 15 to < 30 mL/min; n=6) renal impairment or with normal renal function (CrCl ≥ 90 mL/min; n=10). Subjects were administered a single oral dose of 600mg adagrasib following an overnight fast. Results of a sensitivity analysis performed with body weight as a covariate in the ANOVA model showed that adagrasib total exposure (AUC) in subjects with mild renal impairment was approximately 44% lower than that in subjects with normal renal function. Compared to subjects with normal renal function, adagrasib AUC in subjects with moderate and severe renal impairment was increased approximately 1.3- and 1.2-fold, respectively. These differences are not considered clinically meaningful and are further supported by negligible renal excretion of adagrasib in all impaired renal function groups, no association of renal impairment severity with apparent total clearance of adagrasib, and similar arithmetic mean $t_{1/2}$ of adagrasib between subjects with normal renal function (21.0 hours) and subjects with severe renal impairment (21.4 hours). All TEAEs reported were either Grade 1 (mild) or Grade 2 (moderate) in severity and all recovered/resolved. The most common treatment-related TEAEs were gastrointestinal disorders, including diarrhoea (reported by 4 of 10 [40.0%] subjects with normal renal function, 2 of 8 [25.0%] subjects with mild renal impairment, 3 of 7 [42.9%] subjects with moderate renal impairment, and 3 of 6 [50.0%] subjects with severe renal impairment); nausea (reported by 2 [20.0%] subjects with normal renal function, 1 [12.5%] subject with mild renal impairment, 1 [14.3%] subject with moderate renal impairment, and 1 [16.7%] subject with severe renal impairment); and vomiting (reported by 2 [25.0%] subjects with mild renal impairment and 1 [14.3%] subject with moderate renal impairment) (Study 849-004 CSR).
Patients with cardiovascular impairment	Patients with cardiac abnormalities within the last 6 months such as unstable angina pectoris, congestive heart failure ≥ NYHA Class 3, and QTc > 480 milliseconds or family history or medical history of Long QT Syndrome were excluded from participation (Module SIV.1).

Type of special population	Exposure
Immunocompromised patients	Patients with known HIV seropositivity were excluded from participation (Module SIV.1). However, other patients with underlying immunodeficiency were not specifically excluded and it is likely that many patients would have some decrease in immune function related to their prior systemic therapy. Decreased lymphocyte count has been observed in NSCLC patients treated with adagrasib (17/188 [9.0%]; 2.7.4 Summary of Clinical Safety), though the clinical implications in patients who are immunocompromised is unknown.
Patients with a disease severity different from inclusion criteria in clinical trials	The proposed indication for adagrasib monotherapy is for the treatment of adult patients with advanced NSCLC with *KRAS* G12C mutation and disease progression after at least one prior systemic therapy. Based on the mode of action, adagrasib would be expected to be active in patients regardless of disease stage, but there are no comparative data against standards for earlier stage disease. Study 849-001 recruited 188 subjects with NSCLC who received adagrasib 600 mg BID. Of these subjects 181 (96.3%) had histology defined as adenocarcinoma, 6 as squamous NSCLC and 1 (< 1%) as 'other'. The majority of subjects had metastatic NSCLC (90.4%) as opposed to locally advanced (9.6%). All subjects, bar 1, had had at least 1 prior systemic regimen with 37.2 %, 30.3%, 14.9%, 17.0% subjects having 1, 2, 3, or 4 prior therapies (2.7.4 Summary of Clinical Safety).
Population with relevant different ethnic origin	In the 188 NSCLC patient pool, receiving adagrasib 600 mg BID, most patients were white (87.2%), followed by black (6.4%), and Asian (3.2%) (Table 6). A small percentage of patients were Hispanic or Latino (4.8%) (2.7.4 Summary of Clinical Safety). Population PK analysis showed that no clinically meaningful differences in the PK of adagrasib were observed based on race (White, Black, and Asian) (2.7.2 Summary of Clinical Pharmacology Studies).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Adagrasib was approved for marketing in the US on 12 December 2022; no post-authorisation exposure data are available.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

No studies have been conducted to evaluate the abuse and dependence potential of adagrasib. Based on its mechanism of action and safety profile in NSCLC, adagrasib is not expected to be associated with the potential for misuse for illegal purposes.

PART II: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

Reason for not including an identified or potential risk 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):**

Adverse reactions reported in clinical trials but with minimal clinical impact on patients are presented below. Within each SOC, adverse reactions are listed in the order of decreasing seriousness:

- Blood and lymphatic system disorders: Anaemia, Lymphocyte count decreased
- General disorders and administration site conditions: Fatigue (including asthenia), Peripheral oedema
- Metabolism and Nutrition Disorders: Hyponatraemia, Decreased appetite
- Nervous System Disorders: Dizziness (including vertigo)
- Renal and urinary disorders: Blood creatinine increased

All these adverse reactions were reported with a very common (≥ 1/10) frequency. NSCLC is a diagnosis associated with a significant reduction in life expectancy, despite treatment, in many instances. Patients with NSCLC would be treated in a clinical oncology setting equipped to recognise, and to manage appropriately, the complications of treatment listed in this section.

- **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**

None.

- **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):**

Gastrointestinal Disorders

Adverse events of gastrointestinal disorders were identified using the preferred terms: Diarrhoea, Nausea, Retching, and Vomiting. TEAEs occurred in 89.9% (169/188) NSCLC patients treated with 600 mg BID adagrasib, which were treatment-related in 163/188 (86.7%) of patients according to the investigator. Sixteen (8.5%) patients experienced Grade 3 gastrointestinal events and no patients had a Grade 4 event, with 3.7% of patients having a serious gastrointestinal

event. Gastrointestinal events resolved in 34.9% (59/169) of those patients experiencing such a TEAE, with 65.1% cases remaining unresolved (Table 8)

Table 8: Summary of Gastrointestinal TEAEs in Study 849-001

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Patients with Gastrointestinal TEAEs[1], n (%)	103 (88.8)	169 (89.9)
Total Gastrointestinal TEAEs[2]	369	681
Exposure-adjusted Incidence Rate - Patients with AEs/100 PY [95% CI]	1237.5 [1010.1, 1500.9]	1488.1 [1272.2, 1730.2]
Severity[3]		
Grade 1	58 (50.0)	88 (46.8)
Grade 2	39 (33.6)	65 (34.6)
Grade 3	6 (5.2)	16 (8.5)
Grade 4	0	0
Grade 5	0	0
Serious[4]	4 (3.4)	7 (3.7)
Relationship to treatment[5]		
Related	98 (84.5)	163 (86.7)
Not related	5 (4.3)	6 (3.2)
Not known	0	0
Outcome[6]		
Unknown	0	0
Resolved	34 (29.3)	59 (31.4)
Not resolved	69 (59.5)	110 (58.5)
Fatal	0	0

Source: SmPC Table 8.1
Cutoff Date: 15OCT2021 Run Date: 16DEC2022 9:13
AE=adverse event; BID=twice daily; CI=confidence interval; NSCLC=non-small cell lung cancer; PY=patient years; TEAE=treatment-emergent adverse event
[1] Includes all patients who had one or more occurrences of an adverse event that met the criteria of the risk, the patient is counted only once regardless of the number of events or the number of occurrences
[2] Includes all occurrences of an adverse event that met the criteria of the risk, the patient can be counted more than once if experienced multiple adverse events
[3] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing
[4] Only the most serious event is counted - Seriousness: Serious>Nonserious
[5] Only the most related event is counted - Relationship to treatment: Related>Not related>Not known
[6] Only the most severe outcome is counted - Outcomes: Fatal>Not Resolved>Resolved>Unknown+Missing
Gastrointestinal events include preferred terms: diarrhoea, nausea, retching, and vomiting.
NSCLC (tumour tissue mutation) is the pivotal efficacy study including patients with non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation detected in tumour tissue.

The median time to onset of the first Grade ≥ 3 event of gastrointestinal events in all NSCLC patients (N=188) was 11.0 days. The median duration of such events was 9.5 days (Table 9).

Table 9: Summary of Grade ≥ 3 Gastrointestinal Adverse Events in NSCLC Patients

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Time to 1st Grade ≥ 3 Gastrointestinal events (days)		
n	6	16
Mean (Std)	24.7 (34.99)	75.2 (156.21)
Median	11.0	11.0
Q1, Q3	9.0, 13.0	9.0, 46.5
Min, Max	8, 96	1, 567
Duration of Grade ≥ 3 Gastrointestinal events (days)		
n	6	16
Mean (Std)	11.3 (6.15)	9.4 (6.57)
Median	11.0	9.5
Q1, Q3	11.0, 14.0	3.0, 15.5
Min, Max	1, 20	1, 20

Source: SmPC Table 6.1
Data Cutoff Date: 15OCT2021 Run Date: 16DEC2022 15:55
Adverse events were coded using MedDRA version 21.0. CTCAE grading v5.0 applied.
Gastrointestinal events include preferred terms: diarrhoea, nausea, retching, and vomiting.

The occurrence of the individual adverse events comprising the gastrointestinal group across the NSCLC (tumour tissue mutation) subgroup (n=116) and the total NSCLC group (n=188) are presented in Table 10.

Table 10: Gastrointestinal TEAEs in Patients who Received MRTX849 600 mg Twice Daily in Study 849-001

Adverse Event	NSCLC (tumour tissue mutation) (N=116)		All NSCLC 600 mg BID (N=188)	
	Grade 1-4 n (%)	Grades 3/4 n (%)	Grade 1-4 n (%)	Grade 3/4 n (%)
Gastrointestinal (group)[a]				
Diarrhoea	82 (70.7)	1 (0.9)	133 (70.7)	8 (4.3)
Nausea	81 (69.8)	5 (4.3)	132 (70.2)	9 (4.8)
Vomiting	66 (56.9)	1 (0.9)	108 (57.4)	4 (2.1)

Source: ISS Table 14.3.4.1.1
BID=twice daily
[a] Gastrointestinal (group) includes preferred terms: Diarrhoea, Nausea, and Vomiting.

Gastrointestinal adverse reactions (diarrhoea, nausea, and vomiting) leading to dose interruption or reduction in the total NSCLC group (n=188) occurred in 56.9% (107/188) patients, with 48.3% (56/116) in the NSCLC (tumour tissue mutation, n=116) subgroup (ISS Table 14.3.2.10.3). No gastrointestinal adverse reactions were fatal.

Gastrointestinal events are not an important risk of adagrasib as they can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents, patient monitoring, adagrasib dose interruption or modification. Gastrointestinal events are manageable using supportive care, including anti-diarrhoeals, antiemetics, or fluid replacement.

The product information for Krazati requires that it should be initiated by a physician experienced in the use of anti-cancer medicinal products. The Krazati SmPC instructs physicians to monitor patients and manage them with supportive care, including antidiarrhoeals, antiemetics, or fluid replacement, as indicated. Based on the severity of the adverse reaction, the dose of Krazati should either be reduced, temporarily withheld until recovery to ≤ Grade 1 or return to baseline and then resumed at a reduced dose.

QT prolongation

Adverse events of QT prolongation were identified using the preferred term Electrocardiogram QT prolonged. QT prolongation TEAEs occurred in 19.1% (36/188) NSCLC patients treated with 600 mg BID adagrasib, which were treatment-related in 32/188 (17.0%) of patients according to the investigator. Ten (5.3%) patients experienced Grade 3 QT prolongation and no patients had a Grade 4 event, with 1.1% of patients having a serious QT event. QT prolongation resolved in 66.7% (24/36) of those patients experiencing such a TEAE, with a third of cases remaining unresolved (Table 11).

Table 11: Summary of QT Prolongation TEAEs in Study 849-001

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Patients with QT prolongation TEAEs[1], n (%)	23 (19.8)	36 (19.1)
Total QT prolongation TEAEs[2]	32	59
Exposure-adjusted Incidence Rate - Patients with AEs/100 PY [95% CI]	42.9 [27.2, 64.3]	38.8 [27.2, 53.7]
Severity[3]		
Grade 1	11 (9.5)	15 (8.0)
Grade 2	5 (4.3)	11 (5.9)
Grade 3	7 (6.0)	10 (5.3)
Grade 4	0	0
Grade 5	0	0
Serious[4]	1 (0.9)	2 (1.1)
Relationship to treatment[5]		
Related	19 (16.4)	32 (17.0)
Not related	4 (3.4)	4 (2.1)
Not known	0	0
Outcome[6]		
Unknown	0	0
Resolved	14 (12.1)	24 (12.8)
Not resolved	9 (7.8)	12 (6.4)
Fatal	0	0

Source: RMP Table 14.6.1.1
AE=adverse event; BID=twice daily; CI=confidence interval; NSCLC=non-small cell lung cancer; PY=patient years; TEAE=treatment-emergent adverse event
[1] Includes all patients who had one or more occurrences of an adverse event that met the criteria of the risk, the patient is counted only once regardless of the number of events or the number of occurrences
[2] Includes all occurrences of an adverse event that met the criteria of the risk, the patient can be counted more than once if experienced multiple adverse events
[3] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing
[4] Only the most serious event is counted - Seriousness: Serious>Nonserious
[5] Only the most related event is counted - Relationship to treatment: Related>Not related>Not known
[6] Only the most severe outcome is counted - Outcomes: Fatal>Not Resolved>Resolved>Unknown+Missing
QT prolongation includes term: Electrocardiogram QT prolonged.
NSCLC (tumour tissue mutation) is the pivotal efficacy study including patients with non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation detected in tumour tissue.

The median time to onset of the first Grade ≥ 3 event of Electrocardiogram QT prolonged in all NSCLC patients (N=188) was 8.0 days. The median duration of such events was 4.0 days (Table 12).

Table 12: Summary of Grade ≥ 3 Electrocardiogram QT prolonged Adverse Events in NSCLC Patients

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Time to 1st Grade ≥ 3 Electrocardiogram QT prolonged (days)		
n	7	10
Mean (Std)	11.9 (7.63)	11.9 (7.46)
Median	8.0	8.0
Q1, Q3	8.0, 20.0	8.0, 20.0
Min, Max	1, 22	1, 22
Duration of Grade ≥ 3 Electrocardiogram QT prolonged (days)		
n	7	10
Mean (Std)	8.0 (8.41)	7.8 (7.27)
Median	4.0	4.0
Q1, Q3	3.0, 17.0	3.0, 12.0
Min, Max	2, 23	2, 23

Source: ISS Adhoc Table 14.3.5.1.1
Adverse events were coded using MedDRA version 21.0. CTCAE grading v5.0 applied.

Electrocardiogram QT prolonged adverse reactions leading to dose interruption or reduction in the total NSCLC group (n=188) occurred in 5.9% (11/188) patients, with 6.9% (8/116) in the NSCLC (tumour tissue mutation, n=116) subgroup (ISS Table 14.3.2.10.3). No adverse reactions of electrocardiogram QT prolonged were fatal.

Among the 188 NSCLC patients who initiated treatment at 600 mg BID there did not appear to be any clinically significant mean or median change from baseline for heart rate, according to electrocardiogram results. Specifically for all NSCLC patients, 69 patients (37.3%) had QTcF ≥ 450 to ≥ 480 msec, 17 patients (9.2%) had QTcF > 480 to ≤ 500 msec, and 13 patients (7.0%) had QTcF > 500 msec. The maximum change from baseline in QTcF was > 30 to ≤ 60 msec for 84 (45.4%) patients and > 60 msec for 22 (11.9%) patients. Twenty-four patients (13.0% of 185 patients with results) had a shift from CTCAE Grade ≤ 2 at baseline to Grade 3 at any time postbaseline (2.7.4 Summary of Clinical Safety).

QTc prolongation is not an important risk of adagrasib as it can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents, patient monitoring, adagrasib dose interruption or modification. QT prolongation is manageable with dose interruption and reduction.

The product information for Krazati requires that it should be initiated by a physician experienced in the use of anti-cancer medicinal products. It is recommended that a baseline ECG prior to treatment initiation be performed in all patients and repeated during treatment. The Krazati SmPC instructs physicians to avoid use of Krazati in patients with congenital long QT syndrome, in patients with concurrent QTc prolongation, and in patients who have experienced *torsades de pointes* arrhythmia in the past. Periodic monitoring with ECGs and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Based on the severity of the adverse reaction, and after correction of any possible electrolyte disturbances, treatment with Krazati can be continued with a reduced dose or temporarily discontinued followed by resumption at a reduced dose after recovery to ≤ Grade 1 or return to to baseline. In patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia, Krazati should be permanently discontinued. The use of medicinal products known to prolong the QTc interval should be avoided.

Hepatotoxicity

Adverse events of hepatoxicity were identified using the preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Liver function test increased, and Mixed liver injury.

Hepatotoxicity TEAEs occurred in 43.1% (81/188) NSCLC patients treated with 600 mg BID adagrasib, which were treatment-related according to the investigator in 37.2% (70/188) of patients. Sixteen (8.5%) patients experienced Grade 3 hepatotoxicity and only 1 (0.5%) patient had a Grade 4 event, with 1.1% of patients having a serious event. Hepatotoxicity resolved in 59.3% (48/81) of those patients experiencing hepatotoxicity events, with 40.7% cases remaining unresolved (Table 13).

Table 13: Summary of Hepatotoxicity TEAEs in Study 849-001

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Patients with Hepatotoxicity TEAEs[1], n (%)	43 (37.1)	81 (43.1)
Total Number of Hepatotoxicity events TEAEs[2]	180	321
Exposure-adjusted Incidence Rate - Patients with AEs/100 PY [95% CI]	92.0 [66.6, 123.9]	111.4 [88.5, 138.5]
Severity[3]		
Grade 1	15 (12.9)	36 (19.1)
Grade 2	16 (13.8)	28 (14.9)
Grade 3	11 (9.5)	16 (8.5)
Grade 4	1 (0.9)	1 (0.5)
Grade 5	0	0
Serious[4]	2 (1.7)	2 (1.1)
Relationship to treatment[5]		
Related	36 (31.0)	70 (37.2)
Not related	7 (6.0)	11 (5.9)
Not known	0	0
Outcome[6]		
Missing	0	0
Resolved	28 (24.1)	48 (25.5)
Not resolved	15 (12.9)	33 (17.6)
Fatal	0	0

Source: SmPC Table 9

Cutoff Date: 15OCT2021 Run Date: 30NOV2022 13:30

AE=adverse event; BID=twice daily; CI=confidence interval; NSCLC=non-small cell lung cancer; PY=patient years; TEAE=treatment-emergent adverse event

[1] Includes all patients who had one or more occurrences of an adverse event that met the criteria of the risk, the patient is counted only once regardless of the number of events or the number of occurrences

[2] Includes all occurrences of an adverse event that met the criteria of the risk, the subject can be counted more than once if experienced multiple adverse events

[3] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing

[4] Only the most serious event is counted - Seriousness: Serious>Nonserious

[5] Only the most related event is counted - Relationship to treatment: Related>Not related>Not known

[6] Only the most severe outcome is counted - Outcomes: Fatal>Not Resolved>Resolved>Unknown+Missing

Hepatotoxicity includes preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Liver function test increased, and Mixed liver injury.

NSCLC (tumour tissue mutation) is the pivotal efficacy study including patients with non-small cell lung cancer (NSCLC) with KRAS G12C mutation detected in tumour tissue.

The median time to onset of the first Grade ≥ 3 event of increased transaminases in NSCLC patients (N=188) was 27.0 days. The median duration of such events was 13.0 days (Table 14).

Table 14: Summary of Grade ≥ 3 Hepatotoxicity Adverse Events in NSCLC Patients

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Time to 1st Grade ≥3 Hepatotoxicity adverse event (days)		
n	12	17
Mean (Std)	35.5 (22.04)	51.1 (76.27)
Median	24.5	27.0
Q1, Q3	16.0, 57.0	15.0, 57.0
Min, Max	12, 72	12, 337
Duration of Grade ≥3 Hepatotoxicity adverse event (days)		
n	12	17
Mean (Std)	12.8 (10.13)	38.9 (78.24)
Median	12.5	13.0
Q1, Q3	3.5, 18.0	8.0, 21.0
Min, Max	1, 32	1, 297

Source: SmPC Table 7
Data Cutoff Date: 15OCT2021 Run Date: 30NOV2022 8:37
Adverse events were coded using MedDRA version 21.0. CTCAE grading v5.0 applied.
Hepatotoxicity includes preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Liver function test increased, and Mixed liver injury.

The occurrence of the individual adverse events comprising the hepatotoxicity group across the NSCLC (tumour tissue mutation) subgroup (n=116) and the total NSCLC group (n=188) are presented in Table 15.

Table 15: Hepatotoxicity TEAEs in Patients who Received MRTX849 600 mg Twice Daily in Study 849-001

Adverse Event	NSCLC (tumour tissue mutation) (N=116)		All NSCLC 600 mg BID (N=188)	
	Grade 1-4 n (%)	Grades 3/4 n (%)	Grade 1-4 n (%)	Grade 3/4 n (%)
Hepatotoxicity (group)[a]				
Alanine aminotransferase increased	33 (28.4)	6 (5.2)	61 (32.4)	10 (5.3)
Aspartate aminotransferase increased	31 (26.7)	6 (5.2)	61 (32.4)	10 (5.3)
Blood alkaline phosphatase increased	23 (19.8)	5 (4.3)	41 (21.8)	7 (3.7)
Blood bilirubin increased	3 (2.6)	2 (1.7)	7 (3.7)	3 (1.6)
Gamma-glutamyltransferase increased	0	0	1 (<1)	0
Hepatic enzyme increased	0	0	1 (<1)	0
Liver function test increased	1 (<1)	0	1 (<1)	0
Mixed liver injury	1 (<1)	1 (<1)	1 (<1)	1 (<1)

Source: ISS Table 14.3.3.1.4a
BID=twice daily
[a] Transaminases increased (group) includes preferred terms: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Liver function test increased, and Mixed liver injury.

In both the NSCLC (tumour tissue mutation) subgroup (n=116) and all NSCLC (n=188) patients, adverse reactions leading to dose interruption or reduction included alanine aminotransferase increased 13.8%, aspartate aminotransferase increased 11.2%, and liver function test increased < 1%. Blood creatinine increased and blood alkaline phosphatase increased each led to dose interruption or reduction in 6.9% patients in the NSCLC (tumour tissue mutation) subgroup and 5.9% and 5.3%, respectively, in the NSCLC group. Hepatic enzyme increased < 1% and gamma-glutamyltransferase increased < 1% both occurred in the NSCLC group but not in the NSCLC (tumour tissue mutation) subgroup (ISS Table 14.3.2.3.7). No hepatotoxicity adverse reactions were fatal.

Increased transaminases occurred in some patients treated with Krazati. Based on the clinical laboratory data from Study 849-001, elevations in aspartate aminotransferase > 5 × upper limit of normal (ULN; Grade 3/4) occurred in 6.2% patients in NSCLC (tumour tissue mutation) subgroup, and alanine aminotransferase > 5 × ULN occurred in 4.4% patients. Increases in transaminases were typically mild to moderate. Among 260 patients treated at 600 mg BID, there were no cases meeting Hy's Law due to drug-induced liver injury, no Grade 5 events, and 1 Grade 4 event in a patient who recovered after treatment discontinuation.

Hepatotoxicity is not an important risk of adagrasib as it can be managed in clinical practice through healthcare professional awareness of the precautions to take with oncology therapeutic agents, patient monitoring, adagrasib dose interruption or modification.

The Krazati SmPC instructs physicians to monitor liver laboratory tests, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and blood bilirubin prior to the start of treatment and monthly for 3 months after starting treatment with Krazati and as clinically indicated, with more frequent testing in patients who develop transaminase and/or alkaline phosphate elevations. Based on the severity of the adverse reaction, the adagrasib dose should either be reduced, temporarily withheld until recovery to ≤ Grade 1 or return to baseline then resumed at a reduced dose, or permanently discontinued. Specific guidance regarding dose management of adagrasib in patients with increased transaminases is provided in section 4.2 of the Krazati SmPC.

Increased amylase/lipase

Adverse events of increased amylase and/or lipase were identified using the preferred terms: Amylase increased, and Lipase increased.

Increased amylase/lipase TEAEs occurred in 21.3% (40/188) NSCLC patients treated with 600 mg BID adagrasib, of which 19.1% (36/188) were treatment-related according to the investigator. Twelve (6.4%) patients experienced Grade 3 increased amylase/lipase, 1 (0.5%) patient experienced Grade 4 increased amylase/lipase, and there were no Grade 5 events reported. Only 2 (1.1%) patients had serious events. Amylase/lipase increased resolved in 67.5% (27/40) of those patients experiencing increased amylase or lipase, with 32.5% cases remaining unresolved (Table 16).

Table 16: Summary of Amylase/lipase Increased TEAEs in Study 849-001

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Patients with Amylase/lipase Increased TEAEs[1], n (%)	25 (21.6)	40 (21.3)
Total Amylase/lipase Increased TEAEs[2]	95	135
Exposure-adjusted Incidence Rate - Patients with AEs/100 PY [95% CI]	45.8 [29.6, 67.6]	44.3 [31.7, 60.3]
Severity[3]		
Grade 1	8 (6.9)	13 (6.9)
Grade 2	8 (6.9)	14 (7.4)
Grade 3	9 (7.8)	12 (6.4)
Grade 4	0	1 (0.5)
Grade 5	0	0
Serious[4]	1 (0.9)	2 (1.1)
Relationship to treatment[5]		
Related	23 (19.8)	36 (19.1)
Not related	2 (1.7)	4 (2.1)
Not known	0	0
Outcome[6]		
Unknown	0	0
Resolved	15 (12.9)	27 (14.4)
Not resolved	10 (8.6)	13 (6.9)
Fatal	0	0

Source: RMP Table 14.6.1.3
AE=adverse event; BID=twice daily; CI=confidence interval; NSCLC=non-small cell lung cancer; PY=patient years; TEAE=treatment-emergent adverse event
[1] Includes all patients who had one or more occurrences of an adverse event that met the criteria of the risk, the patient is counted only once regardless of the number of events or the number of occurrences
[2] Includes all occurrences of an adverse event that met the criteria of the risk, the patient can be counted more than once if experienced multiple adverse events
[3] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing
[4] Only the most serious event is counted - Seriousness: Serious>Nonserious
[5] Only the most related event is counted - Relationship to treatment: Related>Not related>Not known
[6] Only the most severe outcome is counted - Outcomes: Fatal>Not Resolved>Resolved>Unknown+Missing
Amylase/lipase increased includes preferred terms: Amylase increased and Lipase increased.
NSCLC (tumour tissue mutation) is the group in the pivotal efficacy study including patients with non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation detected in tumour tissue.

The occurrence of the individual adverse events of lipase increased and amylase increased across the NSCLC (tumour tissue mutation) subgroup (n=116) and the total NSCLC group (n=188) are presented in Table 17.

Table 17: Increased Amylase/Lipase TEAEs in Patients who Received MRTX849 600 mg Twice Daily in Study 849-001

Adverse Event	NSCLC (tumour tissue mutation) (N=116)		All NSCLC 600 mg BID (N=188)	
	Grade 1-4 n (%)	Grades 3/4 n (%)	Grade 1-4 n (%)	Grade 3/4 n (%)
Investigations				
Lipase increased	18 (15.5)	9 (7.8)	30 (16.0)	13 (6.9)
Amylase increased	21 (18.1)	1 (<1)	30 (16.0)	2 (1.1)

Source: ISS Table 14.3.3.1.6a
BID=twice daily

Increased amylase and/or lipase has been observed at baseline and on treatment, and typically in the absence of clinical symptoms. Clinical study observations have shown elevated pancreatic enzyme levels to be nonspecific markers and a poor screening tool for pancreatitis. During clinical study conduct, patients with increased amylase and/or lipase in the absence of clinical symptoms often continued treatment and their usual diet; treatment continuation did not result in progression to frank pancreatitis. There are insufficient data to indicate that treatment with adagrasib is associated with pancreatitis, and routine monitoring of pancreatic enzymes does not appear warranted as clinical symptoms should be used to guide clinical evaluation and management of patients (2.7.4 Summary of Clinical Safety).

Pneumonitis/Interstitial lung disease (ILD)

Adverse events of pneumonitis/ILD were identified using the preferred terms: Pneumonitis and Interstitial lung disease. Pneumonitis/ILD TEAEs occurred in 7.4% (14/188) NSCLC patients treated with 600 mg BID adagrasib, which were treatment-related according to the investigator in 5.9% (11/188) patients. Four (2.1%) patients experienced Pneumonitis/ILD Grade 3 and 1 (0.5%) patient had a Grade 5 event; no Grade 4 events were observed. The TEAEs were serious in 2.1% (4) patients. Pneumonitis/ILD resolved in 57.1% (8/14) of those patients experiencing pneumonitis or ILD, with 35.7% (5/14) cases remaining unresolved. One case had a fatal outcome which was assessed as treatment-related by the investigator (Table 18).

Table 18: Summary of Pneumonitis/ILD TEAEs in Study 849-001

	NSCLC (tumour tissue mutation) (N=116)	All NSCLC 600 mg BID (N=188)
Patients with Pneumonitis/Interstitial Lung Disease TEAEs[1], n (%)	8 (6.9)	14 (7.4)
Total Pneumonitis/Interstitial Lung Disease TEAEs[2]	12	20
Exposure-adjusted Incidence Rate - Patients with AEs/100 PY [95% CI]	12.4 [5.3, 24.4]	12.9 [7.1, 21.7]
Severity[3]		
Grade 1	1 (0.9)	4 (2.1)
Grade 2	4 (3.4)	5 (2.7)
Grade 3	3 (2.6)	4 (2.1)
Grade 4	0	0
Grade 5	0	1 (0.5)
Serious[4]	2 (1.7)	4 (2.1)
Relationship to treatment[5]		
Related	6 (5.2)	11 (5.9)
Not related	2 (1.7)	3 (1.6)
Not known	0	0
Outcome[6]		
Unknown	0	0
Resolved	5 (4.3)	8 (4.3)
Not resolved	3 (2.6)	5 (2.7)
Fatal	0	1 (0.5)

Source: RMP Table 14.6.1.4
AE=adverse event; BID=twice daily; CI=confidence interval; NSCLC=non-small cell lung cancer; PY=patient years; TEAE=treatment-emergent adverse event
[1] Includes all patients who had one or more occurrences of an adverse event that met the criteria of the risk, the patient is counted only once regardless of the number of events or the number of occurrences
[2] Includes all occurrences of an adverse event that met the criteria of the risk, the patient can be counted more than once if experienced multiple adverse events
[3] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing
[4] Only the most serious event is counted - Seriousness: Serious>Nonserious
[5] Only the most related event is counted - Relationship to treatment: Related>Not related>Not known
[6] Only the most severe outcome is counted - Outcomes: Fatal>Not Resolved>Resolved>Unknown+Missing
Pneumonitis/Interstitial lung disease includes preferred terms: Pneumonitis and Interstitial lung disease.
NSCLC (tumour tissue mutation) is the pivotal efficacy study including patients with non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation detected in tumour tissue.

The fatal case concerned a female with metastatic NSCLC (Phase 1/1b CSR Listing 16.2.4.2; ISS Listing 16.2.7.1, 16.2.7.2), and a history of chronic pneumonitis, which first occurred following administration of pembrolizumab and recurred following administration of navelbine, who enrolled in the Phase 1 expansion study at 600 mg BID. On Day 43 she began experiencing

Grade 3 treatment-related pneumonitis, and treatment was interrupted. Concomitant medications at the time of initiation of treatment of adagrasib included mycophenolic acid for the ongoing treatment of chronic pneumonitis. On Day 68 pneumonitis increased in severity to Grade 5, and the death was considered treatment related. It is also possible that the event was an idiopathic exacerbation of the underlying chronic pneumonitis.

Almost all patients with NSCLC with *KRAS* G12C are smokers, which commonly results in the development of COPD. Pneumonitis can develop in the setting of pneumonia, for which this population is predisposed due to COPD and tumour obstruction. Based on a case-analysis and the overall frequency of pneumonitis in 260 subjects receiving adagrasib, 600 mg twice-daily for a median duration of 7.3 months in pooled clinical studies involving patients with *KRAS* G12C mutation-positive, locally advanced, or metastatic NSCLC (n = 188), colorectal cancer (n = 46), and other solid tumours (n = 26) a causal relationship is possible. Accordingly, pneumonitis is listed as a common adverse reaction (all grades [5.4%], grade ≥ 3 [1.9%], N=260) in the SmPC. If patients with clinical manifestations of pneumonitis have received recent treatment with a PD-1 or PD-L1 inhibitor, considerations for the differential diagnosis should also include an immune-based process, and empiric treatment with corticosteroids should be considered (2.7.4 Summary of Clinical Safety).

Drug Interactions

Study 849-006, a Phase 1, open-label, parallel, 4-arm, fixed-sequence study, investigated the effect of coadministration of P-gp inhibitor, CYP3A4 inhibitor, CYP3A4 inducer, and increased gastric pH on the PK, safety, and tolerability of adagrasib and the effect of adagrasib on the PK of CYP2C9, CYP2D6, CYP3A4, BCRP, and P-gp probe substrates in healthy subjects.

Adagrasib was well-tolerated following oral administration of single doses of 200 or 600 mg alone or coadministered with itraconazole, rifampicin, pantoprazole, or a probe drug cocktail (comprising midazolam, dextromethorphan, warfarin, digoxin, and rosuvastatin) in healthy subjects. In addition, adagrasib was well-tolerated after oral administration of 400 mg BID with a probe drug cocktail (comprising midazolam, dextromethorphan, warfarin, digoxin, and rosuvastatin) in healthy subjects. AEs were manageable, and all AEs resolved; there were no severe TEAEs, or SAEs, reported during the study (2.7.4 Summary of Clinical Safety).

Drug interactions are not an important risk of adagrasib as these can be managed in clinical practice through healthcare professional awareness of the effects of both other drugs on adagrasib and of adagrasib on other drugs.

The product information for Krazati specifies that in vitro studies showed that adagrasib is metabolised primarily by CYP3A4 and is a reversible inhibitor of CYP2B6, CYP2C9, CYP2D6 and CYP3A4, as well as a time-dependent inhibitor of CYP3A4. In vitro, adagrasib is a substrate of BCRP and inhibits P-gp, BCRP, MATE-1/MATE2-K, OATP1B1, and OCT1.

Co-administration of multiple doses of rifampicin 600 mg QD (strong CYP3A4 inducer) with a single 600 mg dose of adagrasib decreased adagrasib C_{max} by 88% and AUC by 95% in healthy subjects. The Krazati SmPC instructs physicians to avoid coadministration of adagrasib with strong CYP3A inducers. Co-administration of multiple doses of itraconazole (a strong CYP3A inhibitor) with a single 200 mg dose of adagrasib increased adagrasib C_{max} by 2.4-fold and AUC by 4-fold in healthy subjects. Concomitant use of strong CYP3A inhibitors should be avoided.

Adagrasib is a strong CYP3A4 inhibitor. Co-administration of medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil for treatment of pulmonary arterial hypertension, oral midazolam, triazolam). Krazati may be administered only after switching to acceptable alternative medicinal products. When adagrasib is co-administered with other medicinal products that are sensitive CYP3A substrates without a narrow therapeutic index, the SmPC for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

Concomitant use of adagrasib with CYP2C9 or CYP2D6 substrates and P-gp substrates, where minimal concentration changes may lead to serious adverse reaction, should be avoided unless otherwise recommended in the SmPC for these substrates. The Krazati SmPC specifies that no clinically significant differences in the pharmacokinetics of a BCRP/OATP1B1 substrate were observed when coadministered with adagrasib. In addition, medicinal products known to prolong the QTc interval should be avoided as the effect of coadministration of such medicinal products with adagrasib is unknown.

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

None

- **Other reasons for considering the risks not important:**

None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

There are no identified or potential risks considered important for inclusion in the list of safety concerns for adagrasib.

SVII.2 New safety concerns and reclassification 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

Not applicable.

SVII.3.2. Presentation of the missing information

Not applicable.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 19: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the safety concerns:

- Not applicable.

Other forms of routine pharmacovigilance activities for the safety concerns:

- Not applicable.

III.2 Additional pharmacovigilance activities

Not applicable; no safety concerns have been identified.

III.3 Summary Table of additional Pharmacovigilance activities

Table 20: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 21: Planned and on-going 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 which are conditions of the marketing authorisation				
Study 849-012 A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with KRAS G12C Mutation Ongoing	*Primary Objective:* To compare the efficacy of adagrasib versus docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior treatment with a platinum-based regimen and immune CIT. *Secondary Objectives:* • To evaluate secondary efficacy endpoints in the study population. • To evaluate the safety and tolerability in the study population. • To evaluate the pharmacokinetics (PK) of MRTX849 administered in the study population. • To evaluate health-related quality of life (HRQOL) and lung cancer-specific symptoms in the study population.		First patient, first visit	03 Aug 2021
			Trial completion	4Q 2023
			CSR filing	3Q 2024
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 22: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
None	Not applicable

V.2. Additional Risk Minimisation Measures

Not applicable; there are no safety concerns.

V.3 Summary of risk minimisation measures

Table 23: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
None	Not applicable	Not applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Krazati (adagrasib)

This is a summary of the risk management plan (RMP) for Krazati®.

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

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

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

I. The medicine and what it is used for

Krazati as monotherapy is authorised for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation and disease progression after at least one prior systemic therapy (see SmPC for the full indication). It contains adagrasib as the active substance and it is given orally.

Further information about the evaluation of Krazati's benefits can be found in Krazati's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to 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;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of Krazati are risks 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 Krazati. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified/potential risk: none	
Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Not applicable
Risk minimisation measures	Not applicable
Additional pharmacovigilance activities	Not applicable
Missing information: none	
Risk minimisation measures	Not applicable
Additional pharmacovigilance activities	Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Study 849-012

Purpose of the study:

To compare the efficacy of adagrasib (MRTX849) versus docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior treatment with a platinum-based regimen and immune CIT.

To evaluate secondary efficacy endpoints in the study population.

To evaluate the safety and tolerability in the study population.

To evaluate the pharmacokinetics (PK) of adagrasib administered in the study population.

To evaluate health-related quality of life (HRQOL) and lung cancer specific symptoms in the study population.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Krazati.

PART VII: ANNEXES

Table of contents

Annex 1: Specific adverse drug reaction follow-up forms

Not applicable.

Annex 2: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.