EUROPEAN UNION RISK MANAGEMENT PLAN

LUMYKRAS® (sotorasib)

Marketing Authorization Applicant:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	3.0
Date:	15 May 2024
Supersedes:	Version 1.3, dated 07 December 2023

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	3.0
Data lock point (DLP) of this RMP:	27 November 2023
Date of final sign-off:	15 May 2024
Rationale for submitting an updated RMP:	To consolidate RMP Version 2.0 with RMP Version 1.3, to update the Product(s) Overview to include the 240 mg tablet and to add the Postauthorization Efficacy Study 20190341 as a new Specific Obligation.

Summary of significant changes in this RMP

This RMP consolidates the updates made in RMP Version 1.3 (approved within procedure EMEA/H/C/005522/II/0007) and RMP Version 2.0 (submitted within procedure EMEA/H/C/005522/II/0010/G). A list of other significant changes can be found below.

Part/Module/Annex	Major Change(s)	Version Number and Date
Part I: Product Overview	Updated the proposed dosage in the EEA and the pharmaceutical form(s) and strength(s)	Version 3.0; 15 May 2024
Part II: Safety Specifications		
SI: Epidemiology of the Indication(s) and target population(s)	Updated	Version 3.0; 15 May 2024
SIII: Clinical Trial Exposure	Updated clinical trial exposure data	Version 3.0; 15 May 2024
SV: Postauthorization Experience	Updated postmarketing exposure data	Version 3.0; 15 May 2024
SVII: Identified and Potential Risks	Removed the New or Reclassification of Safety Concerns table for the important potential risk of "Use in Patients With Moderate and Severe Hepatic Impairment"	Version 3.0; 15 May 2024
Part IV: Plans for Postauthorization Efficacy Studies	Removed the following Specific Obligation Postauthorization Efficacy Study (PAES): • Study 20190009	Version 2.0; 03 February 2023
	Added the following new Specific Obligation PAES: • Study 20190341	Version 3.0; 15 May 2024
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Updated routine risk minimization measures for the important potential risk of "Use in Patients With Moderate and Severe Hepatic Impairment"	Version 3.0; 15 May 2024
Part VI: Summary of the Risk Management Plan	Aligned with the changes in Part IV and Part V	Version 3.0; 15 May 2024
Part VII: Annexes		
Annex 5: Protocols for Proposed and Ongoing Studies in RMP Part IV	Removed the Specific Obligation PAES Study 20190009	Version 2.0; 03 February 2023
	Added the new Specific Obligation PAES Study 20190341	Version 3.0; 15 May 2024

Other RMP versions under evaluation:	
RMP version number:	None
Submitted on:	None
Procedure number:	None
Details of the currently approved RMP:	
Version number:	1.3
Approved with procedure:	EMEA/H/C/005522/II/0007
Date of approval (opinion date):	11 January 2024
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind, Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization applicant´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
ALK	anaplastic lymphoma kinase gene
ASIR	age-standardized incidence rate
ASMR	age-standardized mortality rate
ATC	Anatomical Therapeutic Chemical
BRAF	B-raf gene
COPD	chronic obstructive pulmonary disease
DLP	data lock point
EGFR	epidermal growth factor receptor
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
INN	International Nonproprietary Name
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
$KRAS^{G12C}$	KRAS protein with a G12C amino acid substitution
KRAS p.G12C	*KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine kinase gene
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PI	Product Information

Term/Abbreviation	Explanation
PK	pharmacokinetic
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
ROS1	proto-oncogene tyrosine-protein kinase ROS
RWE	Real World Evidence
SEER	Surveillance, Epidemiology, and End Results Program
SmPC	Summary of Product Characteristics
STD_{10}	severely toxic dose in 10% of animals
UK	United Kingdom
US	United States
VEGF	vascular endothelial growth factor

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Sotorasib
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Antineoplastic agents, ATC code L01XX73
Marketing authorization applicant	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Lumykras®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Antineoplastic agent
Summary of mode of action	Sotorasib is a selective $KRAS^{G12C}$ (Kirsten rat sarcoma viral oncogene homolog) inhibitor, which covalently and irreversibly binds to the unique cysteine of $KRAS^{G12C}$. Inactivation of $KRAS^{G12C}$ by sotorasib blocks tumor cell signaling and survival, inhibits cell growth, and promotes apoptosis selectively in tumors harboring $KRAS^{G12C}$, an oncogenic driver of tumorigenesis.
Important information about its composition	Not applicable.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current	Lumykras as monotherapy is indicated for the treatment of adults with advanced NSCLC with *KRAS G12C* mutation and who have progressed after at least 1 prior line of systemic therapy.
Proposed	Not applicable.

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Abbreviations are defined on the next page of this table.

Table 1. Product(s) Overview

Dosage in the EEA	
Current	The recommended dose is 960 mg sotorasib (eight 120 mg tablets) once daily.
Proposed	The recommended dose is 960 mg sotorasib (eight 120 mg tablets or four 240 mg tablets) once daily.
Pharmaceutical form(s) and strength(s)	
Current	Yellow, film-coated tablet, oblong-shaped (7 mm x 16 mm), debossed with “AMG” on one side and “120” on the opposite side.
Proposed	Yellow, film-coated tablet, oblong-shaped (7 mm x 16 mm), debossed with “AMG” on 1 side and “120” on the opposite side. Yellow film-coated tablet, oval-shaped (8 mm x 18 mm), debossed with “AMG” on 1 side and “240” on the opposite side.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

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ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EU = European Union; INN = International Nonproprietary Name; KRAS = Kirsten rat sarcoma viral oncogene homolog (protein); $KRAS^{G12C}$ = KRAS protein with a G12C amino acid substitution; KRAS p.G12C = KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = non-small cell lung cancer; PI = Product Information; RMP = Risk Management Plan

PART II. SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Previously Treated *KRAS p.G12C*-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Incidence	Lung cancer was the most frequently diagnosed cancer in 2022, responsible for almost 2.5 million new cases, or 1 in 8 cancers worldwide (12.4% of all cancers globally) (Bray, 2024).. In 2022, there were 484 306 new lung cancer cases diagnosed in Europe (Globocan, 2022).
Prevalence	The number of 5-year prevalent cases of lung cancer in Europe was estimated to be 610 169 in 2022 (Globocan, 2022).
Demographics of population in the proposed indication and risk factors for the disease	Lung cancer incidence and mortality rates are higher among men than women (Bray et al, 2018; Malhotra et al, 2016). In Europe, lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death in women (Ferlay et al, 2018; Torre et al, 2016). Those younger than 40 have a low incidence, while incidence peaks among those aged 65 to 84 years old (Duma et al, 2019; Malhotra et al, 2016). Lung cancer incidence and mortality rates vary substantially across geography and demographics in Europe, largely reflecting variations in patterns of tobacco smoking (Duma et al, 2019; Malhotra et al, 2016; Torre et al, 2016; Brennan et al, 2011; Molina et al, 2008). Cigarette smoking is an important risk factor, accounting for 85% to 90% of lung cancers (Duma et al, 2019). For men in Europe, lung cancer incidence rates per 100 000 population are highest in Central and Eastern Europe (ASIR = 49.3), slightly lower in Western (ASIR = 43.3) and Southern Europe (ASIR = 43.1); and lowest in Northern Europe (ASIR = 34). Similar geographical variation is observed for mortality in men. For women in Europe, lung cancer incidence rates are highest in Northern (ASIR = 26.9) and Western (ASIR = 25.7) Europe; and lower rates are found in Southern (ASIR = 15.7) and Central and Eastern Europe (ASIR = 11.9). Similar geographical variation is observed for mortality in women (Ferlay et al, 2018). Over the past 2 decades, lung cancer incidence and mortality among men have been declining in most European countries, whilst among women they have been increasing (Malhotra et al, 2016; Jemal et al, 2010). These trends reflect the difference in smoking patterns; the prevalence of smoking among men has been decreasing for a longer time than it has been for women (Torre et al, 2016).

Table 2. Summary of Epidemiology of Previously Treated KRAS p.G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Demographics of population in the proposed indication and risk factors for the disease (continued)	Risk factors for lung cancer include: • cigarette smoking (Duma et al, 2019; Molina et al, 2008) • passive or secondhand smoking (Molina et al, 2008) • family history of lung cancer including high-penetrance genes and genetic polymorphisms (Brennan et al, 2011; Biesalski et al, 1998) • exposure to non-tobacco procarcinogens, carcinogens, and tumor promoters (Biesalski et al, 1998) • occupational exposures, including asbestos, antifungal outdoor wood preservatives, insecticides, herbicides, beryllium and beryllium oxide (X-ray and radiation technology), inhaled chemicals including cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ester and diesel exhaust (Loomis et al, 2018) • exposure to high particulate matter (Raaschou-Nielsen et al, 2013; Brennan et al, 2011) • previous tobacco-related cancer (Biesalski et al, 1998) • previous chronic inflammatory lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, and tuberculosis (Houghton, 2013; Rosenberger et al, 2012; Liang et al, 2009) Results from Amgen Real World Evidence (RWE) Studies 20200097 and 20200132 in the US showed that patients with *KRAS p.G12C*-mutated advanced NSCLC had similar demographic and clinical characteristics compared with the overall group of patients with advanced NSCLC; however, higher proportions of women, past or present smokers, and non-squamous cell carcinoma histology were observed in patients with *KRAS p.G12C*-mutated advanced NSCLC.
Main existing treatment options	Treatment of advanced or metastatic NSCLC has drastically changed because of recent development of immune checkpoint inhibitors that have established the role of anti-programmed death-ligand 1 programmed cell death-1 (PD-1) or programmed death-ligand 1 (PD-L1) therapy either as a monotherapy, or in combination with platinum-based chemotherapy, as first line treatment for NSCLC without oncogenic driver mutations, depending on PD-L1 expression status (Ettinger et al, 2019; Planchard et al, 2018). Targeted therapies are the recommended treatment options where molecular testing has identified mutations such as *EGFR*, *ALK*, *ROS1*, *BRAF*, or *NTRK (*National Comprehensive Cancer Network [NCCN], 2022). Oncogenic *KRAS* mutations rarely occur concomitantly with other actionable oncogenic driver mutations (Martorell et al, 2017). Thus, most patients with oncogenic *KRAS* mutations, including the *KRAS p.G12C* mutation, are not candidates for currently approved targeted therapies and consequently are typically treated as patients without targetable mutations (ie, with chemotherapy, immunotherapy, or antiangiogenic agents) (Planchard et al, 2018). In first-line therapy, patients with NSCLC without actionable oncogenic driver mutations are typically treated with checkpoint inhibitors (if not contraindicated) with or without chemotherapy (eg, checkpoint inhibitors with or without platinum-containing doublets such as cisplatin/pemetrexed).

Table 2. Summary of Epidemiology of Previously Treated KRAS p.G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Main existing treatment options (continued)	Patients requiring subsequent second-line or later therapy for the disease are commonly treated with other single-line chemotherapy with or without a vascular endothelial growth factor (VEGF) inhibitor or checkpoint inhibitors (if not already given in first-line). Patients without actionable mutations previously treated for NSCLC may also receive approved second-line or later therapies.
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Lung cancer is the leading cause of cancer death in Europe, representing 20% of all cancer deaths (Ferlay et al, 2018). In 2020, the age-standardized mortality rate (ASMR) in Europe was 23.9 per 100 000 population. The ASMR was higher among men (ASMR = 34.2) than women (ASMR = 15.2). There was some geographical variation in mortality rates across Western (ASMR = 23.8), Central and Eastern (ASMR = 22.7), Southern (ASMR = 21.9) and Northern Europe (ASMR = 20.1). Results from the EUROCARE-5 study found that European patients with lung cancer diagnosed between 2000 to 2007 had a mean age-standardized 5-year survival of 13.0%, varying from 9.0% in the UK and Ireland, 10.6% in Eastern Europe, 12.2% in Northern Europe, 13.2% in Southern Europe to 14.8% in central Europe (De Angelis et al, 2014). Non-small cell lung cancer accounts for the majority of lung cancer cases and 5-year survival is approximately 15% (Molina et al, 2008). The Eindhoven Cancer Registry in the Netherlands found that between 1993 to 1997 the relative 5-year survival rate for those with NSCLC in Europe was 19% for those < 70 years old and 16% for those ≥ 70 years old (Janssen-Heijnen and Coebergh, 2003). Survival depends on stage at diagnosis with earlier stage at diagnosis showing better survival (Torre et al, 2016). In Germany, the 5-year survival from diagnosis decreases significantly from Stage III (men: 17%, and female: 17%) and Stage IV (men: 3%, and female: 5%) (Robert Koch Institute, 2019). Similar 5-year net survival rates were observed in the UK, Stage III is 12.6% (men: 11.6%, and female: 13.7%) and decreases to 2.9% for Stage IV (men: 2.3%, and female: 3.4%) (Office for National Statistics, 2019). In comparison, in the US, the 5-year relative survival rate for advanced NSCLC is 5.2% (Surveillance, Epidemiology, and End Results Program [SEER], 2019). Data from the French National Cancer Institute indicate that patients with *KRAS*-mutated NSCLC show a lower proportion of responses to cytotoxic chemotherapy and decreased survival compared with the overall population of patients with NSCLC (Barlesi et al, 2016), and this finding has been supported by other data indicating that patients with *KRAS*-mutated NSCLC have a poor prognosis (Wiesweg et al, 2019; Park et al, 2017; Hames et al, 2016; Svaton et al, 2016; Johnson et al, 2013). Overall, the results from the Amgen natural history studies (Amgen RWE Studies 20200097, 20180277, and 20190344) and published literature show that patients with *KRAS p.G12C*-mutated advanced NSCLC had poor treatment outcomes with existing therapies in second line or later, and their prognosis was as poor as the overall advanced NSCLC population, highlighting the unmet medical need for this patient population.

Table 2. Summary of Epidemiology of Previously Treated KRAS p.G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

<table>
<tr><td>Natural history of the indicated condition in the untreated population, including mortality and morbidity (continued)</td><td>Real-world outcomes for patients with advanced NSCLC and KRAS p.G12C-mutated advanced NSCLC by line of therapy:
<table>
<tr><th></th><th colspan="2">KRAS p.G12C-mutated NSCLC</th><th>All NSCLC</th></tr>
<tr><th>Line of Therapy</th><th>Study 20180277[a]</th><th>Study 20200097[a]</th><th>Study 20200132[a]</th></tr>
<tr><td colspan="4">Median (95% CI) OS (months)</td></tr>
<tr><td>First</td><td>14.9 (12.2, 24.3)</td><td>12.0 (9.6, 15.3)</td><td>12.9 (11.9, 14.2)</td></tr>
<tr><td>Second</td><td>10.1 (7.1, 16.9)</td><td>9.5 (8.1, 13.1)</td><td>10.2 (9.5, 11.3)</td></tr>
<tr><td>Third</td><td>6.5 (5.0, NE)</td><td>6.7 (5.9, 10.7)</td><td>7.9 (6.6, 8.8)</td></tr>
<tr><td>Fourth</td><td>3.0 (2.2, NE)</td><td>5.9 (4.3, 12.9)</td><td>7.4 (6.4, 8.6)</td></tr>
<tr><td colspan="4">Median (95% CI) real-world PFS (months)</td></tr>
<tr><td>First</td><td>6.1 (4.4, 9.3)</td><td>5.0 (4.4, 5.8)</td><td>5.6 (5.3, 5.8)</td></tr>
<tr><td>Second</td><td>3.2 (2.1, 5.3)</td><td>4.0 (2.8, 5.3)</td><td>4.0 (3.7, 4.4)</td></tr>
<tr><td>Third</td><td>2.3 (1.4, 4.1)</td><td>3.1 (2.4, 4.3)</td><td>3.5 (3.1, 3.9)</td></tr>
<tr><td>Fourth</td><td>1.8 (1.4, 15.0)</td><td>2.6 (2.1, 4.7)</td><td>3.0 (2.7, 3.4)</td></tr>
</table>
[a] Retrospective Study 20180277 was conducted using the American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange database in 416 patients with KRAS p.G12C-mutated advanced NSCLC. Retrospective Studies 20200097 and 20200132 were conducted using the United States Flatiron Health - Foundation Medicine Clinico-Genomic Database in 743 patients with KRAS p.G12C-mutated advanced NSCLC and 7069 patients with advanced NSCLC (ie, regardless of KRAS p.G12C mutation), respectively.</td></tr>
<tr><td>Important comorbidities</td><td>Lung cancer is most frequent in smokers, and these patients frequently have tobacco-related conditions, mainly cardiovascular and other respiratory diseases (eg, COPD) (Leduc et al, 2017; Al-Kindi and Oliviera, 2016; Kravchenko et al, 2015; van Herk-Sukel et al, 2013; Young et al, 2009). Other unrelated comorbidities that are frequent include diabetes and its complications (eg, renal insufficiency, cardiovascular disease). The prevalence of these comorbidities vary by country which likely reflects the differences in lifestyle behaviors (eg, smoking and diet) (Herrero Rivera et al, 2019; Linden et al, 2020; Lembicz et al, 2018; Leduc et al, 2017; Kocher et al, 2015).</td></tr>
</table>

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Part II: Module SII – Nonclinical Part of the Safety Specification

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity Key issues identified from single or repeat-dose toxicity studies	Renal tubular degeneration/necrosis was observed in the rat repeat-dose toxicology studies. The incidence and severity of tubular degeneration/necrosis was dependent on dose/exposure levels and treatment duration. In the rat 28-day study, sotorasib was well tolerated at 0, 10, 30, and 200 mg/kg; the severely toxic dose in 10% of animals (STD_{10}) was > 200 mg/kg, based on minimal to mild renal tubular degeneration/necrosis at 200 mg/kg. In the 3 month study (60, 180, and 750 mg/kg), the STD_{10} was 180 mg/kg. Renal tubular degeneration/necrosis increased in both incidence and severity (minimal to marked) compared to the renal changes in the 28-day study. This was attributed to the longer study duration and higher systemic exposures to sotorasib. At the end of the recovery phase, there was partial recovery at all dose levels. The time-course assessment revealed that the renal tubular changes at 750 mg/kg were associated with changes in serum or urine biomarkers such as blood urea nitrogen (BUN), creatinine, Kim-1 and clusterin in early phase (days 2 and 4); therefore, the toxicologically significant renal toxicity was monitorable with these biomarkers in the rat. No renal toxicity was identified in the dog.	Clinical data from pivotal Study 20170543 did not suggest a risk of renal toxicity with sotorasib use. Renal function is assessed in clinical studies. Specific eligibility criteria and dose modification guidelines for sotorasib are provided in the clinical study protocols. Renal toxicity is not considered to be a safety concern in the RMP.

Abbreviations are defined on the last page of this table

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued) Key issues identified from single or repeat-dose toxicity studies (continued)	In a GLP 3-month dog toxicology study (0, 200, and 1000 mg/kg/day administered as 100 and 500 mg/kg twice daily [BID]), there was abnormal content in the gall bladder, and there were microscopic changes in the liver (hepatocellular hypertrophy with increased liver weight), pituitary (hypertrophy of basophils with increased pituitary weight), or thyroid (decreased colloid and hypertrophy of follicular epithelium with decreased thyroid weight) that were considered to be non-severely toxic and attributed to an adaptive or secondary response to hepatocellular enzyme induction. The highest non-severely toxic dose was 1000 mg/kg/day.	Clinical data from pivotal Study 20170543 did not suggest a risk of hypothyroidism or thyroid dysfunction; however, clinical safety data for potential effects on thyroid function have not been accumulated sufficiently enough to conclude the clinical relevance for the findings observed in the dog. Sotorasib clinical study protocols include thyroid function testing at screening, predose on day 1 of each cycle, at the end of treatment, and at safety follow-up. Clinical signs or symptoms concerning for thyroid dysfunction are assessed in clinical studies. Hypothyroidism or thyroid dysfunction are not considered to be a safety concerns in the RMP.
	Decrease in red blood cell (RBC) mass (hemoglobin, RBC count, and hematocrit) was observed in both rat and dog toxicology studies. Due to the small magnitudes of change, the sotorasib-related effects on hematology parameters were considered non-adverse and were reversible after a 28-day recovery in rats. Reversibility was expected based on the normal regenerative capacity of the hematopoietic system and the absence of overt bone-marrow toxicity (eg, hypocellularity).	Clinical data from pivotal Study 20170543 did not suggest a risk of clinically significant changes to RBC parameters with sotorasib use. Monitoring of hemoglobin, hematocrit, and associated adverse events will be conducted in ongoing and planned sotorasib clinical studies. Specific eligibility criteria and dose modification guidelines pertaining to hematology parameters are provided in the sotorasib clinical study protocol. The risk of significant changes to RBC parameters is not considered to be a safety concern in the RMP.

Abbreviations are defined on the last page of this table

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued)		
Reproductive/developmental toxicity	There were no adverse effects on male or female reproductive organs in general toxicology studies conducted in dogs and rats. In the rat and rabbit embryo-fetal development toxicology studies, sotorasib was not teratogenic. In the rat, there were no effects on embryo-fetal development up to the highest dose (540 mg/kg) tested. In the rabbit, lower fetal body weights and a reduction in the number of ossified metacarpals in fetuses were observed only at the dose level (100 mg/kg) associated with decreased body weight gain and food consumption in dams during dosing phase. Reduced ossification as an evidence of growth retardation associated with reduced fetal body weight was interpreted as a non-specific fetal effect in the presence of significant maternal toxicity (Nitzsche, 2017).	There are no data from the use of sotorasib in pregnant women, it is unknown if sotorasib or its metabolites are excreted in human milk, and there are no clinical studies to evaluate the effect of sotorasib on fertility. Sotorasib is not recommended during pregnancy and in women of childbearing potential not using contraception. Patients must be informed of the potential hazards to the fetus if sotorasib is used during pregnancy, or if the patient becomes pregnant whilst taking sotorasib. Sotorasib should not be used during breast-feeding. Use in pregnant and lactating women is not considered a safety concern in the RMP.

BID = twice daily; BUN = blood urea nitrogen; GLP = Good Laboratory Practice; RBC = red blood cell; RMP = Risk Management Plan; STD10 = severely toxic dose in 10% of animals

Part II: Module SIII – Clinical Trial Exposure

Table 4. Total Subject Exposure to Sotorasib in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure by Duration						
Indication/therapy	< 1 Month n (subj-yrs)	1 - < 3 Months n (subj-yrs)	3 - < 6 Months n (subj-yrs)	6 - < 9 Months n (subj-yrs)	9 - < 12 Months n (subj-yrs)	≥ 12 Months n (subj-yrs)	Total n (subj-yrs)
CRC							
Monotherapy sotorasib	6 (0.381)	46 (7.992)	43 (16.162)	13 (8.134)	5 (4.594)	11 (18.541)	124 (55.803)
Combination therapy: sotorasib exposure	29 (1.164)	81 (14.182)	107 (39.395)	61 (37.333)	25 (21.024)	23 (32.654)	326 (145.752)
Total	35 (1.544)	117 (20.112)	146 (54.486)	74 (45.218)	28 (23.828)	37 (56.367)	437 (201.555)
NSCLC							
Monotherapy sotorasib	61 (3.058)	300 (52.055)	252 (92.214)	128 (80.203)	85 (74.051)	188 (305.558)	1014 (607.138)
Combination therapy: sotorasib exposure	16 (0.646)	76 (12.961)	45 (15.789)	33 (21.027)	19 (16.181)	24 (44.438)	213 (111.042)
Total	77 (3.704)	369 (63.702)	298 (108.460)	159 (99.948)	105 (91.274)	211 (351.091)	1219 (718.179)
Other Tumor Types							
Monotherapy sotorasib	10 (0.397)	36 (6.094)	32 (12.268)	9 (6.130)	8 (6.921)	9 (17.366)	104 (49.177)
Combination therapy: sotorasib exposure	9 (0.408)	21 (3.389)	12 (4.871)	5 (3.201)	0 (0.000)	6 (9.552)	53 (21.421)
Total	19 (0.805)	57 (9.484)	43 (16.789)	13 (8.627)	8 (6.921)	15 (27.973)	155 (70.598)
Heathy Volunteers							
Monotherapy sotorasib	346 (3.732)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	346 (3.732)
Combination therapy: sotorasib exposure	112 (2.308)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	112 (2.308)
Total	458 (6.040)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	458 (6.040)
Total							
Monotherapy sotorasib	423 (7.567)	382 (66.141)	327 (120.643)	150 (94.467)	98 (85.566)	208 (341.465)	1588 (715.849)
Combination therapy: sotorasib exposure	166 (4.526)	178 (30.533)	164 (60.055)	99 (61.561)	44 (37.205)	53 (86.645)	704 (280.523)
Total	589 (12.093)	542 (93.175)	487 (179.734)	245 (153.065)	142 (122.875)	263 (435.431)	2268 (996.372)

n = number of subjects exposed to treatment; subj-yrs = total subject-years of exposure

CRC = colorectal cancer; NSCLC = non-small cell lung cancer
All subjects who received at least 1 dose of sotorasib are included in the analysis. For combination therapy, duration of exposure to sotorasib is summarized.
Monotherapy includes subjects in study: 20170543, 20190147, 20190009, 20190288, 20190436, 20190442, 20190135 (sub-protocol G). Combination therapy includes subjects in study: 20170543 (combination cohort), 20190135 and 20190172. Healthy volunteers include subjects in study: 20190315, 20190316, 20190317, 20190318, 20190319, 20190320, 20190321, 20190500, 20200199, 20200362, 20200426, 20210093, 20210088, 20220024.
Subject-years of exposure = (the last exposure date - first non-missing dose date + 1)/365.25, where last exposure date is the min ([date of last non-missing dose + 1 day - 1], end of study date, DLP date).
Subjects who received more than 1 treatment are counted in multiple treatment rows and once in the total.
For subjects who switched treatment across study periods, subject years of exposure is calculated in the periods in which the study treatment is received.
Off-treatment safety follow-up periods do not contribute to exposure calculation.
Subject-years of exposure may not add to the total due to rounding.
Study 20190135 reporting period: inception through 23 May 2023 (snapshot taken on 01 September 2023). Study 20190172 reporting period: inception through 19 June 2023 (snapshot taken on 19 July 2023). Other ongoing studies reporting period: inception through 27 May 2023 (snapshot taken on 29 May 2023, first business day after DLP).
Program: /userdata/stat/amg510/meta/rmp/analysis/rmp_202305/tables/t-rmp-exp-dur-soto.sas
Output: t14-05-001-001-rmp-exp-dur-soto.rtf (Date Generated: 01OCT23:19:56:10) Source: adam.adsl

Table 5. Total Subject Exposure to Sotorasib in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Number of Subjects			Subject-years of Exposure		
Indication/Age Group	Male	Female	Total	Male	Female	Total
CRC						
0 - 17 years	0	0	0	0.000	0.000	0.000
18 - < 65 years	153	164	317	63.912	77.667	141.580
65 - < 75 years	44	47	91	23.721	23.828	47.548
Over 75 years	14	15	29	6.001	6.426	12.427
Total	211	226	437	93.634	107.921	201.555
NSCLC						
0 - 17 years	0	0	0	0.000	0.000	0.000
18 - < 65 years	256	299	555	127.975	174.513	302.489
65 - < 75 years	272	209	481	173.413	118.612	292.025
Over 75 years	94	89	183	59.702	63.964	123.666
Total	622	597	1219	361.090	357.090	718.179
Other tumor types						
0 - 17 years	0	0	0	0.000	0.000	0.000
18 - < 65 years	54	37	91	22.366	17.503	39.869
65 - < 75 years	23	23	46	9.821	9.739	19.559
Over 75 years	9	9	18	3.294	7.877	11.170
Total	86	69	155	35.480	35.118	70.598

Footnotes and abbreviations are defined on the last page of this table.

Table 5. Total Subject Exposure to Sotorasib in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Number of Subjects			Subject-years of Exposure		
Indication/Age Group	Male	Female	Total	Male	Female	Total
Healthy volunteers						
0 - 17 years	0	0	0	0.000	0.000	0.000
18 - < 65 years	392	63	455	5.311	0.720	6.031
65 - < 75 years	3	0	3	0.008	0.000	0.008
Over 75 years	0	0	0	0.000	0.000	0.000
Total	395	63	458	5.320	0.720	6.040
Total						
0 - 17 years	0	0	0	0.000	0.000	0.000
18 - < 65 years	854	563	1417	219.565	270.404	489.969
65 - < 75 years	342	279	621	206.962	152.178	359.140
Over 75 years	117	113	230	68.997	78.267	147.264
Total	1313	955	2268	495.524	500.849	996.372

CRC = colorectal cancer; NSCLC = non-small cell lung cancer.
All subjects who received at least 1 dose of sotorasib are included in the analysis. For combination therapy, duration of exposure to sotorasib is summarized.
Monotherapy includes subjects in study: 20170543, 20190147, 20190009, 20190288, 20190436, 20190442, 20190135 (sub-protocol G). Combination therapy includes subjects in study: 20170543 (combination cohort), 20190135 and 20190172. Healthy volunteers include subjects in study: 20190315, 20190316, 20190317, 20190318, 20190319, 20190320, 20190321, 20190500, 20200199, 20200362, 20200426, 20210093, 20210088, 20220024.
Subject-years of exposure = (the last exposure date - first non-missing dose date + 1)/365.25, where last exposure date is the min ([date of last non-missing dose + 1 day - 1], end of study date, DLP date).
Subjects who received more than 1 treatment are counted in multiple treatment rows and once in the total.
For subjects who switched treatment across study periods, subject years of exposure is calculated in the periods in which the study treatment is received.
Off-treatment safety follow-up periods do not contribute to exposure calculation.
Subject-years of exposure may not add to the total due to rounding.
Age at initial enrollment was considered for rollover subjects.
Study 20190135 reporting period: inception through 23 May 2023 (snapshot taken on 01 September 2023)
Study 20190172 reporting period: inception through 19 June 2023 (snapshot taken on 19 July 2023)
Other ongoing studies reporting period: inception through 27 May 2023 (snapshot taken on 29 May 2023, first business day after DLP)
Program: /userdata/stat/amg510/meta/rmp/analysis/rmp_202305/tables/t-rmp-exp-age-sex-soto.sas

Table 6. Total Subject Exposure to Sotorasib in Clinical Trials by Dose Level and Indication
Safety Analysis Set

Indication	120mg QD n (mean exposure in days) (subj-yrs)	180mg QD n (mean exposure in days) (subj-yrs)	240mg QD n (mean exposure in days) (subj-yrs)	360mg QD n (mean exposure in days) (subj-yrs)	720mg QD n (mean exposure in days) (subj-yrs)	960mg QD n (mean exposure in days) (subj-yrs)	480mg BID n (mean exposure in days) (subj-yrs)
CRC	0 (0.0) (0.000)	3 (133.3) (1.095)	57 (134.5) (20.988)	10 (100.2) (2.743)	4 (153.8) (1.684)	352 (175.0) (168.687)	14 (165.9) (6.357)
NSCLC	13 (156.0) (5.552)	3 (284.3) (2.335)	134 (168.9) (61.982)	38 (201.9) (21.002)	8 (179.9) (3.940)	1005 (221.6) (609.791)	21 (236.1) (13.577)
Other tumor types	0 (0.0) (0.000)	0 (0.0) (0.000)	0 (0.0) (0.000)	1 (588.0) (1.610)	1 (257.0) (0.704)	154 (162.0) (68.285)	0 (0.0) (0.000)
Healthy volunteers	0 (0.0) (0.000)	0 (0.0) (0.000)	146 (4.2) (1.697)	28 (5.0) (0.383)	8 (1.0) (0.022)	276 (5.2) (3.937)	0 (0.0) (0.000)
Total	13 (156.0) (5.552)	6 (208.8) (3.431)	337 (91.8) (84.668)	77 (122.1) (25.739)	21 (110.4) (6.349)	1786 (174.0) (850.700)	35 (208.0) (19.934)

n = number of subjects exposed to treatment; subj-yrs = total subject-years of exposure

BID = twice daily; CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once daily.

All subjects who received at least 1 dose of sotorasib are included in the analysis. For combination therapy, duration of exposure to sotorasib is summarized. Monotherapy includes subjects in study: 20170543, 20190147, 20190009, 20190288, 20190436, 20190442, 20190135 (sub-protocol G). Combination therapy includes subjects in study: 20170543 (combination cohort), 20190135 and 20190172. Healthy volunteers include subjects in study: 20190315, 20190316, 20190317, 20190318, 20190319, 20190320, 20190321, 20190500, 20200199, 20200362, 20200426, 20210093, 20210088, 20220024. Subject-years of exposure = (the last exposure date - first non-missing dose date + 1)/365.25, where last exposure date is the min ([date of last non-missing dose + 1 day – 1], end of study date, DLP date). Subjects who received more than 1 treatment are counted in multiple treatment rows and once in the total. For subjects who switched treatment across study periods, subject years of exposure is calculated in the periods in which the study treatment is received. Off-treatment safety follow-up periods do not contribute to exposure calculation. Subject-years of exposure may not add to the total due to rounding.

Study 20190135 reporting period: inception through 23 May 2023 (snapshot taken on 01 September 2023). Study 20190172 reporting period: inception through 19 June 2023 (snapshot taken on 19 July 2023). Other ongoing studies reporting period: inception through 27 May 2023 (snapshot taken on 29 May 2023, first business day after DLP)

Program: /userdata/stat/amg510/meta/rmp/analysis/rmp_202305/tables/t-rmp-exp-dose-soto.sas
Output: t14-05-003-001-rmp-exp-dose-soto.rtf (Date Generated: 18SEP23:21:11:52) Source: adam.adsl

Table 7. Total Subject Exposure to Sotorasib in Clinical Trials by Race Group
Safety Analysis Set

Indication/therapy	White n (subj-yrs)	Black or African American n (subj-yrs)	American Indian or Alaska Native n (subj-yrs)	Asian n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Multiple n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
CRC									
Monotherapy sotorasib	87 (40.726)	2 (0.843)	0 (0.000)	29 (12.693)	1 (0.235)	2 (0.394)	3 (0.912)	0 (0.000)	124 (55.803)
Combination therapy: sotorasib exposure	209 (88.104)	21 (11.296)	1 (0.263)	83 (41.243)	0 (0.000)	0 (0.000)	12 (4.846)	0 (0.000)	326 (145.752)
Total	287 (128.830)	23 (12.140)	1 (0.263)	108 (53.936)	1 (0.235)	2 (0.394)	15 (5.758)	0 (0.000)	437 (201.555)
NSCLC									
Monotherapy sotorasib	846 (506.018)	16 (10.094)	0 (0.000)	127 (77.927)	0 (0.000)	1 (0.307)	23 (12.238)	1 (0.553)	1014 (607.138)
Combination therapy: sotorasib exposure	183 (97.054)	17 (10.612)	2 (0.263)	6 (2.048)	0 (0.000)	0 (0.000)	5 (1.065)	0 (0.000)	213 (111.042)
Total	1022 (603.072)	32 (20.706)	2 (0.263)	133 (79.975)	0 (0.000)	1 (0.307)	28 (13.303)	1 (0.553)	1219 (718.179)
Other tumor types									
Monotherapy sotorasib	66 (25.525)	4 (0.914)	0 (0.000)	30 (20.496)	0 (0.000)	0 (0.000)	4 (2.242)	0 (0.000)	104 (49.177)
Combination therapy: sotorasib exposure	34 (14.965)	7 (2.475)	0 (0.000)	10 (3.170)	0 (0.000)	0 (0.000)	2 (0.810)	0 (0.000)	53 (21.421)
Total	100 (40.490)	11 (3.389)	0 (0.000)	39 (23.666)	0 (0.000)	0 (0.000)	5 (3.053)	0 (0.000)	155 (70.598)

Footnotes and abbreviations are defined on the last page of this table.

Table 7. Total Subject Exposure to Sotorasib in Clinical Trials by Race Group
Safety Analysis Set

Indication/therapy	White n (subj-yrs)	Black or African American n (subj-yrs)	American Indian or Alaska Native n (subj-yrs)	Asian n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Multiple n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Healthy volunteers									
Monotherapy sotorasib	205 (2.188)	128 (1.402)	2 (0.022)	8 (0.088)	0 (0.000)	3 (0.033)	0 (0.000)	0 (0.000)	346 (3.732)
Combination therapy: sotorasib exposure	55 (0.934)	51 (1.227)	0 (0.000)	4 (0.093)	0 (0.000)	2 (0.055)	0 (0.000)	0 (0.000)	112 (2.308)
Total	260 (3.121)	179 (2.628)	2 (0.022)	12 (0.181)	0 (0.000)	5 (0.088)	0 (0.000)	0 (0.000)	458 (6.040)
Total									
Monotherapy sotorasib	1204 (574.456)	150 (13.254)	2 (0.022)	194 (111.203)	1 (0.235)	6 (0.734)	30 (15.392)	1 (0.553)	1588 (715.849)
Combination therapy: sotorasib exposure	481 (201.057)	96 (25.610)	3 (0.526)	103 (46.554)	0 (0.000)	2 (0.055)	19 (6.721)	0 (0.000)	704 (280.523)
Total	1669 (775.513)	244 (38.864)	5 (0.548)	292 (157.758)	1 (0.235)	8 (0.789)	48 (22.114)	1 (0.553)	2268 (996.372)

n = number of subjects exposed to treatment; subj-yrs = total subject-years of exposure
CRC = colorectal cancer; NSCLC = non-small cell lung cancer
All subjects who received at least 1 dose of sotorasib are included in the analysis. For combination therapy, duration of exposure to sotorasib is summarized. Monotherapy includes subjects in study: 20170543, 20190147, 20190009, 20190288, 20190436, 20190442, 20190135 (sub-protocol G). Combination therapy includes subjects in study: 20170543 (combination cohort), 20190135 and 20190172. Healthy volunteers include subjects in study: 20190315, 20190316, 20190317, 20190318, 20190319, 20190320, 20190321, 20190500, 20200199, 20200362, 20200426, 20210093, 20210088, 20220024. Subject-years of exposure = (the last exposure date - first non-missing dose date + 1)/365.25, where last exposure date is the min ([date of last non-missing dose + 1 day – 1], end of study date, DLP date). Subjects who received more than 1 treatment are counted in multiple treatment rows and once in the total. For subjects who switched treatment across study periods, subject years of exposure is calculated in the periods in which the study treatment is received. Off-treatment safety follow-up periods do not contribute to exposure calculation. Subject-years of exposure may not add to the total due to rounding.
Study 20190135 reporting period: inception through 23 May 2023 (snapshot taken on 01 September 2023). Study 20190172 reporting period: inception through 19 June 2023 (snapshot taken on 19 July 2023). Other ongoing studies reporting period: inception through 27 May 2023 (snapshot taken on 29 May 2023, first business day after DLP).
Program: /userdata/stat/amg510/meta/rmp/analysis/rmp_202305/tables/t-rmp-exp-race-soto.sas
Output: t14-05-004-001-rmp-exp-race-soto.rtf (Date Generated: 01OCT23:19:56:10) Source: adam.adsl

Table 8. Cumulative Subject Exposure to Sotorasib From All Clinical Trials by Special Populations

Special Population	Number of Subjects	Subject-years of Exposure
Hepatic impairment	13	0.036
Total	13	0.036

All subjects who received at least 1 dose of Sotorasib are included in the analysis. For combination therapy, duration of exposure to sotorasib is summarized. Special hepatic impairment population includes patients from Sotorasib studies (moderate and severe hepatic impairment arms): 20200362. Subject-years of exposure = (the last exposure date - first non-missing dose date + 1)/365.25, where last exposure date is the min ([date of last non-missing dose + <dosing frequency> days – 1], end of study date, DLP date). Off-treatment safety follow-up periods do not contribute to exposure calculation. Subject-years of exposure may not add to the total due to rounding.

Reporting period: inception through 27 May 2023 (snapshot taken on 29 May 2023, first business day after DLP).

Program: /userdata/stat/amg510/safety/dsur/analysis/202305/tables/t-exp-special-pop.sas

Output: t-12-exp-special-pop.rtf (Date Generated: 09JUN23:05:06:06) Source: adam.dsur_exp

Part II: Module SIV – Populations Not Studied in Clinical Trials

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

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subject is pregnant or breastfeeding, or planning to become pregnant.	Adequate and well-controlled studies with sotorasib have not been conducted in pregnant women due to the potential risk to the fetus. It is not known if sotorasib or its metabolites are excreted in human milk	No	Non-small cell lung cancer (NSCLC) with *KRAS p.G12C* is mostly a disease of the elderly and it is anticipated to have a low number of female patients of child-bearing potential. The Summary of Product Characteristics (SmPC) states that patients must be informed of the potential hazards to the fetus if sotorasib is used during pregnancy, or if the patient becomes pregnant while taking sotorasib. Sotorasib is not recommended during pregnancy and in women of childbearing potential not using contraception and sotorasib should not be used during breast-feeding.
Hypersensitivity to the active substance or to any of the excipients	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing hypersensitivity to the product.	No	Sotorasib is contraindicated in patients with a known hypersensitivity to the active ingredient or to any of the excipients.
Active infection requiring intravenous (IV) antibiotics within 1 week of study enrollment (day 1)	To ensure that the evaluation for the safety profile in clinical studies was not affected by underlying infection.	No	Data do not suggest that sotorasib affects underlying infection.

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Abbreviations are defined on the last page of this table

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
History or presence of hematological malignancies unless curatively treated with no evidence of disease ≥ 2 years	Due to competing risks of death due to other active cancer the treatment effect of sotorasib in this setting would be confounded. This patient population was excluded from clinical studies to enable clearer interpretation of data.	No	The coexistence of another active malignancy is unlikely to predict adverse outcome with sotorasib. Limited clinical data are available in this population. The safety profile is not expected to differ in this population.
Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Association > class II), unstable angina, or cardiac arrhythmia requiring medication	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing cardiac conditions.	No	No effect of sotorasib on cardiac function is known or suspected. The safety and efficacy of sotorasib is not expected to differ between subjects with or without cardiac disease.
Active brain metastases from non-brain tumors	Due to the poor outcome and short survival of subjects with active (untreated) brain metastases, the efficacy and safety of sotorasib could not be accurately evaluated in the pivotal phase 2 portion of the single cohort study (Study 20170543). Furthermore, the appropriate therapy for untreated brain metastases is brain-directed therapy. Once the brain is treated, subjects were eligible to be enrolled in this pivotal study.	No	No effect of sotorasib on brain tissue is known or suspected. The safety profile is not expected to differ in this population.

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Abbreviations are defined on the last page of this table.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2	Due to the poor outcome and short survival of subjects with ECOG performance ≥ 2, the efficacy and safety of sotorasib may not be accurately evaluated in the pivotal phase 2 part of the single cohort study (Study 20170543).	No	The mechanism of action of sotorasib does not suggest that subjects with ECOG performance of ≥ 2 would have any specific safety issues related to the drug. Subjects with an ECOG performance of 2 were excluded from the pivotal phase 2 part of Study 20170543, but are eligible in some other sotorasib clinical studies. In expanded access protocols 20190436 and 20190442, the safety profile was similar in patients with baseline ECOG performance status of 2 and those with baseline ECOG performance status of 0/1.
Moderate or severe renal impairment	Subjects with moderate or severe renal impairment were excluded to ensure that the interpretation of safety profile in clinical studies was not affected by pre-existing renal dysfunction.	No	Sotorasib is primarily metabolized by the liver, with minimal renal elimination; therefore, the safety profile is not expected to differ in this patient population. Preliminary data do not suggest a risk of renal toxicity with sotorasib use. There is no evidence to suggest that the pharmacokinetics (PK) of sotorasib are affected by renal function impairment.

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Abbreviations are defined on the last page of this table.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Moderate or severe hepatic impairment	Subjects with moderate or severe hepatic impairment were excluded to ensure that the interpretation of safety profile in clinical studies was not affected by pre-existing hepatic dysfunction.	Yes	Completed Study 20200362 evaluated the PK of sotorasib in healthy subjects with normal hepatic function and subjects with moderate and severe hepatic impairment. Results demonstrated that single doses of sotorasib were safe and well tolerated when administered to subjects with moderate or severe hepatic impairment. There are no data on the clinical safety and efficacy of multiple doses of sotorasib when administered to patients with moderate and severe hepatic impairment (Child-Pugh B and C) and no dose recommendation can be made. Sotorasib is not recommended for use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. Use in patients with moderate and severe hepatic impairment is included as an important potential risk (Table 14).

ECOG = Eastern Cooperative Oncology Group; IV = intravenous; *KRAS pG12C* = KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; SmPC = Summary of Product Characteristics.

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

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or those caused by prolonged or cumulative exposure.

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

Table 10. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with hepatic impairment	There were 13 subjects (0.036 subject-years) with hepatic impairment in the clinical development program (Table 8).
Patients with renal impairment	Not included in the clinical development program
Patients with cardiovascular impairment	Not included in the clinical development program
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Table 7 provides the race of subjects included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Part II: Module SV – Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, tablets, vials, or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of patient-time and patient-count (when feasible) using region- and product- specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

The cumulative number of patient-years exposed to sotorasib by region is shown in Table 11 below.

SV.1.2 Exposure

Table 11. Estimated Number of Patient-years of Exposure to Sotorasib, by Region in the Postmarketing Setting

Cumulative[a] Patient-years of Exposure					
AU	CA	EUR	US	Other	Total
22	148	2961	3723	652	7505

AU = Australia; CA = Canada; EUR = Europe (European Union, European Economic Area, United Kingdom, and Switzerland); Other = Countries, not otherwise specified above, where Amgen is the Marketing Authorization Holder; US = United States.
[a] Cumulatively through 27 November 2023.

Part II: Module SVI – Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

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

Table 12. Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Sotorasib will be prescribed by oncologists who know how to monitor, identify, and manage hepatotoxicity in this patient population. Routine risk minimization activities (ie, risk communication through product labeling, or packaging) are considered adequate to address this risk associated with the use of sotorasib. Therefore, hepatotoxicity is a known risk that requires no further characterization and is followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the Product Information will be familiar to prescribers (eg, actions being part of standard clinical practice in each European Union Member state where the product is authorized)	Hepatotoxicity

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

Table 13. List of Safety Concerns in the Initial RMP Submission

Important identified risks	None
Important potential risks	None
Missing information	Use in patients with hepatic impairment

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

Not applicable, as there are no new safety concerns or reclassification of safety concerns.

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

Table 14. Important Potential Risk: Use in Patients With Moderate and Severe Hepatic Impairment

Potential mechanisms	Sotorasib is primarily metabolized by the liver and can cause hepatotoxicity. This hepatotoxicity is primarily characterized by abnormalities in liver function tests including transient elevations of serum transaminases (ALT and AST). Due to this known risk and the lack of data on treatment of subjects with moderate and severe hepatic impairment, use in these populations is not recommended. Therefore, there is a potential risk for subscribers to possibly treat these patients with sotorasib.
Evidence source(s) and strength of evidence	This potential risk was identified based on the lack of data for subjects with moderate and severe hepatic impairment in the sotorasib hepatic impairment Study 20200362.
Characterization of the risk	
Frequency	The safety of sotorasib was evaluated in patients with *KRAS G12C*-mutated solid tumors who received 960 mg orally once daily as monotherapy. Drug induced liver injury has been reported in clinical trials (1.4%). Elevations of ALT occurred in 13.0% of subjects and elevations of AST in 13.0% of subjects. Given this liver risk, there is a possibility that the rate of elevated transaminases in patients with moderate and severe liver injury at baseline may be higher.
Severity	The most common severe (grade ≥ 3) adverse reactions were increased ALT (6.0%) and increased AST (5.0%). There were no cases of acute liver failure or fatal liver disease in sotorasib clinical studies.
Reversibility	Transaminases elevations (ALT and AST) were transient and improved or resolved with dose modification or permanent discontinuation.
Long-term outcomes	Long-term outcome data are not available.
Impact on quality of life	Impact on quality of life would depend on the severity and nature of the symptoms.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Potential Risk: Use in Patients With Moderate and Severe Hepatic Impairment

Risk groups or risk factors	Risk factors for use in patients with moderate and severe hepatic impairment include: • Off-label use (ie, patients with moderate and sever hepatic impairment being treated with sotorasib in spite of label recommendations) • Laboratory errors (ie, failure to recognize patients with moderate and severe hepatic impairment due to laboratory error prior to initiating sotorasib) • Failure to acquire a comprehensive hepatic medical history (ie, failure to identify patients who may already have moderate and severe hepatic impairment prior to initiating sotorasib)
Preventability	Administration of sotorasib in patients with moderate and severe hepatic impairment is not recommended. Patients should be monitored for liver function (ALT, AST, and total bilirubin) prior to the start of sotorasib, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop transaminase and/or bilirubin elevations. Treatment should be stopped if necessary. In addition, patients should be advised to inform their doctor, pharmacist, or nurse if they have a history of liver problems.
Impact on the risk-benefit balance of the product	The risk of use in patients with moderate and severe hepatic impairment has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	LUMYKRAS will be prescribed by oncologists who know how to monitor, identify, and manage hepatotoxicity in this patient population. LUMYKRAS is indicated in a specific and limited population. The public health impact is expected to be low.

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; KRAS p.G12C = KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 15. Summary of Safety Concerns

Important identified risks	• None
Important potential risks	• Use in patients with moderate and severe hepatic impairment
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

There are no further routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

III.2 Additional Pharmacovigilance Activities

Routine pharmacovigilance activities are considered sufficient for sotorasib. Therefore, no additional pharmacovigilance activities are proposed.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned sotorasib category 1 to 3 studies.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table 16. (Table Part IV.1) Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Study 20190341 A Phase 3 study of front-line platinum doublet therapy with sotorasib versus pembrolizumab in PD-L1 negative *KRAS p.G12C* positive advanced/metastatic NSCLC (CodeBreaK 202) Ongoing	Primary Objectives • To compare PFS in subjects who receive sotorasib with platinum doublet chemotherapy versus subjects who receive pembrolizumab with platinum doublet chemotherapy. Key Secondary Objectives • To compare ORR in subjects who receive sotorasib with platinum doublet chemotherapy versus subjects who receive pembrolizumab with platinum doublet chemotherapy. • To compare OS in subjects who receive sotorasib with platinum doublet chemotherapy versus subjects who receive pembrolizumab with platinum doublet chemotherapy.	Preliminary efficacy	CSR for primary analysis Final analysis CSR	Q2 2026 Q2 2028

CSR = clinical study report; *KRAS p.G12C* = KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Q2 = quarter 2

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

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 17. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Use in Patients With Moderate and Severe Hepatic Impairment	Routine risk communication: • SmPC Sections 4.2, 4.4, 4.8, and 5.2 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance that sotorasib is not recommended for use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment is provided in Section 4.2 of the SmPC. • Recommendation to modify the dose or permanently discontinue sotorasib and to consider treatment with corticosteroids based on severity of the laboratory abnormalities is provided in Sections 4.2 and 4.4 of SmPC. • Recommendation to monitor patients for liver function (ALT, AST, and total bilirubin) prior to the start of sotorasib, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients with recent immunotherapy and in patients with serious hepatotoxicity events is included in SmPC Section 4.4. Other routine risk minimization measures beyond the PI: • None

V.2 Additional Risk Minimization Measures

Not applicable.

V.3 Summary of Risk Minimization Measures

Table 18. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Use in Patients With Moderate and Severe Hepatic Impairment	Routine risk minimization measures: • Guidance that sotorasib is not recommended for use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment is provided in Section 4.2 of the SmPC. • Recommendation to modify the dose or permanently discontinue sotorasib and to consider treatment with corticosteroids based on severity of the laboratory abnormalities is provided in Sections 4.2 and 4.4 of SmPC. • Recommendation to monitor patients for liver function (ALT, AST, and total bilirubin) prior to the start of sotorasib, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients with recent immunotherapy and in patients with serious hepatotoxicity is included in SmPC Section 4.4. • SmPC Sections 4.8 and 5.2 • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the Risk Management Plan for sotorasib is presented below.

Summary of Risk Management Plan for Lumykras® (Sotorasib)

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

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

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

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

I. The medicine and what it is used for

Lumykras is authorized as monotherapy for the treatment of adult patients with previously treated Kirsten rat sarcoma viral oncogene homolog *(KRAS) G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) (see SmPC for the full indication). It contains sotorasib as the active substance and it is given orally.

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

II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimize 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 authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed 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 Lumykras is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Lumykras are risks that need special risk management activities to further investigate or minimize 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 Lumykras. 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	• Use in patients with moderate and severe hepatic impairment
Missing information	• None

II.B. Summary of Important Risks

Important Potential risk: Use in Patients With Moderate and Severe Hepatic Impairment	
Evidence for linking the risk to the medicine	This risk was identified based on the lack of data for subjects with moderate and severe hepatic impairment in the sotorasib hepatic impairment Study 20200362.
Risk factors and risk groups	Risk factors for use: Use in patients with moderate and severe hepatic impairment include: • Off-label use (ie, patients with moderate and severe hepatic impairment being treated with sotorasib in spite of label recommendations) • Laboratory errors (ie, failure to recognize patients with moderate and severe hepatic impairment due to laboratory error prior to initiating sotorasib) Failure to acquire a comprehensive hepatic medical history (ie, failure to identify patients who may already have moderate and severe hepatic impairment prior to initiating sotorasib)
Risk minimization measures	Routine risk minimization measures: • Guidance that sotorasib is not recommended for use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment is provided in Section 4.2 of the SmPC. • Recommendation to modify the dose or permanently discontinue sotorasib and to consider treatment with corticosteroids based on severity of the laboratory abnormalities is provided in Sections 4.2 and 4.4 of SmPC. • Recommendation to monitor patients for liver function (ALT, AST, and total bilirubin) prior to the start of sotorasib, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients with recent immunotherapy and in patients with serious hepatotoxicity is included in SmPC Section 4.4. • SmPC Sections 4.8 and 5.2 • PL Sections 2 and 4 Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study Short Name	Purpose of the Study
Study 20190341 A Phase 3 study of front-line platinum doublet therapy with sotorasib versus pembrolizumab in PD-L1 negative *KRAS p.G12C* positive advanced/metastatic NSCLC (CodeBreaK 202)	Primary Objectives: • To compare progression-free survival (PFS) in subjects who receive sotorasib with platinum doublet chemotherapy versus subjects who receive pembrolizumab with platinum doublet chemotherapy. Key Secondary Objectives: • To compare the objective response rate (ORR) in subjects who receive sotorasib with platinum doublet chemotherapy versus subjects who receive pembrolizumab with platinum doublet chemotherapy. • To compare overall survival (OS) in subjects who receive sotorasib with platinum doublet chemotherapy versus subjects who receive pembrolizumab with platinum doublet chemotherapy.

II.C.2. Other Studies in Postauthorization Development Plan

Not applicable.

PART VII: ANNEXES

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

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Annex 8. Summary of Changes to the Risk Management Plan Over Time

Table 20. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
0.1	Date of RMP: 04 December 2020 Procedure: EMEA/H/C/005522/0000	Not applicable
0.2	Date of RMP: 25 June 2021 Submitted Within Procedure: EMEA/H/C/005522/0000	**Safety Concerns** No changes **Pharmacovigilance Plan** Updated the milestone date for Study 20200362 **Postauthorization Efficacy Plan** No change **Risk Minimization Measures** No change **Annexes** • Annex 2 (Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program): Updated the milestone date for Study 20200362 • Annex 3 (Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan): Added the protocol for Study 20200362 • Annex 5 (Protocols for Proposed and Ongoing Studies in RMP Part IV): Added the updated protocol for Study 20190009 **Other changes** • Updated the relevance to human usage part of the key findings from nonclinical studies • Added a brief summary of the clinical trial program in relation to the clinical trial exposure data included in the RMP

Table 20. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
0.3	Date of RMP: 28 September 2021 Approval Date: 11 November 2021 Submitted Within Procedure: EMEA/H/C/005522/0000	**Safety Concerns** No changes **Pharmacovigilance Plan** No changes **Postauthorization Efficacy Plan** Updated the milestone due date for Study 20190009 Clinical Study Report primary analysis **Risk Minimization Measures** Added reference to the Package Leaflet (PL) to Section V.1 (Routine Risk Minimization Measures) and Section V.3 (Summary of Risk Minimization Measures) for the safety concern of 'Use in patients with hepatic impairment'. **Annexes** No change
1.0	Date of RMP: 15 November 2022 Submitted Within Procedure: EMEA/H/C/005522/II/0007	**Safety Concerns** The following safety concern was removed as missing information: • Use in patients with hepatic impairment **Pharmacovigilance Plan** The following additional pharmacovigilance activity was removed as study was completed: • Study 20200362 **Postauthorization Efficacy Plan** No change **Risk Minimization Measures** The following additional risk minimization measure was removed as study was completed: • Study 20200362 **Annexes** • Annex 2: Removed Category 3 PASS Study 20200362 from the tabulated summary of planned and ongoing studies in the pharmacovigilance study program and added it to the tabulation of completed studies in the pharmacovigilance study program • Annex 5: Updated protocol amendment for Study 20190009 added

Table 20. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
1.1	Date of RMP: 07 April 2023 Submitted Within Procedure: EMEA/H/C/005522/II/0007	**Safety Concerns** No change **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** No change **Risk Minimization Measures** No change **Annexes** No change **Other Changes** Reinserted table 'Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP'
1.2	Date of RMP: 24 August 2023 Submitted Within Procedure: EMEA/H/C/005522/II/0007	**Safety Concerns** No change **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** No change **Risk Minimization Measures** No change **Annexes** No change **Other Changes** In Section SVII.1.2, inserted table 'List of Safety Concerns in the Initial RMP Submission'

Table 20. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
1.3	Date of RMP: 07 December 2023 Approval Date: 11 January 2024 Submitted Within Procedure: EMEA/H/C/005522/II/0007	**Safety Concerns** The missing information 'use in patients with hepatic impairment' was renamed and reclassified as the following important potential risk: • Use in patients with moderate and severe hepatic impairment **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** No change **Risk Minimization Measures** Updated to include routine risk minimization measures for the important potential risk of use in patients with moderate and severe hepatic impairment **Annexes** No change **Other Changes** Removed confidentiality statement
2.0	Date of RMP: 03 February 2023 Submitted Within Procedure: EMEA/H/C/005522/II/0010/G	**Safety Concerns** No change **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Removed the following Specific Obligation PAES study: • Study 20190009 **Risk Minimization Measures** No change **Annexes** • Annex 5: Removed the Specific Obligation Study 20190009 **Other Changes** Updated recommended dose

Table 20. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
3.0	Date of RMP: 15 May 2024 Approval Date: To be determined Submitted Within Procedure: EMEA/H/C/005522/II/0010/G	**Safety Concerns** No change **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Added the following new Specific Obligation PAES study: • Study 20190341 **Risk Minimization Measures** • Updated routine risk minimization measures for the important potential risk of "Use in Patients With Moderate and Severe Hepatic Impairment" **Annexes** • Annex 5: o Added the new Specific Obligation Study 20190341 **Other Changes** • Updated to include the 240 mg tablet in the Product(s) Overview. • Updated the Epidemiology of the Indication(s) and Target Population(s) • Updated clinical trial exposure data • Updated postauthorization exposure data • Consolidated Version 1.3 and Version 2.0

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