EU Risk Management Plan for Aumseqa (aumolertinib)

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

List of abbreviations

AE	Adverse event
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate amino transferase
ATP	Adenosine triphosphate
CI	Confidence interval
CLcr	Creatinine clearance
C_{max}	Maximum concentration
CPK	Creatine phosphokinase
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P_{450} 3A4
DILI	Drug-induced liver injury
E-R	Exposure-response
EC	European Commission
ECG	Electrocardiogram
ECIS	European Cancer Information System
ECOG PS	Eastern Cooperative Oncology Group Performance Status Scale
EGFR	Epidermal growth factor receptor
EM	Erythema multiforme
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
Exon19del	EGFR exon 19 deletion
FOB	Functional observation battery
GB	Great Britain
GGT	Gamma glutamyl transferase
HEK	Human embryonic kidney
HER	Human estrogen receptor
hERG	Human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HR	Heart rate
L858R	Presence of a mutation in exon 21 of the EGFR gene, involving the substitution of leucine (L) with a arginine (R) at position 858
IC_{50}	Half-maximal inhibitory concentration
ILAP	Innovative Licensing and Access Pathway
ILD	Interstitial lung disease
LVEF	Left ventricular ejection fraction
MAA	Marketing authorization application
MC	Methylcellulose

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MTD	Maximum tolerated dose
N	Number of patients/subjects
NCI	National Cancer Institute
NICE	National Institute for Clinical Excellence
NMPA	National Medical Products Administration
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
PBPK	Physiologically based pharmacokinetics
PE	Pulmonary embolism
PI3K	Phosphoinositide 3-kinase
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PL	Package leaflet
PopPK	Population pharmacokinetic
PSUR	Periodic safety update report
QD	Quaque die, once daily
QPPV	Qualified person for pharmacovigilance
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fridericia
RMP	Risk management plan
SAE	Serious adverse event
SCAR	Severe Cutaneous Adverse Reactions
SCLC	Small cell lung cancer
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	System organ class
T790M	Presence of a mutation in exon 20 of the EGFR gene, involving the substitution of threonine (T) with a methionine (M) at position 790
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
UK	United Kingdom
ULN	Upper limit of normal
VTE	Venous thromboembolism
WBC	White blood cells

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Part I: Product(s) Overview

Table 1 - Product(s) Overview

Active substance(s) **(INN or common name)**	Aumolertinib
Pharmacotherapeutic group(s) (ATC Code)	L01EB
Marketing Authorization Applicant	SFL Pharmaceuticals Deutschland GmbH Marie-Curie-Strasse 8 79539 Lörrach Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Aumseqa
Marketing authorization procedure	Centralized
Brief description of the product	Small molecule Tyrosine kinase inhibitor
	Aumolertinib is a novel, third-generation, irreversible, small-molecule tyrosine kinase inhibitor (TKI). It has potent inhibitory activity against epidermal growth factor receptors (EGFRs) with the sensitising mutations exon19del and L858R (EGFR exon19del and EGFR L858R, respectively) and with the TKI resistance mutation T790M (EGFR T790M).
	The active substance is N-(5-((4-(1-cyclopropyl-1H-indol-3-yl) pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide methanesulfonate
Hyperlink to the Product Information	Aumseqa Product Information (Module 1.3.1)
Indication(s) in the EEA	Current: Not applicable
	Proposed: Aumolertinib as monotherapy is indicated for • the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. • the treatment of adult patients with advanced EGFR T790M mutation-positive NSCLC.

Dosage in the EEA	Current: Not applicable
	Proposed: The recommended dose of aumolertinib is 110 mg once a day taken orally.
Pharmaceutical form(s) and strengths	Current: Not applicable
	Proposed: Pharmaceutical form: film-coated tablets Strength: 55 mg of aumolertinib
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Aumolertinib was discovered, developed, and patented by Jiangsu Hansoh Pharmaceutical Group Co., Ltd. (hereafter referred to as "Hansoh"), China. SFL Pharmaceuticals acts as applicant of the marketing authorization application (MAA) ad interim for this medicinal product in the EU.

China – Aumolertinib (Ameile®) was approved for marketing by the National Medical Products Administration (NMPA) on 17 March 2020 (marketing authorization license holder is Hansoh) for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have experienced disease progression during or after treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in the past, and who tested positive for the presence of the confirmed EGFR T790M exon 20 substitution mutation (T790M mutation).

An extension of indication to the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR exon19del or exon 21 (L858R) point mutation positive was approved by the NMPA on 14 December 2021.

Two additional indications have recently been approved in China:

- adjuvant therapy after tumor resection in adult patients with stage II-IIIB non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, and whether to receive adjuvant chemotherapy decided by physician. Approved on 30 April 2025.
- treatment for adults patients with locally advanced unresectable (stage III) NSCLC whose tumor have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations and whose disease have not progressed during or after platinum-based chemoradiotherapy therapy. Approved on 04 March 2025.

UK – Aumolertinib was granted the Innovative Licensing and Access Pathway (ILAP) designation by the Medicines and Healthcare products Regulatory Agency (MHRA) on 25 August 2021 (ILAP/IP/21/55471/01). SFL Pharmaceuticals Deutschland GmbH has applied for a marketing authorization on 03 June 2022. The UK marketing authorization was approved on 03 June 2025.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

First-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations and treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC

Incidence:

According to the European Cancer Information System (ECIS) (ECIS - European Cancer Information System, 2021), lung cancer was the second-most common cancer in men and the third-most common cancer in women in the EU (including the United Kingdom [UK]) in 2020 and it is estimated that more than 310,000 adults all over Europe will be diagnosed with lung cancer in 2021 (Carioli, 2021; Lung Cancer Europe (LuCE), 2021). According to a 2018 European Commission (EC) report (European Commission (EC) - The European Commission's science and knowledge service, 2018), lung cancer incidence has been decreasing in men over the past two decades in most EU Member States; however, incidence of lung cancer in women has been increasing.

Among the different types of lung cancer, NSCLC is the most common, accounting for 80 to 90% of all lung cancers (Planchard, 2018). NSCLC includes two main histological subtypes: squamous carcinomas

and non-squamous carcinomas (which includes adenocarcinomas, large cell carcinomas, and other rare types).

The EGFR is a cell-surface receptor tyrosine kinase (TK) that can activate pathways associated with cell growth and proliferation. EGFR mutations can lead to uncontrolled cell division and are found in around 10-20% of adenocarcinomas in Caucasian populations (ESMO, 2020; ESMO Guidelines Committee, 2017; Pentheroudakis, 2020; Planchard, 2018; Postmus, 2017; Remon; Zhang, 2016). Activating EGFR mutations are much less common in squamous NSCLC (~3.3% of patients with squamous NSCLC in Europe, North America, or Australia) (Chiu, 2014; Dearden, 2013).

The most common EGFR mutations (around 90%) involve deletions in exon 19 and the L858R substitution mutation in exon 21 (TKI sensitive mutations). Treatment with first- and second-generation EGFR TKIs is a risk factor for the development of the T790M mutation. This so-called "gatekeeper" mutation causes resistance to first- and second-generation TKIs by increasing the affinity of the domain for adenosine triphosphate (ATP) (Yun, 2008). Accordingly, patients with NSCLC carrying a TKI-sensitive EGFR mutation that have developed resistance to first- and second-generation EGFR TKIs are commonly found to be positive for the T790M mutation (50-60% of cases). This mutation is only rarely found in EGFR TKI-naive disease (Planchard, 2018). Of note, the presence of a T790M mutation before exposure to an EGFR TKI is associated with a family history of NSCLC and the possibility of a germline mutation should be considered in such patients (Gazdar, 2014; Oxnard, 2012).

Considering that NSCLC accounts for 80-90% of lung cancers, adenocarcinomas account for approximately 30% of NSCLCs, and activating EGFR mutations are found in around 10-20% of adenocarcinomas, the incidence of NSCLC with activating EGFR mutations is estimated to be around 12,000 cases per year in the EU.

Prevalence:

The Global Cancer Observatory database GLOBOCAN (GLOBOCAN) reports that the estimated prevalence of all lung cancers in the EU member states ranges from 2.63 to 5.92 cases per 10,000 persons (Global Cancer Observatory (GLOBOCAN), 2020).

Considering that NSCLC accounts for 80-90% of lung cancers, adenocarcinomas account for approximately 30% of NSCLCs, and activating EGFR mutations are found in around 10-20% of adenocarcinomas, the prevalence of NSCLC with activating EGFR mutations in the EU is estimated to be around 0.15 cases per 10,000 persons.

Demographics of the population in the indication and risk factors for the disease:

Cigarette smoking is the main cause of lung cancer in general. Current active cigarette smokers have a 20-fold greater risk of developing lung cancer than people who have never smoked (Alberg, 2008; LungCancer.net, 2016). Other environmental risk factors for lung cancer include exposure to second-hand cigarette smoke; occupational exposure to asbestos, nickel, chromium, and arsenic; exposure to radiation, including radon gas in homes; and exposure to air pollution. A family history of lung cancer is also associated with an increased risk of developing lung cancer, and this may be linked to variants in genes that encode enzymes involved in carcinogen metabolism and detoxification, and in repairing DNA damage (Alberg, 2008; LungCancer.net, 2016).

In general, lung cancer is most frequently diagnosed in people aged 65-84 years and is rarely diagnosed before the age of 55. Between 2013 and 2017, 70.4% percent of new lung cancers were in people aged 65 and older (Alberg, 2008; LungCancer.net, 2016). Lung cancer rates are consistently

higher in men compared with women, and are particularly high amongst African-American men, and people of lower socioeconomic status (Alberg, 2008; LungCancer.net, 2016).

Unlike most lung cancers, EGFR-mutated NSCLC is more frequent in non-smokers (Ren, 2012; Rudin, 2009) and in females (approximately 60:40 female to male ratio) (Choi, 2019; Matsuo, 2007; Shi, 2014; Zhang, 2016). EGFR mutations are also more commonly found in East Asian patients (up to 50% incidence) versus Caucasian patients (approximately 10-20% incidence) (Duma, 2019; Reck, 2014; Zhang, 2016; Zhou, 2011). No specific risk factors for the development of EGFR-mutant NSCLC have been identified.

The main existing treatment options:

Patients with stage I, II, or III NSCLC are generally treated with curative intent using surgery, chemotherapy, radiation therapy, or a combined-modality approach. Some may also receive immunotherapy and/or targeted therapy. Systemic therapy is generally indicated for patients who present with advanced/metastatic disease and the presence or absence of a targetable mutation is an important consideration in these patients. The EGFR TKIs osimertinib, erlotinib (+/- bevacizumab or ramucirumab), gefitinib, afatinib, and dacomitinib are approved in the EU and UK for the first-line treatment of locally advanced or metastatic EGFR-mutated NSCLC, and European Society of Medical Oncology (ESMO) guidelines indicate that osimertinib, the only approved third generation EGFR TKI, is the preferred EGFR TKI in this setting. ESMO guidelines also indicate that gefitinib plus carboplatin and pemetrexed is a treatment option (although not European Medicines Agency [EMA]-approved) (ESMO, 2020; ESMO Guidelines Committee, 2017; Pentheroudakis, 2020; Planchard, 2018; Postmus, 2017; Remon).

In the second-line treatment setting, ESMO guidelines recommend a switch to osimertinib for patients with a T790M mutation who have not already received it. Osimertinib is also recommended by the National Institute for Clinical Excellence (NICE) in this setting (NICE, 2020). For patients who test negative for the T790M mutation, platinum-based doublets are recommended. Finally, a combination of atezolizumab and bevacizumab with carboplatin and paclitaxel should be considered in patients with EGFR-mutated tumors after failure of targeted therapies (ESMO, 2020; ESMO Guidelines Committee, 2017; Pentheroudakis, 2020; Planchard, 2018; Postmus, 2017; Remon).

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

Lung cancer (all types combined) is the leading cause of cancer-related deaths in the EU with over 257,000 expected deaths in 2020 (Organisation for Economic Cooperation and Development (OECD), 2020). Overall, the 5-year survival rate for NSCLC is around 25%. However, 5-year survival is only 7% for patients with metastatic NSCLC (Cancer.Net, 2021). Mean survival for patients with untreated NSCLC is around 7 months (Wao, 2013).

Patients with NSCLC with targetable mutations, including those with an activating EGFR mutation, have a better prognosis than other patients. Median overall survival in clinical trials in patients with metastatic NSCLC with an activating EGFR mutation is now in the range of 3-4 years (ESMO, 2020; ESMO Guidelines Committee, 2017; Pentheroudakis, 2020; Planchard, 2018; Postmus, 2017; Remon).

Lung cancer originates in the lungs, invades locally, and metastasizes to distant sites via the blood and lymphatics. As all other cancer types, lung cancer can be staged according to its size and spread (Cancer Research UK, 2019; Lung Cancer Europe (LuCE), 2021). The most common sites for lung cancer metastasis are the lungs, locoregional lymph nodes, the brain, bones, the liver, and the adrenal glands (Cancer Research UK, 2019).

Common presenting symptoms include cough, hemoptysis, shortness of breath and chest pain due to the local effects of lung cancer. Patients may also present with symptoms due to metastatic disease or occasionally due to paraneoplastic syndromes (Anwar, 2019; Cancer.Net, 2021; Mayo Clinic, 2021; Neal, 2019). Typical features in patients with lung cancer include (Anwar, 2019; Mayo Clinic, 2021):

- Shortness of breath due to obstruction of major airways, segmental or lobar collapse, with or without superimposed infection, often on a background of chronic obstructive pulmonary disease (COPD) or emphysema.
- Pleural effusion which may cause or exacerbate shortness of breath and necessitate fluid drainage.
- Hemoptysis due to local invasion of small or large blood vessels.
- Pain due to local invasion or spread to distant sites such as bones.
- Other metastasis-related complications which vary depending on the site of the metastasis e.g., brain metastasis may cause nausea, headaches and focal symptoms/signs such as speech or visual impairment or hemiparesis.
- Paraneoplastic syndromes which are unrelated to direct tumor invasion or metastases and are due to ectopic hormone secretion, autoimmune, or other causes. These include complex endocrine, neurological, cutaneous, hematological, and renal abnormalities. Lung cancer is the malignancy most frequently associated with paraneoplastic syndromes, but these mostly occur in patients with small cell lung cancer (SCLC).

Important co-morbidities:

Comorbidities are common in patients with lung cancer due to the age of patients at diagnosis (generally > 65 years) and association with cigarette smoking. Elderly lung cancer patients are known to have more comorbidities than the general population of the same age, and severe comorbidity is associated with increased mortality in lung cancer patients (Jørgensen, 2012). Apart from obvious smoking-related diseases (such as COPD, emphysema and cardiovascular disease), links have been reported between lung cancer and a range of other diseases with less clear causal associations, including tuberculosis, diabetes mellitus, and human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) (Leduc, 2017).

In one study of 882 patients with newly diagnosed lung cancer, conducted between 2005 and 2008 in Scotland, 87.3% of patients had at least one comorbidity (Grose, 2014). The most common comorbidities were weight loss (53%), COPD (43%), renal impairment (28%) and ischemic heart disease (27%). A composite score was calculated based on the number and severity of comorbidities. One in seven patients (15.3%) had severe comorbidity scores. Findings were similar in a study of 13,111 lung cancer patients conducted in Germany, in which around 75% of patients had at least one comorbidity (Bossert, 2021). Essential (primary) hypertension was the most frequent comorbidity (74.3%), followed by "disorders of lipoprotein metabolism and other lipidomes" (51.4%) and "other chronic obstructive pulmonary diseases" (46.6%).

In another study of 10,175 Chinese patients with lung cancer, the frequency of comorbidity was much lower: overall 32.2% of patients had at least one comorbid condition. The proportion of patients with one comorbidity was 21.7%, 8.3% had two comorbid conditions, and 2.2% had three or more comorbid conditions (Zhu, 2021). The most prevalent comorbidities were another malignancy (7.5%), hypertension (5.4%), pulmonary disease (3.7%), diabetes mellitus (2.5%), cardiovascular disease (2.4%) and liver disease (2.3%). Comorbidity was positively associated with increased risk of hospital readmission and in-hospital death in this study.

Relatively little data are available in the literature on co-morbidities in the subset of patients with EGFR-mutated NSCLC. It would be reasonable to expect that smoking-related comorbidities might be less frequent in these patients than in patients with lung cancer in general, since patients with EGFR-mutated NSCLC tend to be non-smokers and are more likely to be female. The markedly lower frequency of comorbidities in Chinese lung cancer patients versus European lung cancer patients supports this view (since EGFR-mutated NSCLC is much more frequent in Asian populations than Caucasians). However, the striking differences between the Chinese and European studies might simply reflect differences in sample size, data collection, analysis and methodology in these studies. One European study of real-world data conducted in patients with EGFR-mutated lung cancer treated with first-line osimertinib outside a clinical trial suggests that comorbidities may be just as frequent in patients with EGFR-mutated NSCLC as in other lung cancer setting. In this study of 123 patients, the Charlson Comorbidity Index was > 6 in 93.7% of patients. Since the presence of metastatic disease confers a score of 6, this indicates that almost all patients had at least one comorbidity. In another small study from Poland, 17 of 32 patients with EGFR-mutated NSCLC had comorbidities, most frequently hypertension (Knetki-Wróblewska, 2020).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

Single-dose toxicity:

Single oral doses of aumolertinib up to 900 mg/kg in rats and 200 mg/kg in dogs by gavage were not lethal. Single doses of ≥ 300 mg/kg in rats resulted in rough coat and/or decreased motor activity, and a dose of 900 mg/kg to male rats produced observations of piloerection, prostration, eyelids closed, hunched back, loose/soft stools, and/or dirty anal area. Doses ≥ 20 mg/kg in dogs resulted in emesis, soft, loose, and/or bloody stool; emesis occurred at 200 mg/kg. The maximum tolerated single dose of aumolertinib in rats and dogs was 900 mg/kg and 200 mg/kg, respectively (see Module 2.6.6).

The single dose toxicity findings indicated that gastrointestinal side effects are likely to be encountered with aumolertinib and these are known class effects of EGFR inhibitors.

Repeat-dose toxicity:

Repeated dose oral toxicity studies of up to 26 weeks and 39 weeks were performed in rats and dogs, respectively. In the 13-week rat toxicity studies, lethality occurred after repeated doses of 120 mg/kg/day aumolertinib in female rats (exposure margin to efficacious clinical dose of 3.18). In 26-week rat toxicity study, lethality was observed at dosage of 90 mg/kg in female rats (exposure margin of 3.50). The maximum tolerated dose (MTD) was 30 mg/kg with a margin of 0.51 and 1.44 in male and female rats, respectively. In 13-week dog toxicity studies, lethality occurred at 25 mg/kg (margin of 7.66). The MTD in the 39-week dog toxicity study was 10 mg/kg with a combined sex margin of 6.67. The no observed adverse effect level (NOAEL) of 3 mg/kg in dogs had a combined sex margin of 2.67 (see Module 2.6.6).

Target organs identified in the repeated dose toxicology studies were the gastrointestinal tract (including oral mucosa), skin, eyes, liver, and lungs, consistent with known class effects of EGFR inhibitors. These were all monitored in the clinical studies.

Gastrointestinal System (including mouth)

In rats, drug-related gastrointestinal toxicity was observed when aumolertinib was administered at doses ≥ 60 mg/kg and was evidenced by salivation, soft, loose, or bloody stools, and a dirty or soiled anal area. Similarly, drug-related gastrointestinal toxicity in dogs was observed at doses ≥ 4 mg/kg and was evidenced by vomiting, excessive salivation, soft stools, loose stools, blood in the stools, and stool abnormalities (gel and/or grey) and/or decreased bowel movements. During the 4-week recovery period after the drug was discontinued, the clinical symptoms of all treatment groups gradually recovered (see Module 2.6.6).

In the 13-week rat study, ulceration around the mouth was observed at the high dose of 120 mg/kg. In the 13-week dog study, two out of ten animals administered 25 mg/kg were euthanized because of aumolertinib-related ulceration in the oral mucosa and skin. Observations in the mouth included a dose related increase in the incidence and severity of inflammatory cell infiltrate in epithelium and submucosa of the tongue. Oral cavity rupture, erosion ulceration, and inflammation were observed including ulceration and erosion of the tongue at 25 mg/kg. These findings were partially reversed after the 4-week reversal phase. In the 39-week study, pink oral mucosa, flushing of inner walls of oral cavity and gums, and swelling of gums were associated with histopathological observations of ulcers and mucosal atrophy or proliferation. Flushing of the gums was also observed at 3 mg/kg. After the 4-week recovery period, 1/4 animals in the 10 mg/kg group had subacute inflammation and mucosal hyperplasia under the oral mucosa. The dog was the most sensitive species for oral findings (see Module 2.6.6).

The gastrointestinal toxicity findings indicated that gastrointestinal side effects are likely to be encountered with aumolertinib and these are known class effects of EGFR inhibitors. As predicted by these studies, gastrointestinal toxicity was observed in the aumolertinib clinical trials.

Skin

In the 26-week rat study at the high aumolertinib dose of 90 mg/kg, microscopic findings of minimal/slight folliculitis and disruption of follicular growth pattern were observed in approximately half of the animals. After a 4-week recovery period, these observations were partially recovered. In the 39-week dog study, aumolertinib-related histopathological changes in the 10 mg/kg dose group included a dose-related increase in the severity and incidence of folliculitis, dermal/subcutaneous inflammation, epidermal ulceration of the foot pad, and abscesses. Other skin-related observations (e.g., sparse hair) were seen at ≥ 60 mg/kg in rats and 4 mg/kg in dogs. After a 4-week reversal, all skin-related lesions had reversed (see Module 2.6.6).

The skin toxicity findings indicated that skin-related side effects are likely to be encountered with aumolertinib and these are known class effects of EGFR inhibitors. As predicted by these studies, skin toxicity was observed in the aumolertinib clinical trials.

Ocular

Ocular findings were present in the 13-week study in rats and in the dog studies. In the dog studies, conjunctival congestion was seen at all doses, and corneal and lens opacity, reflective media turbidity and photophobia were observed at 25 mg/kg. In the 39-week dog study, one animal in the 10 mg/kg group had opacity of the right vitreous body at the end of the study. In rats, ophthalmoscopic findings were noted at 120 mg/kg in two males (lens turbidity/lens reflective media turbidity) and one female (abnormal pupil). A second 120 mg/kg female had multiple eye lesions during treatment that were not reversible, and an irregular agglomerate in the lens was noted in a 120 mg/kg female at the recovery examination only (see Module 2.6.6).

The ocular toxicity findings indicated that ocular side effects are likely to be encountered with aumolertinib and these are known class effects of EGFR inhibitors. As predicted by these studies, ocular toxicity was observed in the aumolertinib clinical trials.

Hepatic

In the 13- and 26-week toxicity studies in rats, alanine aminotransferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBL), and/or blood urea nitrogen were elevated, and albumin, and triglycerides were decreased at a 60 mg/kg aumolertinib dose. The observed bile duct vacuolation of the liver is related to the increases in ALT, AST, ALP, TBL, and GGT. There was a dose related increase in the incidence and severity of bile duct vacuolation in the ≥ 60 mg/kg dose groups, which were partially recovered after a 4-week reversal phase. There were no hepatic findings in the dog in doses up to 10 mg/kg administered for 39 weeks (see Module 2.6.6).

The hepatotoxicity findings indicated that hepatic side effects such as abnormalities in liver enzymes are likely to be encountered with aumolertinib and these are known class effects of EGFR inhibitors. As predicted by these studies, abnormalities in liver enzymes were observed in the aumolertinib clinical trials.

Pulmonary System

The 13- and 26-week studies in rats showed that the main target organs for toxicity include the lungs. A dose related increase in the accumulation of foamy macrophages in the lung alveolar cavities was observed microscopically at aumolertinib doses ≥ 30 mg/kg. Increases in white blood cells (WBC), absolute lymphocyte and neutrophil counts were observed and are considered as related to inflammatory reactions in the lungs. All lung findings were reversed after a 4-week recovery period. There were no lung findings in the dog in doses up to 10 mg/kg administered for 39 weeks (see Module 2.6.6).

The pulmonary toxicity findings indicated that pulmonary side effects are likely to be encountered with aumolertinib and these are known class effects of EGFR inhibitors. As predicted by these studies, pulmonary toxicity was observed in the aumolertinib clinical trials.

<u>Reproductive and developmental toxicity:</u>

Fertility and early embryonic development

In a dedicated fertility study and an early embryonic development study in rats, transient salivation was noted in males and in one female at an aumolertinib dose ≥ 30 mg/kg; loose stool, soft stool, and dirty anal area occurred at 100 mg/kg. Body weight, body weight gain, and food consumption were decreased at 100 mg/kg. No statistically significant changes were noted in mating index, male fertility index, female fertility index, pregnancy index, length of estrus cycle, number of nights to cohabitation, or nights to positive mating. However, statistically significant decreases in gravid uterus weight, mean numbers of corpora lutea, implantation sites, live fetuses, and mean live fetus index, along with increases in post-implantation loss, mean number of resorptions, and resorption index occurred at 100 mg/kg. No aumolertinib-related changes were noted in sperm counts, motility, and sperm morphology examinations. The NOAEL for fertility was 100 mg/kg in males and 30 mg/kg in females. The NOAEL for early embryonic development (up to the time of implantation) was 30 mg/kg (see Module 2.6.6).

Reproductive and developmental toxicity findings are relevant to humans and appropriate information regarding fertility, pregnancy, and lactation is provided in the Summary of Product Characteristics (SmPC), Section 4.6.

Embryo-fetal development

In rats, decreases in maternal body weight, body weight gain, and food consumption were noted at 100 mg/kg aumolertinib but there were no aumolertinib-related toxic effects in embryo-fetal development or in fetal external, visceral, or skeletal development. The NOAEL for embryo-fetal development toxicity in rats was 100 mg/kg.

In rabbits, reduced food consumption, decreased body weight, reduced or no fetal output with oliguria or anuria, miscarriage, premature delivery, and fetal growth retardation due to maternal toxicity were seen at doses of 5, 15, and 30 mg/kg. At doses of 15 and 30 mg/kg, maternal death and spontaneous abortion was observed, and at 30 mg/kg premature delivery was observed. Sternum development of fetus was slightly delayed (at 5, 15, and 30 mg/kg the ossification rate of sternum decreased; at 15 and 30 mg/kg the sternum number of fetuses was slightly reduced), and the number of live fetuses at 30 mg/kg was slightly reduced. No NOAEL for embryo-fetal development was identified in this study. No teratogenicity was observed in the dose range of 5-30 mg/kg (see Module 2.6.6).

Embryo-fetal toxicity findings are relevant to humans and appropriate information regarding use during pregnancy or breast-feeding is provided in the SmPC, Section 4.6.

Genotoxicity:

The potential genotoxicity of aumolertinib was assessed in two *in vitro* studies: a bacterial reverse mutation assay in *Salmonella typhimurium (S. typhimurium)* strains TA97a, TA98, TA100, TA102, and TA1535, and an *in vitro* chromosomal aberration assay in Chinese hamster lung fibroblasts. The clastogenic potential was measured *in vivo* in a micronucleus assay in mice. Aumolertinib was negative for genotoxicity in all assays performed (see Module 2.6.6).

Aumolertinib was neither mutagenic nor clastogenic under the conditions of this assay and is therefore considered non-genotoxic for humans.

Impurity genotoxicity:

The results of Ames and chromosome aberration tests of the [redacted] impurity [redacted] of aumolertinib were negative under the conditions of the assay. The Ames test of the intermediate impurity [redacted] was negative under the conditions of the assay (see Module 2.6.6).

No genotoxicity findings relevant to humans were identified.

Carcinogenicity:

No carcinogenicity studies have been conducted with aumolertinib to date (see Module 2.6.6).

Aumolertinib was negative for genotoxicity *in vitro*.

Safety pharmacology

Safety pharmacology studies included *in vitro* and/or *in vivo* evaluations of the effects of aumolertinib on vital physiological functions, including cardiac, respiratory, and central nervous system (CNS) parameters (see Module 2.6.2/2.6.6).

Cardiovascular and respiratory system

Aumolertinib inhibited the human Ether-à-go-go-Related Gene (hERG)-mediated potassium current in human embryonic kidney (HEK) 293 cells with a half-maximal inhibitory concentration (IC_{50}) of 2.958 µM (equivalent to 1.55 µg/mL of aumolertinib freebase). The C_{max} at the clinically efficacious dose of 110 mg in the Phase 1/2 clinical trial was 352.5 ng/mL which, when adjusted for free component (99.5% bound), is 1.763 ng/mL, which provides an almost 900-fold margin relative to the hERG IC_{50}

value. The results of the hERG assay indicate minimal clinical cardiovascular risk under the conditions of this assay.

The effect of aumolertinib on the cardiovascular and respiratory functions was investigated in conscious and unconstrained beagle dogs instrumented with telemetry devices. A total of eight beagle dogs (four/sex) were dosed using a double Latin-square study design. Each animal was administered vehicle, 0.5% methylcellulose (MC), or aumolertinib at 5, 10, or 20 mg/kg via the oral route. Electrocardiogram (ECG), blood pressure, respiratory function, and body temperature data were recorded from at least 2 hours before dosing to approximately 0.5, 1, 1.5, 2, 3, 5, 8, 24, and 48 hours after dosing. Data collected at the following time points were analyzed: within 1 hour pre-dosing and 48 hours after dosing. Aumolertinib had no effect on cardiovascular functions, respiratory functions, or body temperature at doses up to 20 mg/kg in telemetered dogs (see Module 2.6.6).

No findings relevant to humans were identified. The results of the hERG assay indicate minimal clinical cardiovascular risk considering the C_{max} at the clinically efficacious dose of 110 mg aumolertinib in the Phase 1/2 clinical trial was 352.5 ng/mL. When adjusted for free component, this provides an almost 900-fold margin relative to the hERG IC_{50} value.

CNS assessment (functional observation battery) in rats

Rats (n = 5 sex/group) were administered a single oral dose of vehicle control (0.5% MC) or 10, 50, or 250 mg/kg aumolertinib. Two independent observers conducted the Functional Observation Battery (FOB) test 1 day before dosing and 6, 24, and 72 hours after administration of aumolertinib or vehicle. Diazepam (10 mg/kg) was used as a positive control and scored at 1 hour. The FOB test included: home cage observations, hand-held observations, open-field observations, sensory tests, measurements of forelimb grip strength, hindlimb landing foot splay, and body temperature. Under the conditions of this study, aumolertinib had no significant effects on the CNS functions in rats administered single oral doses up to 250 mg/kg (see Module 2.6.6).

No findings relevant to humans were identified. Aumolertinib is considered to have low/no potential for CNS toxicity in humans.

Other toxicity-related information or data

Phototoxicity

The potential phototoxicity of aumolertinib was evaluated *in vitro* by comparing the inhibitory effect of aumolertinib on the neutral red uptake by BALB/c 3T3 cells under the presence or absence of UV light. The results indicate that aumolertinib is not phototoxic under the conditions of the assay (see Module 2.6.6).

No findings relevant to humans were identified. Aumolertinib is considered to have low/no potential for phototoxicity in humans.

Part II: Module SIII - Clinical trial exposure

Subjects exposure to aumolertinib in this risk management plan (RMP) (Table 2 to Table 4) is based on the results of the two pivotal trials, one Phase 1/2 clinical study (HS-10296-12-01) and one Phase 3 study in locally advanced/metastatic NSCLC subjects (HS-10296-03-01). Study HS-10296-12-01 is complete; the primary analysis of Study HS-10296-03-01 is complete but follow-up is ongoing.

In study HS-10296-12-01, in the Phase 1 dose-escalation phase, aumolertinib was administered at doses ranging from 55 to 260 mg once daily (quaque die, once daily [QD]); specifically, six subjects received 55 mg, six subjects received 110 mg, eight subjects received 220 mg, and six subjects

received 260 mg. Subjects received a single dose of treatment on Day 1 and repeated administration was initiated after a washout phase of 7 ± 2 days. In the Phase 1 dose-expansion phase, three dose levels (55, 110, and 220 mg QD) of aumolertinib were assessed; 30 subjects received 55 mg, 33 subjects received 110 mg, and 31 subjects received 220 mg. In the Phase 2 dose-extension phase, 244 subjects received 110 mg QD of aumolertinib on a continuous basis, with a defined 21-day treatment cycle until disease progression or other termination criteria were met.

In study HS-10296-03-01, aumolertinib was administered to 214 subjects as a 110 mg QD dose in 21-day treatment cycles of continuous administration until disease progression or other criteria for terminating treatment were met.

Based on the data from the HS-10296-12-01 and HS-10296-03-01 trials, the dose and duration of exposure, subjects' age group and gender, and subjects' ethnic origin are shown in Table 2 to Table 4 below.

In addition, seven clinical pharmacology studies in healthy subjects (studies EQ143-101, HS-10296-102, HS-10296-103, HS-10296-104, HS-10296-105, HS-10296-106, and HS-10296-107) have been completed but are not included in the tables below because they were single-dose studies.

Table 2 - Dose and duration of exposure

Study No.	Study phase	Aumolertinib dose	Number of subjects	Mean days of exposure
HS-10296-12-01	Phase 1 dose-escalation	55 mg	6	514.3
		110 mg	6	258.2
		220 mg	8	171.4
		260 mg	6	129.0
	Phase 1 dose-expansion	55 mg	30	430.2
		110 mg	33	455.3
		220 mg	31	524.1
	Phase 2 dose-extension	110 mg	244	436.3
HS-10296-03-01	Phase 3	110 mg	214	533.7
Total subjects exposed to aumolertinib			**578**	**470.0**

Data cutoff of study HS-10296-12-01: August 1, 2021.

Data cutoff of study HS-10296-03-01: August 6, 2021.

Table 3 - Age group and gender

Study No.	Age range (years old)	Number of subjects			Mean days of exposure		
		Male	Female	Total	Male	Female	Total
HS-10296-12-01	< 18	0	0	0	-	-	-
	18 - 65	84	144	228	400.9	443.0	427.5
	≥ 65	61	75	136	410.3	465.8	440.9
HS-10296-03-01	< 18	0	0	0	-	-	-
	18 - 65	59	96	155	512.8	587.7	559.2
	≥ 65	21	38	59	356.1	527.6	466.5
Total subjects exposed to aumolertinib	**< 18**	**0**	**0**	**0**	**-**	**-**	**-**
	18 - 65	**143**	**240**	**383**	**447.1**	**500.9**	**480.8**
	≥ 65	**82**	**113**	**195**	**396.4**	**486.6**	**448.7**

Data cutoff of study HS-10296-12-01: August 1, 2021.

Data cutoff of study HS-10296-03-01: August 6, 2021.

Table 4 - Ethnic origin

Study No.	Number of subjects				Mean days of exposure			
	Asians	**Blacks**	**Whites**	**Other**	**Asians**	**Blacks**	**Whites**	**Other**
HS-10296-12-01	358	1	4	1	436.1	90.0	166.5	546.0
HS-10296-03-01	214	0	0	0	533.7	-	-	-
Total subjects exposed to aumolertinib	**572**	**1**	**4**	**1**	**472.6**	**90.0**	**166.5**	**546.0**

Data cutoff of study HS-10296-12-01: August 1, 2021.

Data cutoff of study HS-10296-03-01: August 6, 2021.

Part II: Module SIV - Populations not studied in clinical trials

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

Exclusion criteria from the pivotal Phase 1/2 and Phase 3 studies excluded patient populations that may experience a different safety profile compared to the population included in the trials, are described below. The following exclusion criteria are not included in this list:

- Criteria intended to ensure a homogeneous population for evaluation of efficacy, e.g., previous treatment with an EGFR TKI.
- Criteria intended to avoid confounding factors for interpretation of trial data, e.g., presence of another malignancy.
- Criteria that are part of routine oncology practice when assessing a patient's suitability for treatment, e.g., ability to swallow and absorb oral medication and to comply with treatment requirements; adequate performance status; recovery from previous surgery, radiotherapy, or systemic therapy.

Criterion 1:

Treatment with medications that are strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers or sensitive substrates of CYP3A4 with a narrow therapeutic range within 7 days of the first dose of study drug.

Reason for exclusion: Concomitant CYP3A4 strong inhibitors may lead to increased exposure to aumolertinib and increase the risk of side effects. Concomitant CYP3A4 strong inducers could decrease the exposure to aumolertinib and reduce its efficacy. Therefore, patients receiving concomitant strong CYP3A4 inhibitors or inducers were excluded from clinical trials. Patients receiving sensitive CYP3A4 substrates were also excluded from the pivotal trials although non-clinical data indicate that aumolertinib does not significantly inhibit or induce CYP3A4.

Is it considered to be included as missing information? No.

Rationale: In vitro data indicated that aumolertinib is primarily metabolized by CYP3A4 and Phase 1 studies and physiologically based pharmacokinetic (PBPK) analyses confirmed that aumolertinib is a CYP3A4 substrate. Specifically, in Phase 1 studies, co-administration of aumolertinib with a CYP3A4 inhibitor significantly increased aumolertinib exposure, while co-administration with a CYP3A4 inducer significantly decreased aumolertinib exposure. Accordingly, the SmPC states that drugs which are moderate or strong CYP3A4 inhibitors should be avoided during treatment with aumolertinib. Co-administration of aumolertinib with moderate or strong CYP3A4 inducers is not recommended (SmPC

Section 4.5 [Interaction with other medicinal products and other forms of interaction]). Aumolertinib does not significantly inhibit or induce CYP3A4, therefore, there is no need to exclude patients taking sensitive substrates of CYP3A4 from treatment with aumolertinib.

Criterion 2:

Any of the following cardiac criteria:

- **Mean resting corrected QT interval (QTc) > 470 ms obtained from 3 ECGs, using the screening clinic's ECG machine and Fridericia's formula for QT interval correction (QTcF).**
- **Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG (e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval > 250 ms).**
- **Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QTc interval.**
- **Left ventricular ejection fraction (LVEF) ≤ 40%.**

Reason for exclusion: QTc prolongation is a known side effect of third generation EGFR TKIs and cases of prolonged QTc interval were observed in the clinical studies of aumolertinib. QTc prolongation is a risk factor for life-threatening cardiac arrhythmias.

Low LVEF reflects impaired cardiac contractility which may lead to cardiac failure and may be observed with treatment with therapies targeting the human estrogen receptor (HER) family of TK receptors, which includes EGFR.

Is it considered to be included as missing information? No.

Rationale: QTc prolongation and cardiac failure with the use of aumolertinib have been observed in clinical trials with aumolertinib. The protocol exclusion criteria concerning cardiac risk factors were implemented based on prior knowledge of the safety profile of third generation EGFR TKIs. QTc prolongation leading to torsade de pointes and cardiac arrest is considered an important identified risk of aumolertinib. Accordingly, the use of aumolertinib is contraindicated in subjects with congenital long QT syndrome, familial history of sudden cardiac death or polymorphic ventricular arrhythmia, and with QT/QTc interval > 500 msec (SmPC Section 4.3 [Contraindications]). Appropriate warnings and precautions related to QTc interval prolongation and cardiac failure are included in the SmPC in Section 4.4 (Special warnings and precautions for use). Dose adjustments for QTc interval prolongations and LVEF declines are included in the SmPC (Section 4.2 Table 1 [Recommended Aumseqa dose modifications due to adverse reactions]).

Criterion 3:

Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease.

Reason for exclusion: Interstitial lung disease (ILD) is a known class risk of EGFR TKIs and the risk factors for this condition are well established. Exclusion of this group of subjects was to preclude the enrolment of subjects with current or past lung disorders who may be at higher risk of developing ILD.

Is it considered to be included as missing information? No.

Rationale: ILD has been observed in clinical trials with aumolertinib and is a known class risk of EGFR TKIs. ILD is regarded an important identified risk of aumolertinib and is included in the SmPC (Section 4.4 [Special warnings and precautions for use]) together with possible signs and symptoms. Permanent aumolertinib treatment discontinuation is advised for patients with confirmed ILD in the SmPC (Section 4.2 Table 1 [Recommended Aumseqa dose modifications due to adverse reactions]).

Criterion 4:

AST/ALT > 2.5 × upper limit of normal (ULN) if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases. TBL > 1.5 × ULN if no liver metastases or > 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases.

Reason for exclusion: The exclusion of this group of patients from the pivotal clinical studies was a precautionary measure to preclude the enrolment of patients with significant hepatic impairment who may be at higher risk of side effects due to the hepatic disease itself and/or due to impaired metabolism of aumolertinib.

Is it considered to be included as missing information? No.

Rationale: There are available clinical data on the use of aumolertinib in patients with mild, moderate, and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively; Studies HS-10296-106 and EQ143-102). Based on these data, there are no safety concerns related to the use of aumolertinib in patients with hepatic impairment and no dose modification is required in the SmPC (Section 4.2 [Posology and method of administration]).

Criterion 5:

Creatinine > 1.5 × ULN concurrent with creatinine clearance (CLcr) < 50 mL/min (measured or calculated by the Cockcroft-Gault equation); confirmation of CLcr is only required when creatinine is > 1.5 × ULN.

Reason for exclusion: The exclusion of this group of patients from pivotal clinical studies was a precautionary measure to preclude the enrolment of patients with renal disorders who may be at higher risk of side effects.

Is it considered to be included as missing information? No.

Rationale: Available clinical data demonstrate that renal clearance of aumolertinib is negligible. Aumolertinib has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease; however, considering the negligible renal contribution to total clearance, a major effect on exposure is unlikely. Accordingly, the SmPC advises that no dose modification is required in patients with mild or moderate renal impairment, but that caution should be exercised when treating patients with severe or end-stage renal impairment (SmPC Section 4.2 [Posology and method of administration]).

Criterion 6:

Women who are breastfeeding or have a positive urine or serum pregnancy test at the Screening Visit.

Reason for exclusion: The exclusion of this group of patients from pivotal clinical studies was a precautionary measure to prevent the exposure of the developing embryo/fetus and of infants to aumolertinib, which may be harmful.

Is it considered to be included as missing information? No.

Rationale: Animal studies with aumolertinib indicate that aumolertinib may cause reproductive, developmental, and embryo-fetal toxicity. There are no data on the use of aumolertinib in pregnant women and it is unknown whether aumolertinib or metabolites are excreted in human milk. Accordingly, the SmPC states that breastfeeding should be discontinued during treatment with aumolertinib and for 4 weeks after completion of treatment with aumolertinib (SmPC Section 4.6 [Fertility, pregnancy and lactation]). The SmPC also states that women of childbearing potential should be advised to avoid becoming pregnant while receiving aumolertinib, that female patients should be advised to use highly effective contraception during treatment and for 4 weeks after completion of treatment with aumolertinib, and that the use of aumolertinib is not recommended during pregnancy (SmPC Section 4.6 [Fertility, pregnancy and lactation]).

Criterion 7:

History of hypersensitivity to any active or inactive ingredient of aumolertinib or to drugs with a similar chemical structure or class to aumolertinib.

Reason for exclusion: Exclusion of this group of patients was a precautionary measure to preclude the enrolment of patients who may experience severe and potentially life-threatening hypersensitivity reactions to aumolertinib.

Is it considered to be included as missing information? No.

Rationale: The SmPC states that the use of aumolertinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients (SmPC Section 4.3 [Contraindications]).

Criterion 8:

Any serious or uncontrolled eye disease that may increase the safety risk of the subject according to a physician's judgment.

Reason for exclusion: Exclusion of this group of patients was a precautionary measure since ocular toxicity is a known class effect of EGFR inhibitors and such patients may be predisposed to the ocular complications of aumolertinib.

Is it considered to be included as missing information? No.

Rationale: Adverse ocular reactions have been observed in clinical trials with aumolertinib and are known side effects of treatment with a range of TKIs, including EGFR-TKIs. Appropriate risk communication is included as Eye disorders in the SmPC (Section 4.8 [Undesirable effects – description of selected adverse reactions]).

Criterion 9:

Patients with ECOG PS (Eastern Cooperative Oncology Group Performance Status Scale) > 1.

Reason for exclusion: Exclusion of this group of patients was to ensure the inclusion of a relatively homogeneous population.

Is it considered to be included as missing information? No.

Rationale: No major deviations in the safety profile are expected in patients with PS > 1 based on the mechanism of action of aumolertinib. These patients would not be exposed to any additional risks compared to subjects included in the trials. Accordingly, there is also no reason to preclude these patients from receiving aumolertinib and experiencing the potential benefits derived from treatment.

Criterion 10:

Patients who have inadequate bone marrow reserve or organ function as demonstrated by the following laboratory test limits: Absolute neutrophil count < 1.5 × 10^9/L; platelet count < 100 × 10^9/L; and hemoglobin < 90 g/L (< 9 g/dL).

Reason for exclusion: Exclusion of this group of patients was a precautionary measure based on the available information on the safety profile of other EGFR TKIs and the preclinical data with aumolertinib at the time of the trials and/or to exclude patients that may have a too advanced disease.

Is it considered to be included as missing information? No.

Rationale: No major deviations in the safety profile are expected in patients with cytopenia based on the mechanism of action of aumolertinib. These patients would not be exposed to any additional risks compared to patients included in the trials. Accordingly, there is also no reason to preclude these patients from receiving aumolertinib and experiencing the potential benefits derived from treatment (provided that treatment is initiated and managed appropriately as with any other agents used to treat cancer).

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program for aumolertinib 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 since the life expectancy of patients with advanced NSCLC is short (< 5 years, and for many patients is < 2 years (ECIS - European Cancer Information System, 2021)).

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

Table 5 - Exposure of special populations included or not in clinical trial development program

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	In line with the study exclusion criteria, the following patients were excluded from the pivotal studies (HS-10296-12-01 and HS-10296-03-01): • with AST/ALT > 2.5 × upper limit of normal (ULN) if no demonstrable liver metastases or > 5 × ULN in the presence of liver metastases; • with total bilirubin (TBL) > 1.5 × ULN if no liver metastases or > 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases. The effect of hepatic impairment on the pharmacokinetics (PK), safety, and tolerability of aumolertinib and its primary metabolite HAS-719 were evaluated in two dedicated Phase 1 studies

	(HS-10296-106: mild and moderate hepatic impairment and healthy matched control subjects; EQ143-102: severe hepatic impairment and healthy matched control subjects).
• Patients with renal impairment	In line with study exclusion criteria, patients with creatinine > 1.5 × ULN concurrent with creatinine clearance (CLcr) < 50 mL/min (measured or calculated by the Cockcroft-Gault equation with confirmation of CLcr only required when creatinine is > 1.5 × ULN), were excluded from the clinical development program. Data from the clinical studies show that subjects with creatinine ≤ 1.5 ULN and CLcr of > 30 mL/min were included in the clinical development program.
• Patients with cardiovascular impairment	Patients with clinically significant abnormalities in cardiac rhythm or conduction (e.g., QTc > 470 ms) and patients with LVEF ≤40% were 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	The primary clinical development program included subjects of Asian (660 subjects), Caucasian (four subjects), African American (one subject), and other (one subject) origin. A PK bridging study (Study EQ143-101) found no statistically significant difference in aumolertinib exposure between subjects of Asian (Chinese) and other (non-Chinese) ethnicities including Caucasian, African American, and Hispanic subjects. An additional study to further assess the PK of aumolertinib and metabolites in European NSCLC patients (HS-10296-106) was conducted, and has shown comparable exposures between European and Chinese patients.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Pediatric population	Not included in clinical development program. A product-specific waiver for pediatric studies for the treatment of lung cancer was granted to aumolertinib by the EMA on 17 December 2021 (EMEA-003106-PIP01-21).

	A product-specific waiver for pediatric studies was granted by the MHRA to aumolertinib for the treatment of lung cancer on 17 January 2022 (MHRA-100368-PIP01-21). The waiver was granted on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified pediatric subsets.
Elderly population	Clinical development program included elderly subjects ≥ 65 years old (see Table 3) including subjects ≥ 80 years old.

Part II: Module SV - Post-authorization experience

SV.1 Post-authorization exposure

Aumolertinib was initially developed by Hansoh Pharmaceutical Group Company Ltd., in China. Aumolertinib (Ameile®) was approved for marketing by the National Medical Products Administration (NMPA) on March 17, 2020 for the treatment of adult patients with locally advanced or metastatic NSCLC who have experienced disease progression during or after treatment with EGFR TKIs in the past, and who tested positive for the presence of the confirmed EGFR T790M mutation. An extension of indication to the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR ex19del or exon 21 (L858R) replacement mutation was approved by the NMPA on December 14, 2021.

[redacted]

Two additional indications have recently been approved in China:

- adjuvant therapy after tumor resection in adult patients with stage II-IIIB non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, and whether to receive adjuvant chemotherapy decided by physician. Approved on 30 April 2025.
- treatment for adults patients with locally advanced unresectable (stage III) NSCLC whose tumor have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations and whose disease have not progressed during or after platinum-based chemoradiotherapy therapy. Approved on 04 March 2025.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Given the pharmacological class of aumolertinib and the absence of psychotropic or anabolic effects or enhancement of hemoglobin levels, the potential for drug abuse or misuse for illegal purposes is considered negligible.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

This is the first RMP submitted in the EU based on the Guidance on the Format of the RMP in the EU – in Integrated Format Rev.2 (EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2). The current list of safety concerns included in this RMP will be considered as the "initial submission" and will be locked moving forward.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Diarrhoea

Reason for not including an identified or potential risk in the list of safety concerns in the RMP: Diarrhoea is a known EGFR TKI-associated risk.

Diarrhoea is a known risk associated with EGFR TKIs. The underlying mechanisms are not completely understood but excessive chloride secretion is thought to be an important component (resulting in a secretory diarrhoea) (Harada, 2021); intestinal barrier dysfunction may also play a part (Kim, 2020).

Overall, the incidence and severity of diarrhoea with aumolertinib in subjects with advanced NSCLC was within or better than expectations for patients with advanced NSCLC treated with an EGFR TKI. The lack of treatment discontinuations, dose reductions and dose interruptions (bar one subject with colitis) indicate that this toxicity is manageable and reversible with routine measures. Hence, in relation to the severity of the indication treated, diarrhoea is considered as having a limited impact on the risk-benefit balance of aumolertinib and on public health.

Ocular toxicity

Reason for not including an identified or potential risk in the list of safety concerns in the RMP: Ocular toxicity is a known EGFR TKI-associated risk.

Adverse ocular events have been observed with a range of TKIs, including EGFR TKIs (Davis, 2016). EGFR is present in ocular and periocular tissue, including the eyelids, eyelash follicles, tear glands, conjunctiva, and cornea. EGFR-mediated processes are essential for eyelash growth, wound healing, and proliferation of corneal epithelial cells. Treatment with EGFR inhibitors can cause corneal thinning and erosion, and inhibition of EGFR on the eyelashes can cause significant growth and trichomegaly. EGFR also stimulates proliferation of the epithelial cells of the meibomian glands in the eyelids; with inhibition, the eyelids and meibomian glands can become inflamed, causing blepharitis and meibomitis (Davis, 2016).

Blurred vision, loss of vision, dry eyes and other ocular symptoms resulting from TKI treatment can negatively affect the quality of life of patients receiving EGFR TKIs. In subjects treated with aumolertinib, adverse ocular reactions were mostly Grade 1-2 in severity. In general, the risk of permanent visual loss with EGFR TKIs is low. Based on these observations, and in relation to the severity of the indication treated, ocular toxicity is considered as having a limited impact on the risk-benefit balance of aumolertinib in the intended patient population and on public health.

Cardiac failure

Reason for not including an identified or potential risk in the list of safety concerns in the RMP: cardiac failure is a known TKI-associated risk, furthermore, this risk is adequately characterized and described in the SmPC together with appropriate risk mitigation measures.

Cardiac failure is a known side effect of treatment with a range of HER-targeted agents (notably HER2-targeted agents) and TKIs (Chen, 2008). Declines in cardiac contractility and ejection fraction have been reported in third-generation EGFR TKI-treated patients (Tagrisso SmPC). TKI-targeted pathways are involved in the regulation of the survival of cardiomyocytes and treatment with EGFR TKIs may lead to on-target cardiotoxicity by interfering with survival-promoting functions of the EGFR pathway. Agents targeting the HER family of receptors, particularly HER2, are well known to cause LVEF declines and cardiac failure. Since HER family members, including EGFR (HER1), can homo- and heterodimerize resulting in downstream pathway activation that can be blocked by TKIs, there is a potential risk of cardiac failure with EGFR TKIs (Chen, 2008; Copeland-Halperin, 2019).

The number of subjects treated with aumolertinib who developed cardiac failure or had a clinically significant decline in LVEF during the pivotal studies was low. Five reports of cardiac failure have been received since aumolertinib was marketed in China. Overall, these observations do not suggest that aumolertinib impairs cardiac contractility or leads to cardiac failure and the risk of developing cardiac failure due to aumolertinib is considered low. Based on these observations and considering the severity of the indication treated and the risk mitigation measures included in the SmPC, the risk of cardiac failure is considered as having a limited impact on the risk-benefit balance of aumolertinib in the intended patient population and on public health.

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

Important Identified Risk 1: QTc prolongation leading to torsade de pointes and cardiac arrest

QTc prolongation is a known side effect of treatment with EGFR TKIs (Shah, 2019), including a third-generation EGFR TKI (Tagrisso SmPC). The precise mechanisms by which TKIs prolong the QTc are unknown but several direct and indirect mechanisms have been proposed, including a direct interaction with the hERG potassium ion channels, which regulate myocardial repolarization and inhibition of phosphoinositide 3-kinase (PI3K) signaling (Lu, 2012; Schiefer, 2018).

Risk-benefit impact:

QTc prolongation is associated with an increased risk of sudden cardiac death due to ventricular arrhythmias, notably torsade de pointes. In general, a QTc prolongation beyond 500 ms is considered clinically important and should prompt cessation of QTc prolonging drugs (Schiefer, 2018). Therefore, QTc prolongation leading to torsade de pointes and cardiac arrest is considered an important identified risk to be included in the list of safety concerns for aumolertinib.

Important Identified Risk 2: CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage

Increase in blood creatine phosphokinase (CPK) is known to be associated with treatment with EGFR TKIs including EGFR antagonists and a third-generation EGFR TKI (Adenis, 2012; Parafianowicz, 2020; Sugimoto, 2021). CPK is involved in ATP homeostasis, and is important in high energy-consuming tissues, such as skeletal and cardiac muscle. Thus, increased levels of CPK can be indicative of striated muscular damage (notably due to trauma, rhabdomyolysis, muscular dystrophy, and autoimmune myositis) or myocardial injury (typically myocardial infarction) (Bais, 1982). Other conditions can occasionally cause elevation in CPK (e.g., infections and myopathies) (Kessler, 1983; Moghadam-Kia,

2016). Evaluation of CPK isoenzymes may be helpful in distinguishing the origin of CPK when there is uncertainty (Roberts, 1976).

Risk-benefit impact:

Rhabdomyolysis is a clinical syndrome characterized by primary (mechanical) or secondary (metabolic) skeletal muscle injury, resulting in cell death and release of potentially toxic substances into circulation (Kodadek, 2022). It is associated with muscle pain, weakness, vomiting, confusion, myoglobinuria and renal failure (Gupta, 2021). Since rhabdomyolysis and some of the other clinical manifestations of CPK increase are serious conditions that can be fatal or result in permanent disability, this is considered an important risk to be included in the list of safety concerns for aumolertinib.

Important Identified Risk 3: Interstitial lung disease

ILD is a well-known risk of treatment with EGFR TKIs (Shah, 2019). ILD includes several lung diseases affecting the tissue and space around the air sacs of the lungs (the interstitium).

Risk-benefit impact:

ILD is a condition which can cause significant symptoms and morbidity and may potentially have a fatal outcome. In mild cases, it can be asymptomatic and only present with abnormal imaging findings. In more severe cases, it causes shortness of breath (dyspnoea), progressing to a severe inflammatory reaction of the lung tissue and acute respiratory distress syndrome, which can be life-threatening (Long, 2020). Therefore, ILD is considered an important risk to be included in the list of safety concerns for aumolertinib.

Important Identified Risk 4: Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)

Venous thromboembolism (VTE) comprises pulmonary embolism (PE) and deep vein thrombosis (Shoji, 2022). There are mixed reports in the literature regarding whether VTE is indeed associated with EGFR TKIs or not. This is likely because cancer patients are already at high risk of VTE, and it is therefore hard to distinguish between the high background risk and the additional risk coming from the treatment (Lei, 2022; Roopkumar, 2021; Shoji, 2022). Nonetheless, some studies report that treatment with first- and second-generation EGFR TKIs is a risk factor for VTE. This is in line with the ability of EGFR TKIs to trigger platelet activation, which may promote the formation of a thrombus via their adhesion, aggregation, and release of coagulation factors (Shoji, 2022; Yang, 2012).

Risk-benefit impact:

VTE is an important complication associated with cancer and a leading cause of death in cancer patients (Shoji, 2022). VTE occurs when a blood clot forms in a vein. The most serious complication of VTE happens when a part of the clot breaks off and reaches the lung by traveling through the bloodstream. This causes PE, which can lead to damage to the lungs and can be fatal if the clot is large enough to completely stop blood from reaching the organ. PE can also lead to acute heart failure and cardiac arrest by suddenly increasing blood pressure in the pulmonary artery. Venous thromboembolic events (e.g. PE, deep vein thrombosis) are serious, life-threatening conditions that require immediate medical attention. Early diagnosis and treatment can often lead to recovery, but long-term complications may still occur (American Heart Association, 2017; CDC, 2022; Goldhaber, 2003).

Therefore, venous thromboembolic events (e.g. PE, deep vein thrombosis) is considered an important risk to be included in the list of safety concerns for aumolertinib.

Important Potential Risk 1: Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme

In clinical trials with aumolertinib, the most frequently reported cutaneous reactions included rash, pruritus, dry skin, urticaria, and maculo-papular rash. Based on the ongoing routine pharmacovigilance of aumolertinib clinical trials and spontaneously reported events from the post-marketing setting, the symptoms of skin reactions consistent with Stevens-Johnson Syndrome (SJS) have been reported. Two post-marketing reports of erythema multiforme (EM) have been received and were reviewed in detail. One of the events, while reported as EM, had a clinical presentation consistent with characteristics of SJS. SJS is a rare but serious skin reaction that is usually caused by taking certain medicines (NHS, 2022). Rare cases of SJS have been reported in patients treated with EGFR TKIs, including first-, second-, and third-generation EGFR TKIs (Coleman, 2021; Li, 2022; Tagrisso SmPC). Although several hypotheses on the pathophysiological mechanism of SJS have been formulated, the precise mechanism by which some drugs, including EGFR TKIs, cause SJS is still unknown (Frantz, 2021; Hasegawa, 2020; Li, 2022). In the past, EM was assumed to be a less severe form of SJS because of similar clinical and histopathologic features, but it is currently not considered a SCAR and can be distinguished from SJS using clinical characteristics such as lesion appearance. Additionally, EM occurs in younger patients and is exclusively associated with infections whereas SJS is predominantly a SCAR which affects older adults (CIOMS, 2024).

Risk-benefit impact:

SJS is characterized by widespread epidermal necrosis and sloughing of skin. Without treatment, its symptoms can become life-threatening and therefore, early diagnosis and treatment are critical in achieving favorable outcomes for patients (Frantz, 2021; NHS, 2022). SJS requires hospitalization and often requires the patient to be transferred to an intensive care unit (Frantz, 2021; NHS, 2022). Since SJS is often triggered by medication, any suspect of SJS should prompt cessation of treatment. Therefore, Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme is considered an important potential risk to be included in the list of safety concerns for aumolertinib.

Important Potential Risk 2: Drug-induced liver injury (DILI) and hepatitis

Hepatotoxicity is a well-known risk of treatment with EGFR TKIs (Shah and Shah 2019), though the mechanism underlying this toxicity is complex and not well understood (Shah, Morganroth, and Shah 2013b). Some studies suggest that the hepatotoxicity of EGFR TKIs is associated with their metabolic intermediates, others link hepatotoxicity to autoimmune injury or direct EGFR inhibition (Kim et al. 2018; Wu et al. 2021). However, pharmacologically diverse TKIs (not just those targeting EGFR) are known to be hepatotoxic, suggesting that inhibition of EGFR specifically is not the cause. Moreover, TKIs of different chemical classes can cause hepatotoxicity; therefore, this is unlikely to be due to a particular chemical class.

In patients treated with aumolertinib, adverse reactions due to hepatotoxicity were common, and most were Grade 1-2 in severity, and manifested only as transient elevations in liver enzymes (ALT and/or AST); clinical manifestations were reported with low frequency. Transient fluctuations in ALT and AST are very common in routine oncology practice and are generally asymptomatic. One case each of drug-induced liver injury (DILI) and Hy's law were reported in the clinical trials.

Risk-benefit impact:

Based on these observations, and in relation to the severity of the indication treated, Drug-induced liver injury (DILI) and hepatitis are considered as having a limited impact on the risk-benefit balance of aumolertinib and on public health.

Missing information: None.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable, this is the initial RMP submission to the EMA.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk 1: QTc prolongation leading to torsade de pointes and cardiac arrest

Analysis by Standardized MedDRA Query: Torsade de pointes/QT prolongation (SMQ) [20000001].

Potential mechanism:

The precise mechanisms by which TKIs prolong the QTc are unknown but several direct and indirect mechanisms have been proposed, including a direct interaction with the human hERG potassium ion channels, which regulate myocardial repolarization (Lenihan, 2013). Studies conducted in animal models also suggest that QTc prolongation may be caused by inhibition of PI3K signaling (a downstream effect of EGFR inhibitors, as well as a range of other agents) (Lu, 2012; Schiefer, 2018).

Evidence source(s) and strength of evidence:

QTc prolongation is a known side effect of treatment with some, but not all, EGFR TKIs. Agents known to cause QTc prolongation include a TKI which inhibits both HER2 and EGFR and a third -generation EGFR TKI (Shah, 2019). A concentration-response effect has been observed for both. For example, in the FLAURA study, changes in QTc were reported in a higher percentage of patients treated with a third-generation EGFR TKI (10%) than in patients treated with the first -generation EGFR TKI (control group) (5%) (Soria, 2018). Data on a first-generation EGFR TKI are suggestive but not conclusive for an effect on QTc (Shah, 2013). No clinically relevant effect on QTc has been seen in clinical studies of other first- and second-generation EGFR TKIs (Shah, 2019).

Although QTc prolongation is an established adverse reaction to a third-generation EGFR TKI, torsade de pointes is much less commonly reported. Only anecdotal cases could be found in the literature, sometimes in patients with other contributing factors (Bian, 2020; Ikebe, 2021; Matsuura, 2021).

Evidence of QTc prolongation with the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China.

Characterization of the risk:

Clinical data:

Analysis of adverse event (AE) data (by SMQ) from subjects treated with 110 mg aumolertinib in the HS-10296-12-01 and HS-10296-03-01 studies (N = 545) revealed the following:

- Overall, 58 subjects (10.6%) developed QTc prolongation during the pivotal studies. In 8 subjects (1.5%), the events were Grade ≥ 3 and in 4 of those subjects, the Grade ≥ 3 treatment-emergent AEs (TEAEs) were symptomatic events (cardiac arrest, cardio-respiratory arrest, sudden cardiac death, and syncope) rather than an asymptomatic ECG change. Two (0.4%) events in this SMQ were fatal, one due to sudden cardiac death and one due to cardio-respiratory arrest.
- To evaluate the risk of QT interval prolongation and pro-arrhythmic potential of aumolertinib, a QTc analysis was conducted to assess the effect of aumolertinib on the QTc interval corrected for heart rate (HR) using the Fridericia method (QTcF) in subjects with NSCLC. In addition, the effect of aumolertinib on other ECG parameters (HR, PR, QRS interval and ECG morphology) in subjects with NSCLC was assessed.
    - In the central tendency (by-time point) analysis, the upper bound of the 90% confidence interval (CI) of change from baseline QTcF (ΔQTcF) was below the 20 ms threshold at all post-dose time points in the 110 mg dose group, indicating no clinically relevant concern on the QTc prolongation following once daily oral administration of 110 mg aumolertinib. In the 220 and 260 mg dose groups (higher than the therapeutic dose of 110 mg), the upper bound of the 90% CI of ΔQTcF (30.8 ms at 24 hours postdose in the 220 mg dose group and 27.7 ms at 6 hours postdose in the 260 mg dose group) exceeded the 20 ms threshold during Cycle 2 post-dose time points.
    - Based on the concentration-QT analysis, the predicted drug-related mean ΔQTcF interval prolongation at the proposed aumolertinib therapeutic dose of 110 mg was 8.0 ms with an upper bound of the associated two-sided 90% CI of 9.8 ms; the upper bound of the 90% CI fell below the pre-specified threshold of 20 ms. At the 220 and 260 mg dose groups, the predicted drug-related mean ΔQTcF interval prolongation was 14.16 and 21.10 ms with an upper bound of the associated two-sided 90% CI of 17.44 and 26.79 ms, respectively.
    - Aumolertinib had no clinically relevant effects on heart rate, PR interval, or QRS duration at the therapeutic dose and at doses higher than the therapeutic dose.

Overall, these data suggest that the risk of aumolertinib causing clinically significant QTc prolongation or predispose to cardiac arrhythmias at the recommended dose of 110 mg QD is low but important given the seriousness of the potential outcomes.

Post-marketing data:

There was a total of 321 post-marketing reports received between 17 Mar 2020 and 16 Mar 2023 (a 36-month period), out of which there was one report of QT interval prolongation.

Risk factors and risk groups:

An analysis to identify specific risk factors and risk groups for QTc prolongation has not been conducted for aumolertinib.

QTc prolongation itself is asymptomatic but associated with an increased risk of sudden cardiac death due to ventricular tachyarrhythmias, notably torsade de pointes. The risk of developing life-threatening arrhythmias from QTc prolongation is difficult to quantify as the degree of prolonged QTc does not reliably correlate with the incidence of torsade de pointes and sudden death. However, longer QTc is likely to be associated with an increased risk of torsade de pointes (Lenihan, 2013). In general, QTc prolongation beyond 500 ms is considered clinically important and an indication to stop QTc-prolonging drugs (Schiefer, 2018).

Indirect predisposing factors for QTc prolongation in patients with cancer treated with TKIs include intrinsic intra-patient repolarization variability; comorbid disease; concomitant medications with the potential for drug-drug interactions; and electrolyte disturbances secondary to decreased oral intake, or severe nausea, vomiting, or diarrhoea (Lenihan, 2013). A family history of long QT syndrome or sudden death; heart failure; left ventricular hypertrophy; extreme bradycardia; strenuous physical activity; hypothermia; hypothyroidism; female sex and increasing age are additional risk factors (Schiefer, 2018).

Preventability:

There are currently no means of preventing QTc prolongation with aumolertinib (or other EGFR TKIs). However, ECG monitoring of QTc is a reliable way to make individual patient decisions regarding continuation or suspension of treatment with anticancer agents known to predispose to QTc prolongation in general, particularly in patients with risk factors for QTc prolongation such as patients with congestive heart failure, electrolyte abnormalities or who are using drugs which are known to prolong the QTc interval. Careful management of side effects which could predispose to electrolyte disturbance (such as diarrhoea, nausea, and vomiting), and avoidance of concurrent medications known to prolong QTc or to increase exposure to aumolertinib are also sensible medical precautions.

Impact on the risk-benefit balance of the product:

Torsade de pointes has not been observed with aumolertinib to date, although cases of sudden or unexplained death have been reported. However, in patients with advanced malignancy, such deaths are not necessarily suspicious of a cardiac arrhythmia due to QTc prolongation. QTc prolongation has been observed with aumolertinib (10.6% of subjects), but the events were generally Grade 1-2 in severity and asymptomatic. Overall, the risk of developing QTc prolongation and torsade de pointes due to aumolertinib is considered low, and considering the severity of the indication (advanced/metastatic lung cancer) and the ease with which QTc interval can be monitored, the risk of QTc prolongation leading to torsade de pointes and cardiac arrest is considered as having a limited impact on the risk-benefit balance of aumolertinib.

Public health impact

Although QTc prolongation has been observed with aumolertinib, torsade de pointes has not been reported in the clinical trials of aumolertinib to date. One report of QTc interval prolongation has been received from post-marketing use in China; however, it was not associated with torsade de pointes. Based on these observations, the impact of QTc prolongation leading to torsade de pointes and cardiac arrest with aumolertinib on public health is considered very low.

Important Identified Risk 2: CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage

Analysis by Standardized MedDRA Query: Rhabdomyolysis/myopathy (SMQ) [20000002].

Potential mechanism:

Drugs are a well-known cause of CPK increase (notably statins) and other clinical manifestations of muscle damage such as rhabdomyolysis (Moghadam-Kia, 2016; Sakamoto, 2013). However, the mechanism by which EGFR TKIs may cause these is still unknown (Jiang, 2021).

Evidence source(s) and strength of evidence:

Evidence of rhabdomyolysis and blood CPK increases linked to the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China.

Blood CPK increase is a safety concern for a range of TKIs including EGFR antagonists and a third-generation EGFR TKI (Adenis, 2012; Parafianowicz, 2020; Sugimoto, 2021). In one recent review, 8 cases (0.08%) of serum CPK elevation were noted in the post-marketing surveillance study of a first-generation EGFR TKI, 4 cases (0.17%) in the international joint Phase 3 study of a second-generation EGFR TKI, and 4 cases (0.7%) in the international joint Phase 3 study of a third-generation EGFR TKI according to the pharmaceutical interview forms (Obayashi, 2022). Reports of rhabdomyolysis and other clinical manifestations of muscle damage are much less common than reports of CPK increases with EGFR TKIs. These include a report of rhabdomyolysis following an overdose of a first-generation EGFR TKI (Obayashi, 2022) and a report of rhabdomyolysis following 3 months of treatment with standard doses of another first-generation EGFR TKI (Moscetti, 2011). Rhabdomyolysis has also been reported following concurrent treatment with a first-generation EGFR TKI and a statin (Veeraputhiran, 2008). Symptomatic myositis associated with elevated CPK in some cases, has also been reported with a third-generation EGFR TKI (Parafianowicz, 2020).

Characterization of the risk:

Clinical data:

Analysis of AE data (by SMQ) from subjects treated with 110 mg aumolertinib in the HS-10296-12-01 and HS-10296-03-01 studies (N = 545) revealed the following:

- Overall, the incidence of blood CPK increased was 40.9% (n = 223). These events were mostly Grade 1 or 2 in severity. Rhabdomyolysis itself was not reported as an AE and other clinical manifestations of muscle damage were uncommonly reported. The most frequently reported contributing TEAEs were blood CPK increased (31.7%, n = 173), blood creatinine increased (5.9%, n = 31), hypocalcemia (4.6%, n = 25), myalgia (2.2%, n = 12), myoglobin blood increased (2.0%, n = 11), and muscular weakness (1.1%, n = 6). The incidence of other AEs in the blood CPK increased SMQ was either < 1% or absent. The incidence of Grade ≥ 3 blood CPK increased TEAEs was 7.7% (n = 42). The most frequently reported contributing TEAEs were blood CPK increased (7.5%, n = 41), myoglobin blood increased (0.2%, n = 1) and muscular weakness (0.2%, n = 1).
- Subjects with Grade ≥ 3 blood CPK increase were retrospectively assessed according to the following criteria for rhabdomyolysis: Grade 3 CPK increase (with muscle related symptoms) or Grade 4 CPK increase with or without muscle related symptoms. Fourteen subjects (2.6%) (7 subjects with maximum Grade 3 in severity and muscle symptoms, 7 subjects with maximum Grade 4 in severity) retrospectively meet the criteria to be considered rhabdomyolysis.

Overall, these observations suggest that aumolertinib frequently causes CPK elevations. Cases consistent with rhabdomyolysis have been reported, but none of them led to severe renal impairment. No other clinical manifestations of muscle damage were reported at the recommended dose of 110 mg.

Post-marketing data:

There was a total of 321 post-marketing reports received between 17 Mar 2020 and 16 Mar 2023 (a 36-month period), out of which there were 16 reports of blood CPK elevation adverse reactions (2 serious and 14 non-serious) and 1 report of rhabdomyolysis (serious).

Risk factors and risk groups:

An analysis to identify specific risk factors and risk groups for CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage has not been conducted for aumolertinib. Several factors influence CPK levels in healthy individuals including differences in body size and composition, sex, and ethnicity. Additionally, intense exercising, vigorous work or recreation, and nutritional

supplements are associated with moderately elevated blood CPK levels (George, 2016; Moghadam-Kia, 2016).

In theory, any form of muscle damage can initiate rhabdomyolysis. In adults, data show that the most common causes of rhabdomyolysis, other than medicinal drug use, are drug or alcohol abuse, trauma, neuroleptic malignant syndrome, and immobility; therefore, any individual that is subject to any of these may be at increased risk of rhabdomyolysis. Genetic polymorphisms and defects accounting for skeletal muscle diseases increase the risk for episodes of rhabdomyolysis. These defects include enzymes from the glycolysis and glycogenolysis pathway and pentose phosphate pathway, mitochondrial pathways involving fatty acid oxidation, the citric acid cycle, and the mitochondrial respiratory chain, and finally, defects in calcium homeostasis such as in proteins involved in excitation-contraction coupling, myotonias, and skeletal muscle dystrophies (Hohenegger, 2012; Torres, 2015).

Preventability:

There are currently no means of preventing CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage. Acute kidney injury (AKI) is a primary complication of rhabdomyolysis. Electrolyte abnormalities occur secondary to cellular component release associated with induced AKI. The most common laboratory abnormalities associated with rhabdomyolysis include elevated serum concentrations of CPK (> 5× the upper limit of normal or > 1000 IU/L), myoglobin, lactate dehydrogenase, potassium, creatinine, and AST. Elevated urine myoglobin and darkened (tea-colored) urine may provide additional evidence of this condition. To prevent complications and to warrant proper management, strategy for monitoring and dose modification or suspension should be undertaken (Kodadek, 2022).

Patients should be asked to report any unexplained muscular symptoms such as muscle pain, muscle tenderness, muscle twitching or muscle weakness. In case of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 CPK elevation, the aumolertinib dose may require adjustment. Concomitant medications known to increase CPK should be avoided.

Impact on the risk-benefit balance of the product:

Blood CPK increases are generally asymptomatic and manageable with appropriate monitoring and dose adjustment. Elevations in CPK were very commonly reported AEs (31.7%) in subjects with advanced NSCLC treated with 110 mg of aumolertinib. Other clinical manifestations of CPK increase such as myalgia (2.2%), muscular weakness (1.1%), myositis (0.4%), and musculoskeletal pain (0.2%) were uncommonly reported. Fourteen subjects (2.6%) retrospectively meet the criteria to be considered rhabdomyolysis. Considering the severity of the indication treated (advanced/metastatic NSCLC), rhabdomyolysis and other clinical manifestations of CPK increase are considered as having a limited impact on the risk-benefit balance of aumolertinib.

Public health impact:

Blood CPK elevations were common after the use of aumolertinib in clinical trials (31.7%). Fourteen cases were considered rhabdomyolysis, but none of them led to severe renal impairment. No other clinical manifestations of muscle damage were reported. Monitoring, recognition, and treatment of these events is now a routine part of oncology clinical practice. Based on these observations, the impact on public health due to rhabdomyolysis and other clinical manifestations of CPK increase is considered low.

Important Identified Risk 3: Interstitial lung disease

Analysis by Standardized MedDRA Query: Interstitial lung disease (SMQ) [20000042].

Potential mechanisms:

The precise molecular mechanism of TKI-induced ILD is currently unknown, and it seems likely that multiple factors are involved. EGFR is expressed by type II alveolar epithelial cells which are involved in repair of pulmonary damage. EGFR is known to be upregulated in acute lung injury (Madtes, 1994) and in a rodent model of bleomycin-induced pulmonary fibrosis, the addition of a first-generation EGFR TKI was shown to increase fibrosis (Suzuki, 2003). Accordingly, EGFR TKIs may aggravate lung injury due to other causes by inhibiting repair and exacerbating lung fibrosis. Allergic or immunologic mechanisms may also be involved in at least some cases (Huang, 2020; Qi, 2015; Sakao, 2012; Shah, 2016).

Evidence source(s) and strength of evidence:

Evidence of ILD linked to the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China. ILD is a potential safety concern for other EGFR TKIs (Huang, 2020; Qi, 2015; Sakao, 2012; Shah, 2016).

Of note, the frequency of ILD is dependent on the diagnostic approach, and the definition and terminology used. ILD is a difficult diagnosis to make, especially in patients with advanced lung cancer. This is compounded by the difficulty in obtaining histological samples to confirm the diagnosis. Frequently, the respiratory symptoms of ILD cannot be distinguished from those due to progressive tumor or lower respiratory tract infections. Furthermore, lung radiotherapy can cause symptomatic radiation pneumonitis within 1-6 months after completion. It is estimated that 5-15% of lung cancer patients treated with radiotherapy develop symptoms of radiation pneumonitis (Abid, 2001). Chemotherapy is also associated with pulmonary toxicities (< 10% of patients), including ILD (Barlési, 2004; Limper, 2004).

Characterization of the risk:

Clinical data:

Analysis of AE data (by SMQ) from subjects treated with 110 mg aumolertinib in the HS-10296-12-01 and HS-10296-03-01 studies (N = 545) revealed the following:

- Overall, 16 subjects (2.9%) developed ILD. These events were mostly of Grades 1 or 2 in severity. Only in one subject (0.2%), ILD was Grade ≥ 3 in severity.

Post-marketing data:

There was a total of 321 post-marketing reports received between 17 Mar 2020 and 16 Mar 2023 (a 36-month period), out of which there were 18 reports of ILD (10 serious and 8 non-serious).

Risk factors and risk groups:

Risks factors for developing ILD in general include previous radiation therapy to the lungs, previous chemotherapy treatment, pre-existing parenchymal lung disease, metastatic lung disease, and concomitant pulmonary infection (Long, 2020). Additional risk factors for ILD include older age, poor performance status, smoking, a recent diagnosis of NSCLC, reduced normal lung on computed tomography scan, pre-existing ILD, and concurrent cardiac disease (Kudoh, 2008).

In patients receiving EGFR TKIs, including a third-generation one, the risk of developing ILD appears to be increased with concurrent or recent use of a checkpoint inhibitor (Gemma, 2020; Oshima, 2018; Shinno, 2020; Yang, 2019).

The relationship between potential risk factors for developing pulmonary toxicity (in general) for patients who received aumolertinib treatment, was analyzed in an exploratory fashion (there were too

few cases of ILD for a meaningful analysis of this particular event). The following risk factors were identified for pulmonary toxicity:

- Male gender
- Recent history of radiotherapy and chemotherapy
- History of smoking
- Age ≥ 55 years old
- Performance status > 2 points
- Normal lung tissue < 50% on imaging
- History of ILD
- Emphysema or COPD
- Lung infection
- Short time since diagnosis of cancer (< 6 months)
- Co-morbid cardiovascular disorder

These risk factors are intuitively risk factors for poor pulmonary function in general and are consistent with known risk factors for the development of ILD (Kudoh, 2008; Long, 2020).

Preventability:

ILD due to EGFR TKIs is currently not preventable. Patients should be evaluated for risk factors for ILD before starting therapy with aumolertinib. Patients with ILD or a history of ILD are likely to be at particular risk.

During treatment with aumolertinib, patients with acute episodes and/or exacerbations of pulmonary symptoms (difficulty breathing, coughing or fever, etc.) without an alternative explanation should be investigated for ILD and aumolertinib should be withheld during the investigation. If ILD is confirmed, aumolertinib should be permanently discontinued and necessary treatment measures should be taken.

Impact on the risk-benefit balance of the product:

Although the risk of developing ILD with aumolertinib is small, the impact of ILD on quality of life is considerable. Treatment discontinuation is required together with symptomatic treatment and possibly hospitalization. A fatal outcome is possible despite active treatment. Overall, the number of subjects with advanced NSCLC treated with 110 mg of aumolertinib who developed ILD was low (2.9%), and only in one subject the ILD event was Grade ≥ 3 in severity (0.2%). Considering the severity of the indication treated (advanced/metastatic NSCLC), ILD is considered as having a limited impact on the risk-benefit balance of aumolertinib.

Public health impact:

Post-marketing adverse reaction monitoring is ongoing in China. The incidence of ILD to date is low and the potential public health impact of ILD caused by aumolertinib is considered low. Patients receiving aumolertinib for NSCLC are already at risk of respiratory complications due to the disease itself, other treatments (notably surgical resection and/or radiotherapy and chemotherapy), and (in a minority of patients with EGFR-mutated NSCLC) smoking. Additionally, ILD is a known class effect of EGFR inhibitors, and recognition and treatment of this toxicity is now a routine part of oncology clinical practice.

Important Identified Risk 4: Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)

Analysis by Standardized MedDRA Query: Embolic and thrombotic events (SMQ), Central nervous system vascular disorders (SMQ), Thrombophlebitis (SMQ), Vasculitis (SMQ).

Potential mechanisms:

There are mixed reports in the literature regarding whether VTE is indeed associated with EGFR TKIs or not. This is likely because cancer patients are already at high risk of VTE, and it is therefore hard to distinguish between the high background risk and the risk coming from the treatment (Lei, 2022; Roopkumar, 2021; Shoji, 2022). Nonetheless, some studies report that treatment with first- and second-generation EGFR TKIs is a risk factor for VTE. This is in line with the ability of EGFR TKIs to trigger platelet activation, which may promote the formation of a thrombus via their adhesion, aggregation, and release of coagulation factors (Shoji, 2022; Yang, 2012).

Evidence source(s) and strength of evidence:

Evidence of VTEs linked to the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China.

The incidence of VTE is 4- to 7-fold higher in cancer patients compared to non-cancer patients, and the risk of VTE in lung cancer patients is 20-fold higher compared to the general population (Lei, 2022; Roopkumar, 2021). Of note, lung cancer patients have one of the highest VTE incidence rates among all tumour types. Chemotherapy is also associated with a 2- to 6-fold increase in the risk of VTE (Sousou, 2009). Some studies report that VTE is a risk associated with the use of first- and second-generation EGFR TKIs, while the association with a third generation TKI in clinical studies remains unclear (Shoji, 2022).

Characterization of the risk:

Clinical data:

Analysis of AE data (by SMQ) from subjects treated with 110 mg aumolertinib in the HS-10296-12-01 and HS-10296-03-01 studies (N = 545) revealed the following:

- Overall, 66 subjects (12.1%) developed thromboembolic events and in 32 of these subjects (5.9%), the events were Grade ≥ 3 in severity.

Post-marketing data:

There was a total of 321 post-marketing reports received between 17 Mar 2020 and 16 Mar 2023 (a 36-month period), out of which there were 5 reports of VTE events (2 serious and 3 non-serious).

Risk factors and risk groups:

An analysis to identify specific risk factors and risk groups for VTE has not been conducted for aumolertinib.

In general, cancer patients have a higher risk of developing VTE compared to other patients and the general population, with the primary site of cancer being an important risk factor. Patients with lung cancer are among the ones with the highest risk of VTE. Old age, immobility/inactivity, hospitalization, and comorbidities such as infection, obesity, anaemia, pulmonary disease, renal disease, as well as genetic conditions affecting clotting all add to the risk of developing VTE. Finally, major surgery, chemotherapy, and certain novel therapeutics such as anti-angiogenic agents are also associated with an increased risk of VTE (American Heart Association, 2017; Sousou, 2009).

Preventability:

Routine anticoagulant treatment for VTE prophylaxis is not recommended in cancer patients (Shoji, 2022). This leaves only limited options for preventing the development of VTE. The use of mechanical devices such as compression stockings or compression devices may be useful. Early mobilization after surgery is also advised, if possible (American Heart Association, 2017).

Impact on the risk-benefit balance of the product:

Regardless of treatment, lung cancer patients in general already have a significant risk of developing VTE. Overall, VTE occurred in 12.1% of subjects with advanced NSCLC treated with 110 mg of aumolertinib. VTE events of Grade ≥ 3 in severity occurred in 5.9% of subjects.

Early diagnosis of VTE and treatment can often lead to recovery, but VTE remains a serious, life-threatening condition that requires immediate medical attention and that may lead to long-term complications. A fatal outcome is possible despite active treatment. However, considering the severity of the indication treated (advanced/metastatic NSCLC) and the already significant risk of VTE associated with this condition, VTE (e.g. PE and deep vein thrombosis) is considered as having a limited impact on the risk-benefit balance of aumolertinib.

Public health impact:

Post-marketing adverse reaction monitoring is ongoing in China. The number of reports of VTE to date is low and the potential public health impact of VTEs caused by aumolertinib is considered low. Patients receiving aumolertinib for NSCLC are already at risk of VTE due to the disease itself and other anti-cancer treatments (notably surgical resection and/or chemotherapy, and possibly first- and second-generation EGFR TKIs). Monitoring, recognition, and treatment of these events is now a routine part of oncology clinical practice. Based on these observations, the impact on public health due to venous thromboembolic events (e.g. PE, deep vein thrombosis) is considered low.

Important Potential Risk 1: Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme

Potential mechanism:

SJS is believed to be a type IV hypersensitivity reaction associated with an immune response that leads to epidermal necrosis (Frantz, 2021). There are a number of hypotheses on how drugs can generate an immunological response that causes SJS, all of which involve direct or indirect binding of the drug to human leukocyte antigen (HLA) molecules leading to T cell activation. However, the precise mechanisms by which EGFR TKIs or other agents cause SJS are still unknown (Frantz, 2021; Hasegawa, 2020; Li, 2022).

Evidence source(s) and strength of evidence:

Skin toxicity is a well-known risk of treatment with EGFR TKIs. Rare cases of SJS have been reported in patients treated with EGFR TKIs, including first-, second-, and third-generation EGFR TKIs (Coleman, 2021; Li, 2022; Tagrisso SmPC). Specifically, SJS has been reported with a frequency of 0.02% in clinical trials with a third-generation EGFR TKI (Tagrisso SmPC).

Symptoms of a skin reaction consistent with SJS have been reported in the post-marketing setting with aumolertinib.

Characterization of the risk:

Clinical data:

No cases of SJS were reported in clinical trials with aumolertinib.

Post-marketing data:

Two post-marketing reports of EM have been received in China and were reviewed in detail. One of the events, while reported as EM, had a clinical presentation consistent with characteristics of SJS. The occurrence of EM in this case was closely related to the time of the medication, and the symptoms improved after drug withdrawal. Therefore, this event was considered consistent with SJS and assessed as possibly related to aumolertinib.

Risk factors and risk groups:

An analysis to identify specific risk factors and risk groups for SJS has not been conducted for aumolertinib.

Studies have found that high male hormones, high sebum secretion, and smoking are risk factors for more severe adverse skin reactions in male lung cancer patients (Li, 2022). Therefore, these factors may also increase the risk of SJS in the same patient population.

Other factors that increase the general risk of developing SJS include (Mayo Clinic, 2023):

- Cancer and certain cancer treatments such as chemotherapy.
- HIV infection. Among people with HIV, the incidence of SJS is about 100 times greater than among the general population.
- A weakened immune system.
- Previous or family history of SJS.
- Genetic factors, especially when taking concomitant medications for seizures, gout, or mental illness.

Preventability:

There are currently no means of preventing SJS with aumolertinib (or other EGFR TKIs). Monitoring for early signs and symptoms of SJS is critical to identify patients who may be developing the condition and immediately suspend treatment.

Impact on the risk-benefit balance of the product:

Symptoms of a skin reaction consistent with SJS have been reported. Although SJS is a serious condition, overall, the risk of developing SJS due to aumolertinib is considered very low. Considering the severity of the indication (advanced/metastatic lung cancer) and the rarity of SJS, the risk of SJS is considered as having a limited impact on the risk-benefit balance of aumolertinib.

Public health impact

Symptoms of skin reactions consistent with SJS have been observed with aumolertinib in the post-marketing setting. Based on the rarity of the condition and the intended patient population, the impact of SJS with aumolertinib use on public health is considered very low.

Important Potential Risk 2: Drug-induced liver injury (DILI) and hepatitis

Potential mechanism:

Hepatotoxicity is a well-known risk of treatment with EGFR TKIs (Shah and Shah 2019), though the mechanism underlying this toxicity is complex and not well understood (Shah, Morganroth, and Shah 2013b). Some studies suggest that the hepatotoxicity of EGFR TKIs is associated with their metabolic intermediates, others link hepatotoxicity to autoimmune injury or direct EGFR inhibition (Kim et al. 2018; Wu et al. 2021). However, pharmacologically diverse TKIs (not just those targeting EGFR) are known to be hepatotoxic, suggesting that inhibition of EGFR specifically is not the cause. Moreover, TKIs of different chemical classes can cause hepatotoxicity; therefore, this is unlikely to be due to a particular chemical class.

Evidence source(s) and strength of evidence:

Evidence of hepatotoxicity linked to the use of aumolertinib comes from ongoing clinical studies and post marketing surveillance in China.

Hepatotoxicity has been reported for most other EGFR TKIs. The frequency of hepatotoxicity Grade $\geq$ 2 was 17.2% (Kim et al. 2018) in patients treated with a first-generation EGFR TKI. The frequency of hepatotoxicity Grade $\geq$ 3 in patients treated with two first- and one second-generation EGFR TKIS was 5.4%, 18%, and 1.7%, respectively (Takeda, Okamoto, and Nakagawa 2015).

Characterization of the risk:

Clinical data:

Analysis (by SMQ) of AE data from patients treated with 110 mg aumolertinib in the HS-10296-12-01 and HS-10296-03-01 studies (N = 545) revealed the following:

- Overall, AEs within the drug related hepatic disorders SMQ were frequently reported (37.4% of patients). However, most events were Grade 1-2 in severity; Grade $\geq$ 3 AEs were reported in 20 patients (3.7%). Most events (all Grades and Grade $\geq$ 3) were elevations in transaminases (ALT and AST).

- AEs of AST and ALT elevation (and other tests of liver function) were consistently more frequently elevated in patients treated with gefitinib vs patients treated with aumolertinib in the HS-10296-03-01 study.

Overall, these observations indicate that aumolertinib, in common with other EGFR TKIs, can cause disturbances in liver function tests. However, the frequency of hepatic toxicity is lower than that seen with gefitinib.

One case each of drug-induced liver injury (DILI) and Hy's law were reported in the clinical trials.

Post-marketing data:

Up to the cutoff date of 16 March 2023, 18 serious hepatobiliary disorders were reported. Serious hepatobiliary disorders included abnormal hepatic function (6 reports), drug-induced liver injury (9 reports), acute hepatic failure (1 report), and liver injury (2 reports).

Risk factors and risk groups:

An analysis to identify specific risk factors and risk groups for hepatotoxicity has not been conducted for aumolertinib.

Risk factors for hepatotoxicity identified with a first-generation EGFR TKI, were concomitant use of CYP3A4 inducers and co administration of H2-antagonist/proton pump inhibitor (PPI) (Kim et al. 2018). These increased the frequency of hepatotoxicity by 2.7 and 3.5-fold, respectively. Liver metastasis

were a significant risk factor in all study patients with an attributable risk of 46.3%. Age ≥ 65 years was a significant risk factors in NSCLC patients with an attributable risk factor of 71.8%. The use of nivolumab or pembrolizumab immediately before initiation of treatment with a third-generation EGFR TKI has been linked to a significantly higher frequency of Grade ≥ 3 hepatotoxicity in patients with advanced NSCLC (Yamaguchi et al. 2020; Gianni et al. 2021). In these situations, it appears that the third-generation EGFR TKI was precipitating or exacerbating the immune-related hepatotoxicity of the checkpoint inhibitor. High rates of severe hepatotoxicity were also reported with concurrent use of one of the two available first-generation EGFR-TKI and pembrolizumab (Yang, Gadgeel, et al. 2019).

Preventability:

There is currently no way of preventing EGFR TKI-associated hepatotoxicity. However, close monitoring of liver function tests (transaminases and bilirubin) and dose adjustment is the mainstay of preventing severe liver dysfunction for all EGFR TKIs (Shah, Morganroth, and Shah 2013b).

Where possible, other drugs which strongly induce or inhibit CYP3A4 enzymes should be avoided due to the fact that aumolertinib is metabolized by CYP3A4.

Impact on the risk-benefit balance of the product:

Liver enzyme elevation may also necessitate treatment suspension or dose reduction. In general, EGFR TKI-associated liver toxicity is usually reversible but may occasionally lead to the patient's death (Lee and Chan 2016). Fatal hepatotoxicity has not been described for aumolertinib.

Hepatotoxicity was frequently reported in patients with advanced NSCLC treated with 110 mg of aumolertinib. However, this was mostly Grade 1-2 elevations in AST, ALT and other liver function tests. The incidence and severity of such abnormalities were lower than seen with gefitinib. Overall, considering the severity of the indication treated (advanced/metastatic NSCLC), hepatotoxicity is considered as having a limited impact on the risk-benefit balance of aumolertinib.

Public health impact

Based on these observations, and in relation to the severity of the indication treated, Drug-induced liver injury (DILI) and hepatitis are considered as having a limited impact on the risk-benefit balance of aumolertinib and on public health.

SVII.3.2. Presentation of the missing information

Missing information: None.

Part II: Module SVIII - Summary of the safety concerns

Table 6 - Summary of safety concerns

Summary of safety concerns	
Important identified risks	QTc prolongation leading to torsade de pointes and cardiac arrest CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage Interstitial lung disease Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)

Summary of safety concerns	
Important potential risks	Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme Drug-induced liver injury (DILI) and hepatitis
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorization safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme:

Enhanced pharmacovigilance practices will be implemented during the collection, collation, assessment and reporting of Severe Cutaneous Adverse Reaction (SCAR) and erythema multiforme (EM) events:

All SCAR and EM events will be actively followed up to achieve a complete dataset for each case. A targeted questionnaire for Postmarketing AE reports (see Annex 4) will be implemented to solicit case details of all reports of Severe Cutaneous Adverse Reaction (SCAR) and erythema multiforme.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned.

III.3 Summary Table of additional Pharmacovigilance activities

Table 7 – 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 authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Not applicable				

Part IV: Plans for post-authorization efficacy studies

No post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations are planned.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety concerns are considered sufficiently addressed with routine risk minimization measures (Table 8), i.e., by providing relevant information in the SmPC and Patient Information Leaflet (PIL) (Module 1.3.1).

V.1. Routine Risk Minimization Measures

Table 8 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
QTc prolongation leading to torsade de pointes and cardiac arrest	Routine risk communication: *SmPC sections 4.2, 4.3, 4.4, and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Recommendation for dose modification is included in the SmPC section 4.2.* *Contraindications are included in the SmPC section 4.3.* *Description of patients who should undergo regular ECG and electrolyte monitoring, who should have dose modification, or who should permanently discontinue this product is included in the SmPC section 4.4.* *Description of drugs that should be avoided during treatment with this product is included in the SmPC sections 4.2, 4.4 and 4.5.* *PIL section 2 advises patients to not take aumolertinib and talk to their doctor if they have or had a heart rhythm disorder, such as abnormally fast or irregular heartbeat or a condition called "QT prolongation" or blood-related family members who have had abnormally fast or irregular heart rhythm or died suddenly from heart problems.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have or had any rapid or*

	irregular heartbeats, dizziness, light-headedness, chest discomfort, shortness of breath, fainting, severe diarrhoea or vomiting. *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience side effects such as very fast or irregular heartbeat causing fainting, dizziness, light headedness, chest discomfort, or shortness of breath.*
CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage	Routine risk communication: *SmPC sections 4.2, 4.4, and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Recommendation for dose modification is included in the SmPC section 4.2.* *Section 4.4 of the SmPC instructs to advise patients to report any unexplained muscle pain, tenderness, weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination.* *Section 4.4 of the SmPC instructs to withhold aumolertinib and initiate treatment for rhabdomyolysis if rhabdomyolysis occurs.* *Description of drugs that should be avoided during treatment with this product is included in the SmPC sections 4.2, 4.4 and 4.5.* *Section 4.4 of the SmPC instructs about renal monitoring.* *PIL section 2 advises patients to talk to their doctor if they have unexplained muscle pain, tenderness, weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination.*
Interstitial lung disease	Routine risk communication: *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk:

	Pulmonary symptoms that warrant further investigation are included in the SmPC section 4.4. *Instructions for treatment interruption, discontinuation and initiation of appropriate treatment for ILD are included in the SmPC section 4.4.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have suffered from inflammation on their lungs.* *PIL section 2 advises patients to talk to their doctor if they have sudden difficulty in breathing together with a cough or fever.* *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience sudden difficulty in breathing together with a cough or fever, shortness of breath at rest or made worse by exertion, or dry cough that will not go away.*
Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)	Routine risk communication: *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Section 4.4 of the SmPC instructs to promptly evaluate patients if symptoms of thromboembolic events occur or are suspected.* *Section 4.4 of the SmPC instructs to withhold aumolertinib and stabilize the patient before resuming therapy.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have had a blood clot (thrombus) in a blood vessel.* *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience any of the following symptoms: shortness of breath, chest pain, cough with blood, rapid or irregular heartbeat, light headedness, excessive sweating, fever, leg pain or swelling, clammy skin.*
Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme	None
Drug-induced liver injury (DILI) and hepatitis	*Routine risk communication:* *Section 4.4 of the SmPC instructs about liver function monitoring.*

V.2. Additional Risk Minimization Measures

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

V.3 Summary of risk minimization measures

Table 9 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
QTc prolongation leading to torsade de pointes and cardiac arrest	Routine risk communication: *SmPC sections 4.2, 4.3, 4.4, and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Recommendation for ECG monitoring and dose modification is included in the SmPC section 4.2.* *Contraindications are included in the SmPC section 4.3.* *Recommendations on regular ECG and electrolyte monitoring, dose modification, or permanent discontinuation are included in the SmPC section 4.4.* *Description of drugs that should be avoided during treatment with this product is included in the SmPC sections 4.2, 4.4 and 4.5.* *PIL section 2 advises patients to not take Aumseqa and talk to their doctor if they have or had a heart rhythm disorder, such as abnormally fast or irregular heartbeat or a condition called "QT prolongation" or blood-related family members who have had abnormally fast or irregular heart rhythm or died suddenly from heart problems.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have or had any rapid or irregular heartbeats, dizziness, light-headedness, chest*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	discomfort, shortness of breath or fainting. *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience side effects such as very fast or irregular heartbeat causing fainting, dizziness, light headedness, chest discomfort, or shortness of breath.* Additional risk minimization measures: None	
CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage	Routine risk communication: *SmPC sections 4.2, 4.4, and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Recommendation for dose modification is included in the SmPC section 4.2.* *Section 4.4 of the SmPC instructs to advise patients to report any unexplained muscle pain, tenderness, weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination.* *Section 4.4 of the SmPC instructs to withhold aumolertinib and initiate treatment for rhabdomyolysis if rhabdomyolysis occurs.* *Recommendations on monitoring of renal function is included in the SmPC section 4.4.* *Description of drugs that should be avoided during treatment with this*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	product in the SmPC sections 4.2, 4.4 and 4.5. *PIL section 2 advises patients to talk to their doctor if they have unexplained muscle pain, tenderness, weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination.* Additional risk minimization measures: None	
Interstitial lung disease	Routine risk communication: *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Pulmonary symptoms that warrant further investigation are included in the SmPC section 4.4.* *Instructions for treatment interruption, discontinuation, and initiation of appropriate treatment for ILD are included in the SmPC section 4.4.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have suffered from inflammation on their lungs.* *PIL section 2 advises patients to talk to their doctor if they have sudden difficulty in breathing together with a cough or fever.* *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience sudden difficulty in breathing together with a cough or fever, shortness of breath at rest or*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	made worse by exertion, or dry cough that will not go away. Additional risk minimization measures: None	
Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)	Routine risk communication: *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Section 4.4 of the SmPC instructs to promptly evaluate patients if symptoms of thromboembolic events occur or are suspected.* *Section 4.4 of the SmPC instructs to withhold aumolertinib and stabilize the patient before resuming therapy.* *PIL section 2 advises patients to talk to their doctor, pharmacist, or nurse before taking aumolertinib if they have had a blood clot (thrombus) in a blood vessel.* *PIL section 4 advises patients to stop taking aumolertinib and seek medical help if they experience any of the following symptoms: shortness of breath, chest pain, cough with blood, rapid or irregular heartbeat, light headedness, excessive sweating, fever, leg pain or swelling, clammy skin.* Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Specific adverse reaction follow-up questionnaire for Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme Additional pharmacovigilance activities: None
Drug-induced liver injury (DILI) and hepatitis	Routine risk communication: *SmPC sections 4.4* Routine risk minimization activities recommending specific clinical measures to address the risk: *Section 4.4 of the SmPC instructs about monitoring of liver function.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Aumseqa (aumolertinib)

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

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

This summary of the RMP for Aumseqa 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 Aumseqa's RMP.

I. The medicine and what it is used for

Aumseqa is a small-molecule tyrosine kinase inhibitor (TKI). Aumseqa is authorized for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), and the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations (see SmPC for the full indication). It contains aumolertinib as the active substance and it is given by once daily oral administration (two 55 mg tablets/day).

Further information about the evaluation of Aumseqa's benefits can be found in Aumseqa'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 minimize or further characterize the risks

Important risks of Aumseqa, together with measures to minimize such risks and the proposed studies for learning more about Aumseqa'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 PL 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 patient (e.g., 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 periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of Aumseqa 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 Aumseqa. 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 (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	QTc prolongation leading to torsade de pointes and cardiac arrest Creatine phosphokinase (CPK) increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage Interstitial lung disease Venous thromboembolic (VTE) events and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)
Important potential risks	Severe Cutaneous Adverse Reaction (SCARs) and erythema multiforme Drug-induced liver injury (DILI) and hepatitis

II.B Summary of important risks

Important identified risk 1: QTc prolongation leading to torsade de pointes and cardiac arrest	
Evidence for linking the risk to the medicine	Evidence of potential QTc interval prolongation associated with the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China. QTc prolongation is a known side effect of treatment with some EGFR TKIs, notably a TKI which inhibits both HER2 and EGFR and a third-generation EGFR TKI. A concentration-response effect has been observed for both. In the FLAURA clinical study, changes in QTc were reported in a higher percentage of patients treated with a third-generation EGFR TKI (10%) than in the first-generation EGFR TKIs group (5%). Data on one of the first-generation EGFR TKI are suggestive but not conclusive for an effect on QTc. No clinically relevant effect on QTc has been seen in clinical studies of various TKIs including first- and second-generation EGFR TKIs. Although QTc prolongation is an established adverse reaction to a third-generation EGFR TKI, torsade de pointes is rarely reported. Only

	anecdotal cases could be found in the literature, sometimes in patients with other contributing factors.
Risk factors and risk groups	An analysis to identify specific risk factors and risk groups for QTc prolongation has not been conducted for Aumseqa. QTc prolongation itself is associated with an increased risk of sudden cardiac death due to ventricular tachyarrhythmias, notably torsade de pointes. The risk of developing life-threatening arrhythmias from QTc prolongation is difficult to quantify. Although the degree of prolonged QTc is not correlated with the incidence of torsade de pointes and sudden death, longer QTc are likely to be associated with an increased risk of torsade de pointes. In general, QTc prolongation beyond 500 ms is considered clinically important and an indication to stop QT-prolonging drugs. Indirect predisposing factors for QTc prolongation in patients with cancer treated with TKIs include intrinsic intra-patient repolarization variability; comorbid disease; concomitant medications with the potential for drug-drug interactions; and electrolyte disturbances secondary to decreased oral intake, severe nausea, vomiting, or diarrhoea. Additional risk factors are a family history of long QT syndrome or sudden death; heart failure; left ventricular hypertrophy; extreme bradycardia; strenuous physical activity; hypothermia; hypothyroidism; female sex, and increasing age.
Risk minimization measures	Routine risk minimization measures *SmPC sections 4.2, 4.3, 4.4, and 4.8* *PIL sections 2 and 4*

Important identified risk 2: CPK increase, rhabdomyolysis, and other clinical manifestations of muscle and renal damage	
Evidence for linking the risk to the medicine	Evidence of rhabdomyolysis and blood CPK increases linked to the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China. Blood CPK increase is a safety concern for a range of TKIs including EGFR antagonists and a third-generation EGFR TKI. In one recent review, 8 cases (0.08%) of serum CPK elevation were noted in the post-marketing surveillance study of a first-generation EGFR TKI, 4 cases (0.17%) in the international joint Phase 3 study of a second-generation EGFR TKI, and 4 cases (0.7%) in the international joint Phase 3 study of a third-generation EGFR TKI according to the pharmaceutical interview forms. Reports of rhabdomyolysis and other clinical manifestations of muscle damage are much less common than reports of CPK increases with EGFR TKIs. These include a report of rhabdomyolysis following an overdose of a first-generation EGFR TKI and a report of rhabdomyolysis following 3 months of treatment with standard doses of another first-generation EGFR TKI. Rhabdomyolysis has also been reported following

	concurrent treatment with a first-generation EGFR TKI and a statin. Symptomatic myositis associated with elevated CPK in some cases, has also been reported with a third-generation EGFR TKI.
Risk factors and risk groups	An analysis to identify specific risk factors and risk groups for CPK increase, rhabdomyolysis, and other clinical manifestations of muscle damage has not been conducted for aumolertinib. Several factors influence CPK levels in healthy individuals including differences in body size and composition, sex, and ethnicity. Additionally, intense exercising, vigorous work or recreation, and nutritional supplements are associated with moderately elevated blood CPK levels. In theory, any form of muscle damage can initiate rhabdomyolysis. In adults, data show that the most common causes of rhabdomyolysis, other than medicinal drug use, are drug or alcohol abuse, trauma, neuroleptic malignant syndrome, and immobility; therefore, any individual that is subject to any of these may be at increased risk of rhabdomyolysis. Genetic polymorphisms and defects accounting for skeletal muscle diseases increase the risk for episodes of rhabdomyolysis. These defects include enzymes from the glycolysis and glycogenolysis pathway and pentose phosphate pathway, mitochondrial pathways involving fatty acid oxidation, the citric acid cycle, and the mitochondrial respiratory chain, and finally, defects in calcium homeostasis due to mutations in proteins involved in excitation-contraction coupling, myotonias, and skeletal muscle dystrophies.
Risk minimization measures	Routine risk minimization measures *SmPC sections 4.2, 4.4, and 4.8* *PIL sections 2 and 4*

Important identified risk 3: Interstitial lung disease	
Evidence for linking the risk to the medicine	Evidence of interstitial lung disease (ILD) linked to the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China. ILD is a potential safety concern for other EGFR TKIs. Of note, the frequency of ILD is dependent on the diagnostic approach, and the definition and terminology used. ILD is a difficult diagnosis to make, especially in patients with advanced lung cancer. This is compounded by the difficulty in obtaining histological samples to confirm the diagnosis. Frequently, the respiratory symptoms of ILD cannot be distinguished from those of progressive tumor or lower respiratory tract infections. Furthermore, lung radiotherapy can cause symptomatic radiation pneumonitis within 1-6 months after completion. It is estimated that 5-15% of lung cancer patients treated with radiotherapy develop symptoms of radiation pneumonitis. Chemotherapy is also associated with pulmonary toxicities (< 10% of patients), including ILD.

Risk factors and risk groups	Risks factors for developing ILD in general include previous radiation therapy to the lungs, previous chemotherapy treatment, pre-existing parenchymal lung disease, metastatic lung disease, and concomitant pulmonary infection. Additional risk factors for ILD include older age, poor performance status, smoking, a recent diagnosis of NSCLC, reduced normal lung on computed tomography scan, pre-existing ILD, and concurrent cardiac disease. In patients receiving EGFR TKIs, including a third-generation one, the risk of developing ILD appears to be increased with concurrent or recent use of a checkpoint inhibitor. The relationship between potential risk factors for developing pulmonary toxicity (in general) for patients who received aumolertinib treatment, was analyzed in an exploratory fashion (there were too few cases of ILD for a meaningful analysis of this particular event). The following risk factors were identified for pulmonary toxicity: • Male gender • Recent history of radiotherapy and chemotherapy • History of smoking • Age ≥ 55 years old • Performance status > 2 points • Normal lung tissue < 50% on imaging • History of ILD • Emphysema or chronic obstructive pulmonary disease • Lung infection • Short time since diagnosis of cancer (< 6 months) • Co-morbid cardiovascular disorder These risk factors are intuitively risk factors for poor pulmonary function in general and are consistent with known risk factors for the development of ILD.
Risk minimization measures	Routine risk minimization measures *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4*

Important identified risk 4: Venous thromboembolic events (VTE) and complications (e.g. pulmonary embolism, deep vein thrombosis, cerebral infarction/thrombosis)	
Evidence for linking the risk to the medicine	Evidence of VTEs linked to the use of aumolertinib comes from Study HS-10296-12-01, Study HS-10296-03-01 and post-marketing surveillance in China.

	The incidence of VTE is 4- to 7-fold higher in cancer patients compared to non-cancer patients, and the risk of VTE in lung cancer patients is 20-fold higher compared to the general population. Of note, lung cancer patients have one of the highest VTE incidence rates among all tumor types. Chemotherapy is also associated with a 2- to 6-fold increase in the risk of VTE. Some studies report that VTE is a risk associated with the use of first- and second-generation EGFR TKIs, while the association with a third generation TKI in clinical studies remains unclear.
Risk factors and risk groups	An analysis to identify specific risk factors and risk groups for VTE has not been conducted for aumolertinib. In general, cancer patients have a higher risk of developing VTE compared to other patients and the general population, with the primary site of cancer being an important risk factor. Patients with lung cancer are among the ones with the highest risk of VTE. Old age, immobility/inactivity, hospitalization, and comorbidities such as infection, obesity, anaemia, pulmonary disease, renal disease, as well as genetic conditions affecting clotting, all add to the risk of developing VTE. Finally, major surgery, chemotherapy, and certain novel therapeutics such as anti-angiogenic agents are also associated with an increased risk of VTE.
Risk minimization measures	Routine risk minimization measures *SmPC sections 4.4 and 4.8* *PIL sections 2 and 4*

Important Potential risk 1: Severe Cutaneous Adverse Reactions (SCARs) and erythema multiforme	
Evidence for linking the risk to the medicine	Skin toxicity is a well-known risk of treatment with EGFR TKIs. Rare cases of SJS have been reported in patients treated with EGFR TKIs, including first-, second-, and third-generation EGFR TKIs. Specifically, SJS has been reported with a frequency of 0.02% in clinical trials with a third-generation EGFR TKI. Symptoms of a skin reaction consistent with SJS have been reported in the post-marketing setting with aumolertinib.
Risk factors and risk groups	An analysis to identify specific risk factors and risk groups for SJS has not been conducted for aumolertinib. Studies have found that high male hormones, high sebum secretion, and smoking are risk factors for more severe adverse skin reactions in male lung cancer patients. Therefore, these factors may also increase the risk of SJS in the same patient population. Other factors that increase the general risk of developing Stevens-Johnson syndrome include: • Cancer and certain cancer treatments such as chemotherapy.

	• HIV infection. Among people with HIV, the incidence of SJS is about 100 times greater than among the general population. • A weakened immune system. • Previous or family history of Stevens-Johnson syndrome. • Genetic factors, especially when taking concomitant medications for seizures, gout, or mental illness.
Risk minimization measures	None

Important Potential Risk 2: Drug-induced liver injury (DILI) and hepatitis	
Evidence for linking the risk to the medicine	Evidence of hepatotoxicity linked to the use of aumolertinib comes from ongoing clinical studies and post marketing surveillance in China. Hepatotoxicity has been reported for most other EGFR TKIs. The frequency of hepatotoxicity Grade ≥ 2 was 17.2% in patients treated with a first-generation EGFR TKI. The frequency of hepatotoxicity Grade ≥ 3 in patients treated with two first- and one second-generation EGFR TKIs was 5.4%, 18%, and 1.7%, respectively. One case each of drug-induced liver injury (DILI) and Hy's law were reported in the clinical trials.
Risk factors and risk groups	An analysis to identify specific risk factors and risk groups for hepatotoxicity has not been conducted for aumolertinib. Risk factors for hepatotoxicity identified with a first-generation EGFR TKI, were concomitant use of CYP3A4 inducers and co administration of H2-antagonist/proton pump inhibitor (PPI). These increased the frequency of hepatotoxicity by 2.7 and 3.5-fold, respectively. Liver metastasis were a significant risk factor in all study patients with an attributable risk of 46.3%. Age ≥ 65 years was a significant risk factors in NSCLC patients with an attributable risk factor of 71.8%. The use of nivolumab or pembrolizumab immediately before initiation of treatment with a third-generation EGFR TKI has been linked to a significantly higher frequency of Grade ≥ 3 hepatotoxicity in patients with advanced NSCLC. In these situations, it appears that the third-generation EGFR TKI was precipitating or exacerbating the immune-related hepatotoxicity of the checkpoint inhibitor. High rates of severe hepatotoxicity were also reported with concurrent use of one of the two available first-generation EGFR-TKI and pembrolizumab.
Risk minimization measures	Routine risk minimization measures *SmPC section 4.4*

Missing information : None.

II.C Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Aumseqa.

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

There are no studies required for Aumseqa.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Aumseqa (aumolertinib) Specific Adverse Reaction Follow-Up Questionnaire for Severe Cutaneous Adverse Reactions (SCARs) and Erythema Multiforme

You have received this questionnaire because you have reported a Severe Cutaneous Adverse Reaction (SCARs) and/or erythema multiforme with Aumseqa. Please provide additional information below, if available to you. By providing this information, you are actively participating in safety monitoring of Aumseqa use.

Reporter

Name: _____

Address: _____ City: _____ Country: _____

Phone: _____ Email: _____

Relationship to patient: ☐ Physician (if yes: Dermatologist? ☐ Yes ☐ No)

☐ Nurse ☐ Pharmacist

☐ Other (please specify) _____

Patient

Initials: _____ Gender: _____

Age: _____ Weight: _____

Previous relevant history and concurrent disorders:

☐ Skin diseases (if yes, please specify: _____)

☐ Other diseases (if yes, please specify: _____)

☐ Allergic reactions (if yes: to what? _____)

☐ Asthma ☐ Allergic rhinitis ☐ Atopic dermatitis

Other relevant information: _____

_____

_____

_____

Adverse Reaction

Date of onset: _____

Diagnosis - type of skin disorder:

☐ Stevens-Johnson Syndrome (SJS)
☐ Toxic Epidermal Necrolysis (TEN)
☐ Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
☐ Acute Generalised Exanthematous Pustulosis (AGEP)
☐ Generalized Bullous Fixed Drug Eruption (GBFDE)
☐ Erythema Multiforme (EM)

☐ Other: _____

Type of skin disorder:

☐ Macular or maculopapular rash ☐ Scarlatiniform rash
☐ Exfoliative dermatitis ☐ Bullous or vesiculous eruption
☐ Purpura (platelet count needed)
☐ palpable purpura ☐ necrotic purpura
☐ visceral involvement: ☐ Kidney ☐ GI tract
☐ Nerves ☐ Others: _____

Associated symptoms:

☐ Pruritus ☐ Contact dermatitis or eczematiform eruption
☐ Urticaria ☐ Cutaneous angioedema ☐ Mucosal angioedema
☐ Burning or pain ☐ Oozing ☐ Edema
☐ Infection ☐ Fever ☐ Arthralgia/myalgia
☐ Nodes enlargement

Associated signs:

☐ Dyspnea ☐ Tachycardia
☐ Hypotension ☐ Anaphylactic shock

☐ Other skin disorders (specify): _____

Extent of the rash: ☐ ≥50% of the body surface area ☐ <50% of the body surface area

Did the subject undergo skin biopsy? ☐ Yes ☐ No
If "Yes", select one option:
☐ Result suggestive of a severe cutaneous adverse reaction (SCAR), such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
☐ Result not suggestive of a severe cutaneous adverse reaction (SCAR)
☐ Inconclusive result

Has the subject had facial swelling during the event? ☐ Yes ☐ No ☐ Unknown

Has the subject had enlarged lymph nodes? ☐ Yes ☐ No ☐ Unknown

Were atypical lymphocytes detected at some point during the hypersensitivity event? ☐ Yes ☐ No

Did the subject have eosinophilia (>0.5×10^9/l or 500/µL) detected at some point during the evolution of the hypersensitivity event? ☐ Yes ☐ No

Have infectious causes been excluded? Has an infection screening been conducted due to the events of fever + rash (e.g. blood count, CRP, blood culture, chest X-ray, urinalysis + urine culture)?
☐ Yes ☐ No ☐ Unknown
If "Yes": description of tests: _____

Did the subject have evidence of internal organ involvement? Select in case there is evidence of other organs being affected concomitantly to the event of rash, resulting in liver, renal, cardiac, or pulmonary function alteration: ☐ Yes ☐ No ☐ Unknown
If "Yes": select all that apply:

☐ AST/ALT increase
☐ Renal involvement (creatinine and/or BUN increase, urinalysis alteration)
☐ Cardiac involvement (clinical, laboratory or echocardiographic evidence of myocarditis)
☐ Lung involvement (clinical or radiological evidence of pneumonitis)
☐ Other (specify): ____

Other relevant information or investigations: ____

____

Description of the lesions on the skin:

☐ localized ☐ disseminated
Number of lesions: ☐ <10 ☐ 10 to 30 ☐ >30

Main location(s): ____

☐ Mucosal lesions (specify): ____

☐ Nail/hair lesions (specify): ____

General description of lesions: ____

____

Concomitant therapy:

Drug	Route	Daily dose	Duration	Dates of administration Beginning	End	Indication

Suspected Drug

Name: ______________________________ Indication: ____________________________________

Daily Dose: ________________________ Route of administration: _________________________

Date beginning: ________________ Date end: _______________ Duration: _________________

Changes to drug administration after beginning of Severe Cutaneous Adverse Reaction:
☐ Stopped ☐ Continued (same dose) ☐ Reduced dose
☐ Other: ____
Immediate result:

☐ Improvement ☐ Aggravation
☐ No change ☐ Uninterpretable

Readmistration of the drug? ☐ Yes ☐ No
If "Yes": Dose: _____ Date: _____
Recurrence of the reaction? ☐ Yes ☐ No ☐ Uninterpretable
Other relevant information: _____

Previous therapy with the same drug? ☐ Yes, date: _____ ☐ No
If "Yes": Safety issues: _____

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.