EU Risk Management Plan for Sugemalimab

RMP version to be assessed as part of this application:

RMP Version number: 2.0

Data lock point for this RMP: 22 November 2021

Date of final sign-off: See e-signature date

Rationale for submitting an updated RMP:

This EU RMP (Version 2.0) has been updated to add a new indication (sugemalimab as monotherapy is indicated for the treatment of unresectable stage III NSCLC with no sensitising EGFR mutations, or ALK, ROS1 genomic tumour aberrations in adults whose tumours express PD-L1 on ⩾ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiotherapy), see Part I.

Summary of significant changes in this RMP:

Part I:	Updated to include a new indication and dosage regimen.
Part II SI:	Added epidemiology data relevant to the new indication.
Part II SIII:	Added exposure data in support of the new indication.
Part II SIV:	Added exposure data in support of the new indication.
Part II SV:	Updated post marketing exposure data to reflect latest available information.
Part II SVII	Added clinical data in support of the new indication.
Part VI:	Updated to reflect the changes outlined above.
Part VII:	Updated the wording of Annex 6

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

RMP Version Number	Approved With Procedure	Date of Approval (EC decision date)
1.0	EMEA/H/C/006088/0000	24-July-2024

QPPV name: Carmen Arques

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

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Abbreviation	Definition of term
ADA	Anti-drug Antibody
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
CD	Cluster of Differentiation
ChT	Chemotherapy
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPS	Combined Positive Score
CRT	Chemoradiotherapy
CTLA4	Cytotoxic T Lymphocyte-associated Antigen-4
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
G/GEJ	Gastric or Gastroesophageal Junction
GVP	Good Pharmacovigilance Practices
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IgG4	Immunoglobulin G4
IL	Interleukin
ILD	Interstitial Lung Disease
INN	International Non-proprietary Name
imAE	Immune-mediated Adverse Event
irAE	Immune-related Adverse Event

Abbreviation	Definition of term
LAG3	Lymphocyte Activation Gene-3
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NOAEL	No-observed-adverse-effect Level
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OS	Overall Survival
PC	Patient Card
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PFS	Progression-free Survival
PK	Pharmacokinetics
PL	Package Leaflet
PopPK	Population PK
PT	Preferred Term
Q3W	Every 3 Weeks
QPPV	Qualified Person Responsible for Pharmacovigilance
RET	Rearranged During Transfection
RMP	Risk Management Plan
ROS1	c-Ros Oncogene 1
RR	Relative Risk
RT	Radiotherapy
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	Standard of Care
TIM3	T cell Immunoglobulin domain and Mucin domain-3
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States

Part I: Product(s) overview

Table Part I:1: Product(s) overview

Active substance(s) (INN or common name)	Sugemalimab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies, PD-1/PD-L1 (Programmed cell death protein 1/death ligand 1) inhibitors (ATC code: L01FF11)
Marketing Authorisation Applicant	CStone Pharmaceuticals Ireland Limited
Medicinal products to which this RMP refers	Sugemalimab
Invented name(s) in the EEA	Cejemly
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Sugemalimab is a recombinant fully human anti-PD-L1 mAb (IgG4 isotype).
	Summary of mode of action: Sugemalimab is a fully human immunoglobulin G4 monoclonal antibody. It specifically binds to PD-L1, thus blocking its ligation with PD-1. PD-L1, when expressed on tumour cells and tumour-infiltrating- immune cells, can contribute to the inhibition of an anti-tumour immune response. Binding of PD-L1 to the PD-1 and CD80 (B7.1) receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses without inducing antibody dependent cell-mediated cytotoxicity.
	Important information about its composition: Sugemalimab is supplied as a sterile, preservative-free, colourless to light yellow, clear to slightly opalescent, isotonic aqueous concentrate for solution for intravenous infusion, containing sugemalimab 600 mg. Each 20 mL vial contains 600 mg sugemalimab (30 mg/mL).
Hyperlink to the Product Information	Cejemly Product Information (Module 1.3.1)
Indication(s) in the EEA	Current: Sugemalimab in combination with platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-

	small-cell lung cancer (NSCLC) with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations.
	Proposed: Cejemly as monotherapy is indicated for the treatment of unresectable stage III NSCLC with no sensitising EGFR mutations, or ALK, ROS1 genomic tumour aberrations in adults whose tumours express PD-L1 on ⩾ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiotherapy.
Dosage in the EEA	Current: For squamous cell carcinoma: Sugemalimab 1200 mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) is infused intravenously over 60 minutes followed by intravenous infusion of carboplatin and paclitaxel on day 1 for up to 4 cycles every 3 weeks. Thereafter, sugemalimab 1200mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) is administered every 3 weeks for the duration of therapy. For non-squamous cell carcinoma: Sugemalimab 1200 mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) is infused intravenously over 60 minutes followed by intravenous infusion of carboplatin and pemetrexed on day 1 for up to 4 cycles every 3 weeks. Thereafter, sugemalimab 1200mg (for individuals weighing 115 kg or less) or 1500 mg (for individuals weighing more than 115 kg) and pemetrexed are administered every 3 weeks for the duration of therapy.
	Proposed: For Stage III NSCLC consolidation treatment： Sugemalimab 1200 mg (for individuals weighing 115 kg or less) every 3 weeks or 1500 mg (for individuals weighing more than 115 kg) every 3 weeks
Pharmaceutical form(s) and strengths	600 mg concentrate for solution for infusion in a 20 ml vial (30 mg/mL).
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II:Safety specification

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

Non-Small-Cell Lung Cancer (NSCLC)

Incidence:

With almost 2.5 million new cases and over 1.8 million deaths worldwide, lung cancer is the leading cause of cancer morbidity and mortality in 2022, responsible for close to one in eight (12.4%)cancers diagnosed globally and one in five (18.7%) cancer deaths (Freddie 2024) .

According to the European Cancer Information System, lung cancer represents the second most common form of cancer occurring in men and the third most common form of cancer occurring in women in the EU in 2022(ECIS 2022 factsheet). Lung cancer also contributed most common cancer causes of death in the EU. Across the EU-27, lung cancer is the leading cause of death among all cancers for men (22.9%) and the second-leading cause for women (15.3%) behind breast cancer (16.7%) with an estimated about 253,000 deaths in 2022 (ECIS Data explorer) .

Around 49,200 people are diagnosed with lung cancer in England, Scotland, and Wales each year, and lung cancer is the leading cause of cancer death for both men and women in the UK, with more than 34,000 deaths from the condition each year (Cancer Research UK) .

Prevalence:

NSCLC is the most common type of lung cancer, accounting for 85% of all lung cancers (Duma 2019). The most common NSCLC histologies are squamous and non-squamous cell lung cancers (Duma 2019). An estimated 57,200 people who had previously been diagnosed with lung cancer were alive in the UK at the end of 2010 (Cancer Research UK).

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

It is estimated that the global incidence and mortality rate of lung cancer will continue an upward trend, with mortality rates projected to exceed those for breast cancer in women (Goodarzi 2019; Martín-Sánchez 2018). Age is a key factor affecting the occurrence and survivability of lung cancer (Cancer Research UK, Thandra 2021).

Smoking is a major risk factor for lung cancer worldwide, attributing to an estimated 80% and 90% of cases in women and men, respectively (World Cancer Research Fund International). In the EU, approximately 50% of all cancers attributed to smoking are lung cancers (Cancer Prevention Europe). The UK reports a higher incidence of smoking-related lung cancers with rates of approximately 72% (Cancer Research UK).

The carcinogenic effects of air pollution have also attracted widespread attention in recent years, and prolonged exposure to high-density fine particulate matter may increase the risk of lung cancer (Brauer 2012, Chen 2015, Berger 2017). In the UK, 8% of lung cancer cases are attributed to air pollution (Cancer Research UK). Several occupational environmental carcinogens increase the incidence of lung cancer including by-products of aluminium products, arsenic, asbestos, bis-chloromethane, chromium compounds, coke oven gas, mustard gas, nickel containing impurities, and vinyl chloride (Shankar 2019). Approximately 13% of patients with lung cancer in the UK have a history of workplace exposure (Cancer Research UK). Long-term exposure to beryllium, cadmium, silicon, formalin and other substances will also increase the incidence of lung cancer. Air pollution, especially industrial waste gas, can cause lung cancer. Radiation exposure (including radon in the home environment) is also a potential

cause of lung cancer (McCormack 2012, Poinen-Rughooputh 2016). In the UK, 5% of lung cancers are attributed to ionising radiation (Cancer Research UK). Pneumonia, emphysema and COPD can also increase the risk of lung cancer (Cancer Research UK). In patients with pulmonary tuberculosis and bronchiectasis, the bronchial epithelium may metamorphose in rare cases into squamous epithelium and become cancerous during chronic infection.

The main existing treatment options:

Specific therapies and procedural interventions vary depending on the disease stage, tumour size and location, histology, age, the patient's condition, comorbidities, and genomic alterations(National Cancer Institute).While the long-term survival for patients with NSCLC remains poor, in recent years, immunotherapy has emerged as a promising clinical treatment. Today, immune checkpoint inhibitors pembrolizumab, nivolumab, durvalumab, and atezolizumab are considered SOC in the EU and UK and in various stages of disease.

Metastatic (Stage IV) NSCLC

At present, for adult patients with metastatic NSCLC lacking an actionable oncogenic driver, the European Society for Medical Oncology Clinical Guidelines recommend treatment with PD-1/PD-L1 immune checkpoint inhibitors monotherapy or in combination with chemotherapy for the firstline or secondline, including nivolumab, pembrolizumab, or atezolizumab(Planchard 2020). Sugemalimab has been approved by the European Commission on 24 Jul 2024 in combination with platinum-based chemotherapy for the firstline treatment of adults with metastatic nonsmallcell lung cancer (NSCLC) with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations(Cejemly, EMA).

Per NICE guidelines, for patients with metastatic NSCLC lacking an actionable oncogenic driver, the SOC is pembrolizumab, a PD-1 inhibitor, combined with a platinum-based chemotherapy doublet (NICE 2021), with the specific doublet dependent upon whether the individual has squamous or non-squamous histology. There are other immune checkpoint inhibitors recommended either as monotherapy or in combination with other therapies based on PD-L1 expression level. Currently, NICE recommends treatment with PD-1/PD-L1 immune checkpoint inhibitors nivolumab (PD-L1 > 1%), pembrolizumab (PD-L1 > 1%), and atezolizumab (no PD-L1 expression needed) for metastatic NSCLC. The 3 immune checkpoint inhibitors all meet NICE's criteria to be considered a life-extending end-of-life treatment compared to chemotherapy alone. Sugemalimab has also been approved by MHRA on 30 October 2024 for the same indication (Cejemly, MHRA).

Locally advanced (Stage III) NSCLC

Per the ESMO Guidelines on early and locally advanced NSCLC, surgical resection, where possible, is recommended in combination with platinum-based doublets or chemoradiotherapy to treat medically fit patients with early-stage disease (Pentheroudakis, 2020).

The EU has established well-defined diagnostic and management algorithms for locally advanced stage III NSCLC. The treatment of stage III NSCLC is the most complex of all NSCLCs and an experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision including surgery, radiotherapy (RT) and chemotherapy (ChT). For resectable locally advanced NSCLC (LA-NSCLC), surgery followed by adjuvant ChT is recommended and induction ChT followed by surgery or induction chemoradiotherapy (CRT) followed by surgery are options. (Neo)adjuvant anti PD(L)-1 checkpoint inhibitors are currently being evaluated in addition to current standard of care. For unresectable LA-NSCLC, concurrent CRT is the treatment of choice in patients. If concurrent CRT is not possible—for any reason—sequential ChT followed by definitive radiotherapy (RT) represents a valid and effective alternative (Postmus, 2017).

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At present, the consolidation administration of the immune checkpoint inhibitor, durvalumab, after the end of CRT is recommended in patients with unresectable stage III NSCLC whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following palatinum-based ChT (Pentheroudakis, 2020). For patients with stage III NSCLC who have not progressed after sequential chemoradiotherapy, no consolidation therapy has been established. This highlights a significant unmet medical need for patients with stage III NSCLC whose disease has not progressed following sequential chemoradiotherapy.

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

The prognosis and survival for patients with advanced or metastatic lung cancer remains poor. It remains the leading cause of global cancer deaths (ECIS Data explorer). The EU estimated approximately 257,000 male and female deaths were attributed to lung cancer in 2020 (ECIS 2022 factsheet). In the UK, lung cancer accounts for 21% of all cancer deaths, with approximately 35,000 deaths from the condition each year (Cancer Research UK). The survival of patients with lung cancer varies greatly according to the cancer stage, and the 5-year survival rate of patients with Stage IV disease in the UK (2013-2017) was only 2.9% (3.4% in females and 2.3% in males) (Cancer Research UK). Therefore, the prevention and treatment of lung cancer remains a major mission to be solved urgently.

Important co-morbidities:

Co-morbidities are common in patients with cancer and may affect the development of the disease, stage at the time of diagnosis, treatment choice and treatment outcome (Islam 2015). Among all patients with lung cancer, 74% have one or more co-morbidity, and most of them are related to tobacco (Leduc 2017). These include:

- COPD:
  - COPD is closely related to lung cancer, which is mainly attributed to the common risk factors of smoking exposure, which is found in 85% to 90% of patients diagnosed with COPD or lung cancer. COPD is associated with poor postoperative outcome in patients with early NSCLC.
- Cardiovascular disease:
  - Approximately 23% of patients with lung cancer will develop cardiovascular disease, with smoking being one of the most important risk factors. Heart failure, myocardial infarction, and arrhythmia are associated with poor outcome, while baseline hyperlipidaemia is related with better outcome.
- Diabetes mellitus:
  - Approximately 8% to 18% of patients with cancer have diabetes. Lung cancer and diabetes have common risk factors such as age, diet, and smoking. Diabetes is associated with higher mortality in patients with lung cancer, which can increase the risk of cardiovascular events, postoperative complications, and susceptibility to infection.
- Renal insufficiency:
  - Chronic kidney disease is common in patients with lung cancer. As > 30% of patients with lung cancer are elderly, a population in which chronic kidney disease is more common, this has an impact on the survival of patients with early and late-stage lung cancer.
- Tuberculosis:
  - Studies have confirmed that patients with previously diagnosed tuberculosis have a higher incidence of adenocarcinoma, which is a poor prognostic factor for the survival of patients with lung cancer.
- Human immunodeficiency virus and acquired immunodeficiency syndrome.
- Hepatitis B or C.

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

Key safety findings from non-clinical studies and relevance to human usage are summarised in Table Part II: Module SII.1.

Table Part II: Module SII.1: Key safety findings from nonclinical studies and relevance to human use

Study Type	Important Nonclinical Findings	Relevance to Human Use
Single-dose maximum tolerated dose toxicity study	Administration of sugemalimab to cynomolgus monkeys by a single intravenous infusion at dose levels of 100, 300, and 1,000 mg/kg followed by a 14-day observation period was well tolerated with no findings on mortality, clinical signs, body weight, food consumption, macroscopic observations or organ weights. Under the conditions of the study, the maximum tolerated dose was no less than 1,000 mg/kg.	Administration of sugemalimab in this setting was well tolerated and was similarly well tolerated in single-dose studies in humans.
Repeated-dose toxicity studies	In a 4-week repeat-dose toxicity study, administration of sugemalimab to cynomolgus monkeys was well tolerated and did not result in any treatment-related effects on mortality, clinical signs, local irritation, body weight, food consumption, body temperature, safety pharmacology (electrocardiography, blood pressure, heart rate, and respiration examinations), immunology, clinical pathology, or histopathology. A possible treatment-related retinal depigmentation could not be ruled out in 1 female monkey that received 200 mg/kg/week of sugemalimab. The NOAEL for the study was 200 mg/kg/week. Similar to the 4-week toxicity study, the dose level of 200 mg/kg/week was well tolerated in cynomolgus monkeys in a 26-week repeat-dose toxicity study. One female animal that received 200 mg/kg had a medium-sized right eye focal cornea opacity, for which a potential test article relationship could not be ruled out. The NOAEL for the study was 200 mg/kg/week, the highest dose tested. No animals were detected as positive for anti-sugemalimab antibodies during either study.	Administration of sugemalimab in this setting was well tolerated. Similar evidence of immune-mediated ocular toxicity was observed in humans in clinical trials. Immune-mediated ocular toxicity is included as a subtype within the important identified risk of immune-mediated adverse reactions[1] for sugemalimab (refer to Part II: Module SVII).

[1] The terminology "immune-mediated adverse reaction (imAE)" in this RMP is equivalent to "immune-related adverse reaction (irAE)" in other product relevant documents.

Study Type	Important Nonclinical Findings	Relevance to Human Use
Reproductive and developmental toxicity	Animal reproductive and developmental toxicity studies have not been conducted with sugemalimab. However, blockade of PD-L1 signalling in murine models of pregnancy has been shown to disrupt tolerance to the foetus and to increase foetal loss. Reproductive and developmental toxicity has been listed as an important potential risk for other anti-PD-1/PD-L1 products.	It is known that human IgG4 can pass through the placental barrier. Sugemalimab is a recombinant fully human IgG4 mAb against PD-L1. Therefore, sugemalimab may be transported to the developing foetus from the mother. Based on its mechanism of action and data from animal studies, exposure to sugemalimab during pregnancy may have adverse effects in pregnancy maintenance and may increase the risk of developing immune-mediated disorders or altering the normal immune response in the foetus. Sugemalimab is not recommended during pregnancy and in women of childbearing potential not using contraception. Female patients of childbearing potential receiving sugemalimab should use reliable contraception methods during treatment and for at least 4 months after the last dose of sugemalimab.

Study Type	Important Nonclinical Findings	Relevance to Human Use
Genotoxicity Carcinogenicity	Biologics like sugemalimab are designed for highly specific receptor targeting. As such, certain nonclinical studies aimed at characterising the off-target effects seen more commonly in the setting of small molecule drug development are not warranted. For this reason, the nonclinical safety programme did not include genotoxicity or carcinogenicity studies. Mutational or genotoxicity studies are likewise unnecessary; sugemalimab cannot interact with nucleic acid material. Long-term studies to evaluate carcinogenicity are generally not required for therapeutics aimed at the treatment of late stage or advanced disease cancer patients. This approach is in alignment with ICH S6 and S9 guidelines.	Not applicable.
Safety pharmacology, including: • cardiovascular system, including potential effect on the QT interval • nervous system	Safety pharmacological parameters (cardiovascular and respiratory systems) were evaluated in the 4- and 26-week repeat-dose toxicity studies in cynomolgus monkeys, while central nervous system findings were evaluated in the 26-week repeat-dose study. Sugemalimab was not associated with any cardiovascular, respiratory, or neurological changes at intravenous infusion doses of 30, 75, and 200 mg/kg once weekly.	No significant toxicity findings were seen at any dose, thus the NOAEL in both studies were 200 mg/kg/week. The exposure margin of the NOAEL in the 26-week study to the proposed clinical dose (1,200 mg or 1,500mg) is > 8-fold.

Study Type	Important Nonclinical Findings	Relevance to Human Use
Immunotoxicity/ immunogenicity	Immunotoxicity/immunogenicity was evaluated in the 4- and 26-week repeat-dose toxicity studies in cynomolgus monkeys, including ADA detection, lymphocyte phenotyping, cytokine, immunoglobulin and complement analysis. There were no treatment-related effects on ADA, lymphocyte subpopulations (peripheral blood and immune organs), cytokines, immunoglobulins, or complement.	In pivotal Study CS1001-302, 44 (14.2%) participants were ADA positive postbaseline, with an ADA positive case (rate) of sugemalimab induction of 26 (8.4%), positive case/rate of drug enhancement of 2 (0.6%), and overall, ADA positive rate of drug of 9.0% in the sugemalimab group. In pivotal Study CS1001-301,17 (6.7%) participants were ADA positive postbaseline, the positive participants /rate of CS1001 drug-induced ADA was 13 (5.1%), the positive subjects/rate of drug-enhanced ADA was 1 (0.4%), and the overall positive rate of drug-induced ADA was 5.5% in the sugemalimab group. An analysis of safety profile by ADA positive/negative status concluded that there was no evidence that the presence of ADA had any potential impact on safety of sugemalimab.
Other toxicity-related information or data	Local irritation at the intravenous infusion site was evaluated in the 4- and 26-week repeat-dose toxicity studies in cynomolgus monkeys. Sugemalimab did not cause local irritation when administered via intravenous infusion in cynomolgus monkeys. Sugemalimab showed no indication of anaphylaxis when administered to guinea pigs. In an *in vitro* haemolysis study, sugemalimab was not haemolytic and did not induce clotting in rabbit red blood cells. Tissue cross reactivity studies in human, rat, and cynomolgus monkey only identified positive sugemalimab cross-reactivity with human trophoblasts within the placenta.	Hypersensitivity to the active substance or to any of the product excipients is a contraindication.

Part II: Module SIII - Clinical trial exposure

The sugemalimab clinical development programme was initiated in October 2017, with clinical studies evaluating sugemalimab in adults for a variety of haematologic and solid tumour oncology indications, both as monotherapy and as combination therapy. Indications under clinical development include Stage III (locally advanced/unresectable) and Stage IV (metastatic) NSCLC, as well as extra-nodal natural killer/T cell lymphoma, classic Hodgkin lymphoma, gastric cancer, gastro-oesophageal junction adenocarcinoma, and oesophageal carcinoma. The clinical trial exposure is presented for the clinical trial datasets/indications that are included in this RMP.

In the EU/EEA, the approved indication and the newly proposed indication are as follows:

- Sugemalimab in combination with platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small-cell lung cancer (NSCLC) with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations. (Pivotal **Study CS1001-302**)
- Sugemalimab as monotherapy is indicated for the treatment of unresectable stage III NSCLC with no sensitising EGFR mutations, or ALK, ROS1 genomic tumour aberrations in adults whose tumours express PD-L1 on ⩾ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiotherapy. (Pivotal **Study CS1001-301**)

Sugemalimab in combination with chemotherapy

In pivotal **Study CS1001-302**, all participants were of Asian (Chinese) ethnicity and received either a fixed dose of 1,200 mg sugemalimab intravenous infusion, Q3W in combination with platinum-based chemotherapy or placebo in combination with platinum-based chemotherapy. This was a multicentre, randomised, placebo-controlled, double-blind, Phase 3 study of platinum-based chemotherapy with or without sugemalimab in Stage IV NSCLC. A total of 320 participants with metastatic NSCLC have been treated with sugemalimab in combination with platinum-based chemotherapy.

Bridging information from Asian to non-Asian participants is provided by PK from Study CS1001-102 (a US study) and PopPK and exposure-response analyses. Study CS1001-102 evaluated 2 dose levels of sugemalimab sequentially (10 mg/kg intravenous Q3W and 1,200 mg fixed dose intravenous Q3W) in US participants with advanced solid cancers. The PK of sugemalimab in US participants with advanced solid tumours were comparable with that in Chinese participants (Study CS1001-101). In the PopPK and exposure-response analyses, simulations determined that there was no difference in median progression-free survival (Investigator assessed) or median OS between Asian and non-Asian participants. The PopPK analysis showed exposure to sugemalimab decreased with body weight. The subgroup population of subjects weighing more than 80 kg (n=58) from several studies was analysed and a comparative analysis of exposure metrics, including Cmax, C1, Ctrough, C1, and AUC_T, C1, was conducted using the population from Study CS1001-302 as a reference. Simulations showed a comparable exposure to that in study CS1001-302 is achieved with a dose of 1,200 mg Q3W in subjects weighing ≤115 kg, and a dose of 1,500 mg Q3W in subjects weighing >115 kg.

The safety of sugemalimab in combination with chemotherapy has been evaluated in 435 participants who received at least one dose of sugemalimab 1,200 mg intravenous Q3W in combination with chemotherapy (sugemalimab chemotherapy combination safety pool) in clinical studies, including 320 participants from the pivotal Study CS1001-302 and 115 participants from Study CS1001-101b (Total

435 participants) [2]. Summaries of exposure by duration, age group, and sex are presented for these 435 participants in Table Part II: Module SIII.1 and Table Part II: Module SIII.2, respectively.

Table Part II: Module SIII.1: Duration of exposure (435 participants received sugemalimab + chemotherapy)

Duration of Exposure (Months)	Sugemalimab + Chemotherapy	
	Number of Participants Exposed	Cumulative Exposure (Person-Years)
< 1	22	1.164
1 to < 3	66	11.001
3 to < 6	88	34.96
6 to < 9	79	48.999
9 to < 12	38	33.358
12 to < 15	17	18.861
15 to < 18	14	19.039
18 to < 21	23	37.123
≥ 21	88	194.513
Total	435	399.017

Note: The cumulative exposure in person years = Sum (Total Treatment Duration (Days)) / 365.25

Table Part II: Module SIII.2: Duration of exposure by age group and sex (435 participants received sugemalimab + chemotherapy)

Age Group (Years)	Sugemalimab + Chemotherapy					
	Number of Participants Exposed			Cumulative Exposure (Person-Years)		
	M	F	Total	M	F	Total
<65	205	69	274	198.565	63.715	262.281
≥65	137	24	161	117.637	19.099	136.736
65 - 74	135	23	158	114.464	18.541	133.005
≥75	2	1	3	3.173	0.559	3.732
75 - 84	2	1	3	3.173	0.559	3.732
≥85	0	0	0	0.000	0.000	0.000
Total	342	93	435	316.203	82.815	399.017

Note: The cumulative exposure in person years = Sum (Total Treatment Duration (Days)) / 365.25
F = female; M = male.

Sugemalimab monotherapy

In pivotal Study CS1001-301, all participants were of Asian (Chinese) ethnicity and received a fixed dose of 1,200 mg sugemalimab intravenous infusion, Q3W. This was multicentre, randomised, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy, safety, PK profile, and immunogenicity of sugemalimab as consolidation therapy versus placebo in participants with locally advanced or unresectable stage III NSCLC whose disease had not progressed after prior concurrent or sequential chemoradiotherapy. A total of 255 participants have been treated with sugemalimab in monotherapy. Exposure-efficacy simulations showed a comparable exposure to that in study CS1001-301 is achieved

[2] Data cut-off date: pivotal study CS1001-302, 22NOV2021; CS1001-101b,16AUG2021.

with a dose of 1,200 mg Q3W in subjects weighing ≤115 kg, and a dose of 1,500 mg Q3W in subjects weighing >115 kg.

The safety of sugemalimab monotherapy has been evaluated in 568 participants who received at least one dose of sugemalimab 1,200 mg intravenous Q3W (sugemalimab monotherapy safety pool) in clinical studies, including 255 participants from the pivotal Study CS1001-301 , studies providing supportive safety data as follows:45 participants from Study CS1001-302 (crossover phase), 95 participants from Study CS1001-101a/b, 12 participants from Study CS1001-102, 80 participants from Study CS1001-201, and 81 participants from Study CS1001-202 (total 568 participants[3]) . Summaries of exposure by duration, age group, and sex are presented for these 568 participants in Table Part II: Module SIII.3 and Table Part II: Module SIII.4, respectively.

Table Part II: Module SIII.3: Duration of exposure (568 participants received sugemalimab monotherapy)

Duration of Exposure (Months)	Sugemalimab monotherapy	
	Number of Participants Exposed	Cumulative Exposure (Person-Years)
< 1	41	2.220
1 to < 3	138	24.093
3 to < 6	122	47.485
6 to < 9	103	62.661
9 to < 12	38	33.073
12 to < 15	36	40.298
15 to < 18	33	45.791
18 to < 21	20	32.827
≥ 21	37	84.279
Total	568	372.728

Table Part II: Module SIII.4: Duration of exposure by age group and sex (568 participants received sugemalimab monotherapy)

Age Group (Years)	Sugemalimab monotherapy					
	Number of Participants Exposed			Cumulative Exposure (Person-Years)		
	M	F	Total	M	F	Total
<65	332	99	431	228.074	64.101	292.175
≥65	110	27	137	64.370	16.183	80.553
65 - 74	108	22	130	62.930	13.807	76.736
≥75	2	5	7	1.440	2.376	3.817
75 - 84	2	5	7	1.440	2.376	3.817
≥85	0	0	0	0.000	0.000	0.000
Total	442	126	568	292.444	80.285	372.728

[3] Data cut-off date: pivotal study CS1001-301, 08Mar2021. Studies providing supportive safety data: Study CS1001-302 (crossover phase), 22 Nov2021; Study CS1001-101a/b, 16Aug2021; Study CS1001-102, 08Feb2021; Study CS1001-201, 10Nov2021; CS1001-202: 19Feb2020.

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

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

Study CS1001-302 was a randomised, placebo-controlled, Phase 3 pivotal study conducted in China that assessed the efficacy and safety of sugemalimab when combined with platinum-based chemotherapy for first-line treatment of adult participants with Stage IV squamous or non-squamous NSCLC.

Study CS1001-301 was a multicentre, randomised, double-blind, placebo-controlled, Phase 3 pivotal study to evaluate the efficacy, safety, PK profile, and immunogenicity of sugemalimab as consolidation therapy versus placebo in participants with locally advanced or unresectable stage III NSCLC whose disease had not progressed after prior concurrent or sequential chemoradiotherapy.

Important exclusion criteria from these two pivotal studies are discussed below：

Pregnant and lactating women

Reason for exclusion: Exposure to sugemalimab during pregnancy may not only increase the risk of miscarriage and foetal loss, but also increase the risk of immune-mediated disorders or alters normal immune response in the foetus.

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

Rationale: There are no data on the use of sugemalimab in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted with sugemalimab. However, blockade of PD-L1 signalling in murine models of pregnancy has been shown to disrupt tolerance to the foetus and to increase foetal loss. It is also unknown whether sugemalimab is secreted in human milk. In SmPC Section 4.6, use of sugemalimab is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of childbearing potential must be advised to avoid pregnancy during treatment with sugemalimab. Female patients of childbearing potential receiving sugemalimab should use reliable contraception methods during treatment and for at least 4 months after the last dose of sugemalimab.

Patients with moderate or severe hepatic/renal impairment

Reason for exclusion: Participants needed to meet the following inclusion criteria: kidney parameters: Serum creatinine serum < 1.5 X ULN or serum creatinine clearance rate ≥ 40 mL/min (according to Cockcroft-Gault equation; creatinine clearance is only calculated if serum creatinine > 1.5 X ULN) (Study CS1001-301). Serum creatinine clearance creatinine clearance rate ≥ 50 mL/minute (estimated from Cockcroft-Gault formula) (Study CS1001-302).

For liver parameters, inclusion criteria included total bilirubin ≤1.5 X ULN (this item did not apply to participants with Gilbert' s Syndrome; enrolment was decided after discussion with the sponsor) and AST and ALT ≤3 X ULN (Study CS1001-301) or ≤2.5 X ULN (≤5 X ULN for participants with hepatic metastasis) (Study CS1001-302).

This exclusion criterion was established to minimise the potential confounding factors for evaluation of the efficacy and safety of sugemalimab.

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

Rationale: Sugemalimab is catabolised through non-specific pathways and metabolism does not contribute to its clearance. The effect of hepatic impairment on the sugemalimab PK was evaluated using PopPK analyses. Covariate analysis indicated no statistically significant effect of markers of liver function

(AST, ALT, and total bilirubin) on sugemalimab exposure. The SmPC Section 4.2 states that sugemalimab must be administered with caution in patients with moderate or severe hepatic/renal impairment.

History of Interstitial Lung Disease, Pneumonitis or Uncontrolled Systemic Diseases, including Pulmonary Fibrosis, Acute Lung Diseases, Acute Infection.

Reason for exclusion: Immune-mediated pneumonitis has been observed with the use of immune checkpoint inhibitors. This exclusion criterion was established as a precautionary safety measure, and to minimise potential confounding factors for evaluation of the safety of sugemalimab.

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

Rationale: These patients may benefit from treatment with sugemalimab; however, such conditions and associated therapies may confound efficacy and safety assessment of the study and were therefore excluded. Immune-mediated pneumonitis (including different types of pneumonitis) is included as a subtype within the important identified risk of immune-mediated adverse reactions for sugemalimab. The details are presented in Part II: Module SVII. Pneumonitis (including pneumonitis, immune-mediated lung disease, interstitial lung disease) is listed as an adverse reaction in the SmPC Section 4.8, and recommendations for sugemalimab dose modification in the event of immune-mediated pneumonitis and precautions for use are included in SmPC Sections 4.2 and 4.4.

A history of inflammatory bowel disease or active inflammatory bowel disease (for example Crohn's disease or ulcerative colitis)

Reason for exclusion: Immune-mediated colitis has been observed with the use of immune checkpoint inhibitors. This exclusion criterion was established as a precautionary safety measure, and to minimise potential confounding factors for evaluation of the safety of sugemalimab.

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

Rationale: Immune-mediated colitis is included as a subtype within the important identified risk of immune-mediated adverse reactions for sugemalimab. The details are presented in Part II: Module SVII. Colitis is listed as an adverse reaction in the SmPC Section 4.8, and recommendations for sugemalimab dose modification in the event of immune-mediated colitis and precautions for use are included in SmPC Sections 4.2 and 4.4.

> 75 years old on the day of signing the informed consent form

Reason for exclusion: Patients aged older than 75 years frequently have comorbidities that occur with higher frequency and severity, resulting in increased frailty compared to younger patients. These patients are less likely to tolerate intensive treatment. Therefore, this exclusion criterion was established as a precautionary safety measure to avoid any potentially increased risk for these patients.

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

Rationale: Population PK analysis showed non-statistically significant covariate effects of age on sugemalimab exposure. Safety results for participants by age (< 65 years old vs ≥ 65 years old) in Study CS1001-302 and Study CS1001-301 were generally consistent with the overall population, and no treatment modification is required for elderly patients (≥65 years of age).

Patients Aged < 18 Years

Reason for exclusion: Paediatric patients were not included in the clinical development programme.

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

Rationale: Use in paediatric patients is not recommended and is also not expected considering the indications' incidence/prevalence in this age group. The SmPC Section 4.1 states that sugemalimab is indicated for treatment of adults with recommended indications.

Subjects with current active autoimmune disease or prior history of autoimmune disease that probably will relapse or at risk of having these conditions. Subjects with the following conditions are allowed to be screened: type I diabetes mellitus, hypothyroidism that can be managed with thyroxine replacement only, dermatological condition that doesn't require systemic treatment (for example leukoderma, psoriasis or alopecia) or the condition is expected not to relapse without external trigger

Reason for exclusion: By disrupting PD-1-mediated signalling, sugemalimab acts to restore antitumour immunity and halt progression of tumour growth. This restoration of immune function may result in immune-mediated adverse reactions involving one or more body systems, which can be life-threatening or fatal in rare cases. Patients with active or history of autoimmune diseases that probably relapse were excluded from clinical studies as it is unknown if the use of sugemalimab in these patients may worsen the existing autoimmune condition based on the mechanism of action of sugemalimab. Therefore, this exclusion criterion was established to minimise the potential confounding factors for evaluation of the efficacy and safety of sugemalimab.

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

Rationale: Sugemalimab has not been specifically studied in patients with active autoimmune diseases or history of autoimmune diseases. Additionally, the treating physician would be expected to evaluate the benefit and risks in individual patients and follow patients closely for any evidence of immune-mediated adverse events (imAEs) and intervene promptly according to SmPC Section 4.2 and 4.4. Routine monitoring of reports of patients with active autoimmune diseases or history of autoimmune diseases in context of Periodic Reporting appears to adequately contribute to further characterisation.

Immune deficient disease or currently under systemic corticosteroid treatment (equivalent to > 10 mg/day prednisone) or any other form of immune suppressing treatment

Reason for exclusion: Immunosuppressive medications may attenuate the effects of anti-PD-L1 treatment. This exclusion criterion was established as a precautionary safety measure, and to minimise potential confounding factors for evaluation of the safety of sugemalimab.

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

Rationale: Prior to starting sugemalimab, corticosteroids and other immunosuppressants should be avoided because of their potential interference with the pharmacodynamic activity of sugemalimab. For the same reason, these patients were excluded in the clinical studies. However, systemic corticosteroids and other immunosuppressants can be used to treat imAEs (see SmPC Section 4.4).

Severe allergic reaction to other monoclonal antibodies

Reason for exclusion: To reduce the risk of a patient experiencing hypersensitivity to sugemalimab.

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

Rationale: Hypersensitivity to sugemalimab or to any of the excipient is listed as a contraindication in SmPC Section 4.3, and hypersensitivity is listed as an adverse reaction in SmPC Section 4.8.

Any prior treatment of antibody/drug that targets at T-cell coregulatory proteins (immune checkpoints, including PD-1, PD-L1, CTLA4, TIM3 and LAG3, etc.)

Reason for exclusion: Prior therapy targeting PD-1 or PD-L1 may impact the interpretation of study results. This exclusion criterion was established as a precautionary safety measure, and to minimise potential confounding factors for evaluation of the safety of sugemalimab.

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

Rationale: The target population is intended to be naive to treatment with anti-PD-1/PD-L1 therapy (see recommended indications in SmPC Section 4.1).

Has received a live vaccine within 28 days prior to the first dose of investigational product

Reason for exclusion: Use of live vaccines within 4 weeks may impact the interpretation of study results. This exclusion criterion was established as a precautionary safety measure, and to minimise potential confounding factors for evaluation of the safety of sugemalimab.

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

Rationale: Live vaccines are not recommended for patients who are receiving immune-oncology therapies (Kamboj，2024). Accordingly, patients who received live vaccines within 4 weeks from the start of treatment were excluded from clinical studies for sugemalimab. Special Warnings and precautions for use are included in SmPC Section 4.4.

Prior Solid Organ Transplantation

Reason for exclusion: Prior solid organ transplantation may impact the interpretation of study results. Treatment with PD-1 blocking antibodies may increase the risk of rejection in solid organ transplant recipients.

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

Rationale: The treating physician would be expected to evaluate the benefit and risks in individual patients and follow patients closely for evidence of transplant-related complications and intervene promptly.

Major cardiovascular disease (for example heart failure of New York Heart Association (NYHA) Grade 2 or above, unstable angina, unstable arrhythmia)

Reason for exclusion: Cardiovascular impairment may also impact the interpretation of study results; however, the risk of affecting patients' cardiovascular function is considered to be low since no apparent effects on cardiovascular function were identified in nonclinical studies.

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

Rationale: As discussed in Table Part II: Module SII.1, no apparent effects on cardiovascular function were identified in nonclinical studies. Immune-mediated myocarditis is included as a subtype within the important identified risk of immune-mediated adverse reactions for sugemalimab. The details are presented in Part II: Module SVII. Myocarditis and tachycardia are listed as an adverse reaction in the SmPC Section 4.8, and recommendations for sugemalimab dose modification in the event of immune-mediated myocarditis and precautions for use are included in SmPC Sections 4.2 and 4.4.

Subjects who are hepatitis B surface antigen (HBsAg) positive or hepatitis C virus (HCV) antibody positive at screening must receive hepatitis B virus (HBV) DNA quantitative test (excluded if > 2500 copies/mL or 500 IU/mL) and HCV RNA test (excluded if > lower limit of detection) for confirmation. The subjects can only be enrolled when presence of active hepatitis B or C that requires treatment is ruled out, respectively

Reason for exclusion: Immune-mediated hepatitis has been observed with the use of immune checkpoint inhibitors. This exclusion criterion was established as a precautionary safety measure, and to minimise potential confounding factors for evaluation of the safety of sugemalimab.

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

Rationale: There is no evidence that sugemalimab worsens viral infections. These patients may benefit from treatment. Immune-mediated hepatitis is included as a subtype within the important identified risk of immune-mediated adverse reactions for sugemalimab. The details are presented in Part II: Module SVII. Hepatitis is listed as an adverse reaction in SmPC Section 4.8, and recommendations for sugemalimab dose modification in the event of immune-mediated hepatitis and precautions for use are included in SmPC Sections 4.2 and 4.4.

Severe Active Infections Requiring Systemic Therapy

Reason for exclusion: Infection requiring systemic therapy may impact the interpretation of study results.

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

Rationale: There is no evidence that sugemalimab worsens bacterial infections. These patients may benefit from treatment. The treating physician would be expected to evaluate the benefits and risks in individual patients.

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

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, considering the generally short life-expectancy of patients with metastatic NSCLC.

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

Table Part II: Module SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program

Type of special population	Exposure
Population with relevant different ethnic origin	A total of 435 Asian participants received sugemalimab in combination with platinum-based chemotherapy, with a cumulative exposure of 399.017 person-years. A total of 568 participants received sugemalimab monotherapy with a cumulative exposure of 372.728 person-years. Among them there were 556(97.9%) Asian participants, 2(0.4%) black or African American participants and 10(1.8%) white participants.
Subpopulations carrying relevant genetic polymorphisms	Subpopulations with sensitising EGFR mutations or ALK, ROS1 or RET genomic tumour aberrations were not included in the sugemalimab clinical development programme.
Other: Elderly population	Among the participants who received treatment with sugemalimab in combination with platinum-based chemotherapy, 158 participants were aged 65 to 74 years and 3 participants were aged ≥ 75 years old (cumulative exposure, 133.005 and 3.372 person-years, respectively). Among the participants who received sugemalimab monotherapy treatment, 130 participants were aged 65 to 74 years, 7 participants were aged ≥ 75 years old (cumulative exposure, 76.736 and 3.817 person-years, respectively).
Other: Paediatric population	Not included in the clinical development program. A product-specific waiver for paediatric studies for the treatment of NSCLC was granted to sugemalimab by the EMA on 10 Jun 2022 (EMEA-003179-PIP01-22) and MHRA on 26 May 2022 (UK-PIP MHRA-100396-PIP01-21).

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation experience

Indications in China:

Sugemalimab received the first marketing authorisation approval on 20-Dec-2021 with below indication:

- Sugemalimab in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with epidermal growth factor receptor (EGFR) gene mutation-negative and anaplastic lymphoma kinase (ALK) -negative metastatic non-squamous NSCLC.
- Sugemalimab in combination with paclitaxel and carboplatin, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

Then, sugemalimab was authorized for other 4 indications as following:

- Sugemalimab monotherapy is indicated for the treatment of unresectable stage III NSCLC patients whose disease has not progressed following concurrent or sequential platinum-based chemoradiotherapy (authorised on 31-May-2022).

- Sugemalimab monotherapy is indicated for the treatment of adult patients with relapsed/refractory extranodal natural killer/T-cell lymphoma (authorized on 27-Oct-2023).
- Sugemalimab in combination with platinum- and fluoropyrimidine-based chemotherapy is indicated for first-line treatment for unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (authorized on 05-Dec-2023).
- Sugemalimab in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for first-line treatment of unresectable locally advanced or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma with a PD-L1 expression (Combined Positive Score [CPS] ⩾5) (authorized on 12-Mar-2024).

Indications in the EU/EEA:

- Sugemalimab was first granted market authorization on 24-Jul-2024, as first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumor aberrations in combination with platinum-based chemotherapy.

Indications in the UK:

- Sugemalimab was first granted market authorization on 30-Oct-2024, as first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumor aberrations in combination with platinum-based chemotherapy.

SV.1.1 Method used to calculate exposure

Patient exposure was estimated from the data for the distribution of sugemalimab to China (the only country launched with sales data, to date).

It should be noted that the estimations of post-authorisation exposure use the number of units distributed and do not reflect actual utilisation by the patients. Therefore, the calculation of patient exposure will generally be an overestimate for reasons including the holding of drug stocks at pharmacies, distributors or business partners. Owing to the nature of the available data, it is not possible to present post-authorisation exposure by demographics (age, sex etc).

SV.1.2 Exposure

As of 19 Dec 2024, the estimated patient exposure for the cumulative period is based on worldwide sales of CCI Standard Units (SUs) while the patient exposure is approximately CCI patient-years.

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

Potential for misuse for illegal purposes

Sugemalimab is a prescription drug that will only be administered to patients by healthcare professionals. It does not have characteristics that make it attractive for use for illegal purposes. Considering the mechanism of action of sugemalimab, the potential for drug abuse or misuse of sugemalimab 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

Not applicable.

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

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

Important identified risk: immune-mediated adverse reactions

The risk characterisation data in Section SVII.3.1 are based on 435 participants who received at least one dose of sugemalimab 1,200 mg intravenous Q3W in combination with chemotherapy (sugemalimab chemotherapy combination safety pool), and 568 participants who received at least one dose of sugemalimab 1,200 mg intravenous Q3W (sugemalimab monotherapy safety pool) in clinical studies. The Investigator assessed imAEs are the primary presentation for the analysis of the important identified risk of immune related adverse reactions in this RMP.

Potential mechanisms:

The exact pathophysiological mechanism of imAEs is still unclear. The occurrence of such events is believed to be related to the role of immune checkpoint in maintaining immune homeostasis. Some potential mechanisms include enhancing the activity of T cells against antigens present in both tumour and healthy tissues, increasing the level of pre-existing autoantibodies, and increasing the level of inflammatory cytokines (Postow 2018).
PD-1 is generally considered to inhibit T cells in the late stage of peripheral tissue immune response (Dong 2002). Mice lacking PD-1 have more limited and variable model-dependent autoimmune diseases, such as arthritis and cardiomyopathy (Nishimura 1999).
Thyroid disease can occur in patients receiving anti-PD-1 therapy and be found to have anti-thyroid antibodies, whether or not these antibodies are present at baseline or are only detectable after treatment begins. In addition to T--cell--mediated immunity, anti-PD-1 or anti-PD-L1 therapy may also regulate humoral immunity and enhance pre-existing anti-thyroid antibodies (Osorio 2017). Another implication is that PD-1 may be involved in maintaining self-tolerance, a process that prevents the immune system from attacking the individuals it is protecting.
The extent to which autoantibodies (rather than auto reactive T cells) cause imAEs remains unknown and may vary due to toxic effects. In a case report of myocarditis, obvious T cell infiltration was found in myocardium, with no deposition of B cells or antibody (Johnson 2016). Similar T cell clones were found

in both the myocardium and tumour of a patient, suggesting that this T cell population may respond to antigens shared between normal tissues (myocardium) and the tumour. Vitiligo is a depigmentation disease caused by the autoimmune attack of melanocytes. It is also common in patients with melanoma receiving immune checkpoint blocking therapy. This finding suggests a cross reaction between T cells targeting a tumour and T cells targeting related antigens in normal tissues (Byrne 2017).
In addition, cytokines may be involved in the pathophysiological process of imAEs. One study found that the level of IL-17 was increased in patients with ipilimumab-induced colitis (Callahan 2011), and an elevated level of IL-17 was also observed in a pre-clinical model of colitis (Harbour 2015). These findings increase the possibility of using IL-17 blockade as a strategy for the treatment of immune checkpoint block-induced colitis, although there is also a theoretical risk of reversing the good anti-tumour effect of immune checkpoint blockade (Esfahani 2017).

Evidence source(s) and strength of evidence:

Immune-mediated adverse reactions may occur during immunotherapy or following its discontinuation and may involve any tissue or organ. Different signs and symptoms may present depending on the organ involved.
Immune-mediated adverse reactions can be mild, moderate or severe in severity, ranging from asymptomatic to life-threatening, or leading to death. Some serious immune-mediated adverse reactions may have a relatively large impact on the quality of life of patients, but most immune-mediated adverse reactions resolve after active intervention and treatment, with no significant impact on quality of life expected in the future.
Other anti-PD-1/PD-L1 products have confirmed the occurrence of immune-mediated adverse reactions, which have been listed as important identified or potential risks in these products.

Characterisation of the risk:

For the important identified risk of immune-mediated adverse reactions, data from sugemalimab chemotherapy combination safety pool (N=435) and sugemalimab monotherapy safety pool (N=568) are presented separately for each of the following subtypes:

- Immune-mediated endocrine disorders: hypothyroidism, hyperthyroidism, thyroiditis, diabetes mellitus, hypophysitis and adrenal insufficiency.
- Immune-mediated skin adverse reactions
- Immune-mediated hepatitis
- immune-mediated pancreatitis
- Immune-mediated pneumonitis
- Immune-mediated colitis
- Immune-mediated myositis
- Immune-mediated myocarditis
- Immune-mediated nephritis
- Immune-mediated ocular toxicity
- Other immune-mediated adverse reactions (<1%): immune-mediated arthritis, immune-mediated upper gastrointestinal disease, immune-mediated pancytopenia/bicytopenia, immune-mediated meningoencephalitis/encephalitis, immune-mediated Guillain-Barre syndrome/demyelination, immune-mediated rhabdomyolysis/myopathy, immune-mediated hemolytic anemia, immune-mediated vasculitis

The incidence, seriousness, outcomes, severity, and nature of risk are summarised for the sugemalimab chemotherapy combination safety pool (N=435) and sugemalimab monotherapy safety pool (N=568) below, as assessed by the investigator.

- Immune-mediated Endocrine Disorders

- Hypothyroidism

Hypothyroidism events were experienced by 62/435 (14.3%) participants in combination with chemotherapy, and 95/568 (16.7%) participants with monotherapy.

Hypothyroidism	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	62 (14.3)	95(16.7)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	24 (5.5)	52 (9.2)
Resolving	9 (2.1)	10 (1.8)
Unknown	0	0
Sequelae	0	1 (0.2)
Resolved	29 (6.7)	32(5.6)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	1 (0.2)	4(0.7)
AEs leading to treatment discontinuation	1 (0.2)	1(0.2)
AEs leading to treatment interruption	4 (0.9)	9(1.6)

- Hyperthyroidism

Hyperthyroidism events were experienced by 41/435 (9.4%) participants in combination with chemotherapy, and 64/568 (11.3%) participants with monotherapy.

Hyperthyroidism	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	41 (9.4)	64(11.3)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	6 (1.4)	7(1.2)
Resolving	1 (0.2)	4(0.7)
Unknown	0	0
Sequelae	1 (0.2)	2(0.4)
Resolved	33 (7.6)	51(9.0)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	1(0.2)
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	2 (0.4)

- Thyroiditis

Thyroiditis events were experienced by 2/435 (0.5%) participants in combination with chemotherapy, and 3/568 (0.5%) participants with monotherapy.

Thyroiditis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	2 (0.5)	3(0.5)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	1 (0.2)	1(0.2)
Resolving	1 (0.2)	0

Unknown	0	0
Sequelae	0	0
Resolved	0	2(0.4)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	1(0.2)

- Diabetes mellitus

Diabetes mellitus events were experienced by 12/435 (2.8%) participants in combination with chemotherapy, and 13/568 (2.3%) participants with monotherapy.

Diabetes Mellitus	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	12 (2.8)	13(2.3)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	3 (0.7)	3(0.5)
Resolving	0	3(0.5)
Unknown	0	0
Sequelae	0	0
Resolved	9 (2.1)	7(1.2)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	1 (0.2)	1 (0.2)
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	0

- Hypophysitis

Diabetes mellitus events were experienced by 4/435 (0.9%) participants in combination with chemotherapy, and 2/568 (0.4%) participants with monotherapy.

Hypophysitis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	4 (0.9)	2(0.4)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	3 (0.7)	0
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	1 (0.2)	2(0.4)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	0

- Immune-mediated adrenal insufficiency

Adrenal insufficiency events were experienced by 1/435 (0.2%) participant in combination with

chemotherapy, and 1/568 (0.2%) participant with monotherapy.

Adrenal Insufficiency	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	1 (0.2)	1 (0.2)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	1 (0.2)	1 (0.2)
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	0	0
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	0

- Immune-mediated skin adverse reactions
  - Non-severe skin adverse reactions

Skin reactions (excluding severe) were experienced by 46/435 (10.6%) participants in combination with chemotherapy, and 52/568 (9.2%) participants with monotherapy.

Skin Adverse Reaction (excluding severe)	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	46 (10.6)	52(9.2)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	12 (2.8)	9(1.6)
Resolving	6 (1.4)	2(0.4)
Unknown	0	0
Sequelae	0	0
Resolved	28 (6.4)	41(7.2)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	4 (0.9)	0

  - Severe skin adverse reactions

Severe skin adverse reactions were experienced by 7/435 (1.6%) participants in combination with chemotherapy, and 6/568 (1.1%) participants with monotherapy.

Severe Skin Adverse Reaction	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	7 (1.6)	6(1.1)
Seriousness/outcomes, n (%)		
SAEs	2 (0.5)	0
Fatal	0	0
Not resolved	1 (0.2)	2(0.4)

Resolving	1 (0.2)	0
Unknown	0	0
Sequelae	0	0
Resolved	5 (1.1)	4(0.7)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	6 (1.4)	6(1.1)
AEs leading to treatment discontinuation	2 (0.5)	1(0.2)
AEs leading to treatment interruption	4 (0.9)	4(0.7)

- Immune-mediated hepatitis

Hepatitis events were experienced by 42/435 (9.7%) participants in combination with chemotherapy, and 46/568 (8.1%) participants with monotherapy.

Hepatitis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	42 (9.7)	46 (8.1)
Seriousness/outcomes, n (%)		
SAEs	11 (2.5)	4 (0.7)
Fatal	0	1 (0.2)
Not resolved	11 (2.5)	8 (1.4)
Resolving	1 (0.2)	7 (1.2)
Unknown	0	0
Sequelae	0	0
Resolved	30 (6.9)	30 (5.3)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	11 (2.5)	6 (1.1)
AEs leading to treatment discontinuation	7 (1.6)	2 (0.4)
AEs leading to treatment interruption	10 (2.3)	5 (0.9)

- Immune-mediated pancreatitis

Pancreatitis events were experienced by 15/435 (3.4%) participant in combination with chemotherapy, and 7/568 (1.2%) participants with monotherapy.

Pancreatitis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	15 (3.4)	7 (1.2)
Seriousness/outcomes, n (%)		
SAEs	1 (0.2)	0
Fatal	0	0
Not resolved	3 (0.7)	4 (0.7)
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	12 (2.8)	3 (0.5)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	5 (1.1)	1 (0.2)
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	2 (0.5)	1 (0.2)

- Immune-mediated pneumonitis

Pneumonitis events were experienced by 13/435 (3.0%) participants in combination with chemotherapy, and 53/568 (9.3%) participants with monotherapy.

Pneumonitis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	13 (3.0)	53(9.3)
Seriousness/outcomes, n (%)		
SAEs	9 (2.1)	27(4.8)
Fatal	1 (0.2)	2 (0.4)
Not resolved	5 (1.1)	18 (3.2)
Resolving	2 (0.5)	14 (2.5)
Unknown	0	0
Sequelae	0	0
Resolved	5 (1.1)	19 (3.3)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	5 (1.1)	9 (1.6)
AEs leading to treatment discontinuation	8 (1.8)	17 (3.0)
AEs leading to treatment interruption	5 (1.1)	23 (4.0)

- Immune-mediated myositis

Myositis events were experienced by 11/435 (2.5%) participants in combination with chemotherapy, and 13/568 (2.3%) participants with monotherapy.

Myositis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	11 (2.5)	13 (2.3)
Seriousness/outcomes, n (%)		
SAEs	0	4 (0.7)
Fatal	0	0
Not resolved	2 (0.5)	2 (0.4)
Resolving	1 (0.2)	2 (0.4)
Unknown	0	0
Sequelae	0	0
Resolved	8 (1.8)	9 (1.6)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	1 (0.2)
AEs leading to treatment discontinuation	0	3 (0.5)
AEs leading to treatment interruption	1 (0.2)	1 (0.2)

- Immune-mediated colitis

Colitis events were experienced by 11/435 (2.5%) participants in combination with chemotherapy, and 8/568 (1.4%) participants with monotherapy.

Colitis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	11 (2.5)	8 (1.4)
Seriousness/outcomes, n (%)		
SAEs	0	2 (0.4)
Fatal	0	0
Not resolved	2 (0.5)	0
Resolving	0	1 (0.2)

Unknown	0	0
Sequelae	0	0
Resolved	9 (2.1)	7 (1.2)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	1 (0.2)
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	1 (0.2)	2 (0.4)

- Immune-mediated myocarditis

Myocarditis events were experienced by 9/435 (2.1%) participants in combination with chemotherapy, and 16/568 (2.8%) participants with monotherapy.

Myocarditis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	9 (2.1)	16 (2.8)
Seriousness/outcomes, n (%)		
SAEs	3 (0.7)	4 (0.7)
Fatal	0	0
Not resolved	4 (0.9)	8 (1.4)
Resolving	0	1 (0.2)
Unknown	0	0
Sequelae	0	0
Resolved	5 (1.1)	7 (1.2)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	1 (0.2)	1 (0.2)
AEs leading to treatment interruption	5 (1.1)	3 (0.5)

- Immune-mediated nephritis

Nephritis events were experienced by 8/435 (1.8%) participants in combination with chemotherapy, and 7/568 (1.2%) participants with monotherapy.

Nephritis (including renal failure)	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	8 (1.8)	7 (1.2)
Seriousness/outcomes, n (%)		
SAEs	4 (0.9)	0
Fatal	0	0
Not resolved	3 (0.7)	1 (0.2)
Resolving	1 (0.2)	0
Unknown	0	0
Sequelae	0	0
Resolved	4 (0.9)	6 (1.1)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	3 (0.7)	0
AEs leading to treatment discontinuation	1 (0.2)	0
AEs leading to treatment interruption	2 (0.5)	1 (0.2)

- Immune-mediated ocular toxicity

Ocular toxicities were experienced by 6/435 (1.4%) participants in combination with chemotherapy, and

1/568 (0.2%) participant with monotherapy.

Ocular Toxicities	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	6 (1.4)	1 (0.2)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	1 (0.2)	0
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	5 (1.1)	1 (0.2)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	1 (0.2)	0
AEs leading to treatment interruption	2 (0.5)	1 (0.2)

- Immune-mediated arthritis

Arthritis events were experienced by 4/435 (0.9%) participants in combination with chemotherapy, and 1/568 (0.2%) participant with monotherapy.

Arthritis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	4 (0.9)	1 (0.2)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	2 (0.5)	0
Resolving	1 (0.2)	1 (0.2)
Unknown	0	0
Sequelae	0	0
Resolved	1 (0.2)	0
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	2 (0.5)	0

- Immune-mediated upper gastrointestinal disease

Upper gastrointestinal disorder events were experienced by 4/435 (0.9%) participants in combination with chemotherapy, and 3/568 (0.5%) participants with monotherapy.

Upper Gastrointestinal Disorders	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	4 (0.9)	3 (0.5)
Seriousness/outcomes, n (%)		
SAEs	1 (0.2)	0
Fatal	0	0
Not resolved	1 (0.2)	0
Resolving	0	0
Unknown	0	0

Sequelae	0	0
Resolved	3 (0.7)	3 (0.5)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	1 (0.2)	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	0

- Immune-mediated pancytopenia/bicytopenia

Pancytopenia/bicytopenia event was experienced by 1/435 (0.2%) participant in combination with chemotherapy, and 2/568 (0.4%) participants with monotherapy.

Pancytopenia/Binary cytopenia	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	1 (0.2)	2 (0.4)
Seriousness/outcomes, n (%)		
SAEs	1 (0.2)	2 (0.4)
Fatal	0	0
Not resolved	0	2 (0.4)
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	1 (0.2)	0
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	1 (0.2)	2 (0.4)
AEs leading to treatment discontinuation	0	1(0.2)
AEs leading to treatment interruption	0	0

- Immune-mediated meningoencephalitis/encephalitis

Meningoencephalitis/encephalitis event was experienced by 1/435 (0.2%) participant in combination with chemotherapy, and no participants with monotherapy.

Meningoencephalitis/Encephalitis	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	1 (0.2)	0
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	0	0
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	1 (0.2)	0
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	1 (0.2)	0
AEs leading to treatment interruption	0	0

- Immune-mediated Guillain-Barre syndrome/demyelination

Guillain-Barre syndrome/demyelination event was experienced by 1/435 (0.2%) participant in combination with chemotherapy, and no participants with monotherapy.

Guillain-Barre Syndrome/Demyelination	Sugemalimab + Chemotherapy (N = 435)	Sugemalimab Monotherapy (N = 568)
Participants with at least one AE, n (%)	1 (0.2)	0
Seriousness/outcomes, n (%)		
SAEs	1 (0.2)	0
Fatal	0	0
Not resolved	1 (0.2)	0
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	0	0
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	0

- Immune-mediated rhabdomyolysis/myopathy

Rhabdomyolysis/myopathy event was experienced by 1/435 (0.2%) participant in combination with chemotherapy, and 1/568 (0.2%) participant in monotherapy.

Rhabdomyolysis/Myopathy	Sugemalimab + Chemotherapy (N = 435)	Sugemalimab Monotherapy (N = 568)
Participants with at least one AE, n (%)	1 (0.2)	1 (0.2)
Seriousness/outcomes, n (%)		
SAEs	0	0
Fatal	0	0
Not resolved	0	0
Resolving	0	0
Unknown	0	0
Sequelae	0	0
Resolved	1 (0.2)	1 (0.2)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	1 (0.2)	0

- Immune-mediated hemolytic anemia

Hemolytic anemia event was experienced by 1/568 (0.2%) participant in monotherapy, and no participants experienced in combination with chemotherapy.

Rhabdomyolysis/Myopathy	Sugemalimab + Chemotherapy (N = 435)	Sugemalimab Monotherapy (N = 568)
Participants with at least one AE, n (%)	0	1 (0.2)
Seriousness/outcomes, n (%)		
SAEs	0	1
Fatal	0	0
Not resolved	0	0
Resolving	0	0

Unknown	0	0
Sequelae	0	0
Resolved	0	1 (0.2)
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	1
AEs leading to treatment discontinuation	0	0
AEs leading to treatment interruption	0	0

- Immune-mediated Vasculitis

Vasculitis event was experienced by 1/568 (0.2%) participant in monotherapy, and no participants experienced in combination with chemotherapy.

Rhabdomyolysis/Myopathy	**Sugemalimab + Chemotherapy (N = 435)**	**Sugemalimab Monotherapy (N = 568)**
Participants with at least one AE, n (%)	0	1 (0.2)
Seriousness/outcomes, n (%)		
SAEs	0	1 (0.2)
Fatal	0	0
Not resolved	0	0
Resolving	0	1 (0.2)
Unknown	0	0
Sequelae	0	0
Resolved	1 (0.2)	0
Severity and nature of risk, n (%)		
Grade 3 to 5 AEs	0	0
AEs leading to treatment discontinuation	0	1 (0.2)
AEs leading to treatment interruption	1 (0.2)	0

Overall, most imAEs were Grade 1 to 2. Whether in combo or mono therapy, hypothyroidism was the most frequently reported imAE as assessed by the Investigator (62 [14.3%],95 [16.7%], respectively). One participant in combo therapy had an event of immune-mediated pneumonitis (PT: immune-mediated lung disease) with a fatal outcome. 3 participants in monotherapy with outcome of fatal，of which 2 had events of immune-mediated pneumonitis (PT: immune-mediated lung disease) and 1 had an event of immune-mediated hepatitis (PT: acute hepatic failure).

Risk factors and risk groups:

There is an enhanced risk of imAEs in patients with pre-existing autoimmune diseases (Ramos 2020). It is reported that a 50% combined risk of either flare of pre-existing autoimmune disease or development of a new imAE after immune checkpoint inhibitor exposure (Johnson 2016). The mechanism of pre-existing autoimmune disease elevating the risk of imAEs is still under study. In general, auto-antibody production in autoimmune diseases pre-dates symptomatology by many years in a state known as pre-autoimmunity. The administration of immune checkpoint inhibitor may have provided a trigger for the transition from pre-autoimmunity to autoimmunity (Weinmann 2019).

In addition to pre-existing autoimmune disease, other possible risk factors and risk groups are as following:

- Immune-mediated pneumonitis

Chest radiotherapy is one of the risk factors of pneumonitis (including ILD). Possibly due to radiation-induced lung injury, limiting the lung's tolerance to immune-mediated injury. Immune checkpoint inhibitors may have evoked an inflammatory reaction mediated by the lymphocytes and cytokines as a result of radiation exposure in patients' previously irradiated fields (Teng 2020). Other risk factors may include older age, some chemotherapies, smoking history and lung infection.

- Immune-mediated endocrine disorders

Patients with Hashimoto hypothyroidism had a higher incidence of new imAEs (Pizuorno 2023).

- Immune-mediated colitis

Patients with active inflammatory bowel disease.

Preventability:

In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of sugemalimab, administration of corticosteroids and/or supportive care. Treatment modification recommendations in the event of immune-mediated adverse reactions are provided in Section 4.2 of the SmPC. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, withhold, or permanently discontinue sugemalimab and consider administration of corticosteroids. Upon improvement to Grade 0 or 1, initiate corticosteroid taper and continue to taper over at least 1 month. Restart sugemalimab if the adverse reaction remains at Grade 1 or 0 following corticosteroid taper. If another episode of the severe adverse reaction occurs, permanently discontinue sugemalimab. Detailed guidelines for the management of specific immune-mediated adverse reactions including pneumonitis, skin reactions, colitis, hepatitis, nephritis, endocrinopathies, myositis, myocarditis and other immune-mediated adverse reactions are provided in the SmPC Section 4.2.

Impact on the risk-benefit balance of the product:

Most immune-mediated adverse reactions occurred at a low incidence, were of Grade 1 or 2 intensity and resolved after active intervention and treatment. Based on a comprehensive review of clinical data and considering the high unmet medical need of patients with advanced tumours and the poor prognosis of the disease itself, the risk of immune-mediated adverse reactions associated with sugemalimab exposure is considered acceptable, and the therapeutic benefit is expected to outweigh the risk.
Routine pharmacovigilance activities will continuously monitor immune-mediated adverse reactions. The company will continuously assess the impact of this risk on the risk-benefit balance of sugemalimab from ongoing clinical trials. Routine risk minimisation actions are considered adequate to inform patients of this identified risk.

Public health impact:

Most immune-mediated reactions are reversible, and the incidence is low; however, some individuals may experience severe immune-mediated adverse reactions with a high impact on their quality of life. The risk of immune-mediated reactions can be minimised through medication and management according to the SmPC. Overall, the risk is manageable and is not expected to have a major impact on public health.

MedDRA search strategy:

The following are the MedDRA PTs used in the search of sugemalimab chemotherapy combination safety pool for each subtype of immune-mediated adverse reactions.

- Immune-mediated hypothyroidism

Autoimmune hypothyroidism, Hypothyroidic goitre, Hypothyroidism, Myxoedema, Myxoedema coma, Primary hypothyroidism, Secondary hypothyroidism, Tertiary hypothyroidism, Thyroid atrophy, Thyroid stimulating hormone deficiency, Blood thyroid stimulating hormone abnormal, Blood thyroid stimulating hormone increased, Thyroxine abnormal, Thyroxine decreased, Thyroxine free abnormal, Thyroxine free decreased, Tri-iodothyronine abnormal, Tri-iodothyronine free abnormal, Triiodothyronine free decreased, Triiodothyronine decreased, Thyroid function test abnormal, Immune-mediated hypothyroidism.

- Immune-mediated hyperthyroidism

Basedow's disease, Endocrine ophthalmopathy, Exophthalmos, Hyperthyroidism, Malignant exophthalmos, Primary hyperthyroidism, Secondary hyperthyroidism, Thyroid dermatopathy, Thyrotoxic cardiomyopathy, Thyrotoxic crisis, Thyrotoxic myopathy, Thyrotoxic periodic paralysis, Toxic goitre, Toxic nodular goitre, Thyroxine abnormal, Thyroxine free abnormal, Thyroxine free increased, Thyroxine increased, Tri-iodothyronine abnormal, Tri-iodothyronine free abnormal, Tri-iodothyronine free increased, Triiodothyronine increased, Blood thyroid stimulating hormone abnormal, Blood thyroid stimulating hormone decreased, Thyroid function test abnormal, Immune-mediated hyperthyroidism.

- Immune-mediated thyroiditis

Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder, Anti-thyroid antibody positive, Immune-mediated thyroiditis.

- Immune-mediated diabetes mellitus

Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Diabetic ketosis, Euglycaemic diabetic ketoacidosis, Fulminant type 1 diabetes mellitus, Ketosis-prone diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Diabetes mellitus, Hyperglycaemic hyperosmolar nonketotic syndrome, Hyperglycaemic seizure, Hyperglycaemic unconsciousness, Hyperglycaemia, Blood glucose increased.

- Immune-mediated hypophysitis

Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis, Hypopituitarism, Pituitary hypoplasia, Blood corticotrophin decreased, Immune-mediated hypophysitis.

- Immune-mediated adrenal insufficiency

Addison's disease, Adrenal androgen deficiency, Adrenal atrophy, Adrenal insufficiency, Adrenal suppression, Adrenocortical insufficiency acute, Adrenogenital syndrome, Glucocorticoid deficiency, Hypoaldosteronism, Mineralocorticoid deficiency, Primary adrenal insufficiency, Secondary adrenocortical insufficiency, Cortisol decreased, Immune-mediated adrenal insufficiency.

- Immune-mediated skin adverse reactions

Skin reaction (excluding severe): Grade 1 and 2 events of Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Dermatitis, Vitiligo, Psoriasis, Immune-mediated dermatitis, Autoimmune blistering disease, Autoimmune dermatitis, Dermatitis acneiform, Leukoderma, Urticaria, Eczema.

Severe skin reactions: All grades of events of Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Oculomucocutaneous syndrome, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Pemphigoid, Pemphigus, Epidermolysis, Bullous haemorrhagic dermatosis, Necrolytic

acral erythema, Necrotic angiodermatitis Grade 3 or higher events of Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Dermatitis, Vitiligo, Psoriasis, Immune-mediated dermatitis, Autoimmune blistering disease, Autoimmune dermatitis, Dermatitis acneiform, Leukoderma, Urticaria, Eczema.

- Immune-mediated hepatitis

Autoimmune hepatitis, Hepatitis, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Immune-mediated hepatitis, Drug-induced liver injury, Acute hepatic failure, Hepatic failure, Liver disorder, Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Blood bilirubin abnormal, Blood bilirubin increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic function abnormal, Hyperbilirubinaemia, Hypertransaminasaemia, Liver function test abnormal, Liver function test increased, Transaminases abnormal, Transaminases increased, Liver injury, Immune-mediated hepatic disorder, Autoimmune cholangitis, Immune-mediated cholangitis, Immune-mediated cholestasis.

- Immune-mediated pancreatitis

Oedematous pancreatitis, Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis relapsing, Autoimmune pancreatitis, Amylase abnormal, Amylase increased, Hyperamylasaemia, Hyperlipasaemia, Lipase abnormal, Lipase increased, Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, Pancreatic enzymes increased, Immune-mediated pancreatitis, Subacute pancreatitis.

- Immune-mediated pneumonitis

Acute interstitial pneumonitis, Autoimmune lung disease, Idiopathic interstitial pneumonia, Idiopathic pneumonia syndrome, Interstitial lung disease, Pneumonitis, Pulmonary toxicity, Organising pneumonia, Immune-mediated lung disease.

- Immune-mediated colitis

Colitis, Colitis ulcerative, Diarrhoea, Enteritis, Frequent bowel movements, Gastrointestinal perforation, Colitis microscopic, Enterocolitis haemorrhagic, Colitis erosive, Enterocolitis, Necrotising colitis, Autoimmune colitis, Immune-mediated enterocolitis, Microscopic enteritis, Proctitis.

- Immune-mediated myositis

Myositis, Polymyositis, Dermatomyositis, Necrotising myositis, Myalgia, Blood creatine phosphokinase increased, Immune-mediated myositis, Polymyalgia rheumatica.

- Immune-mediated myocarditis

Autoimmune myocarditis, Myocarditis, Hypersensitivity myocarditis, Cardiotoxicity, Myocardial fibrosis, Cardiomyopathy, Cardiomyopathy acute, Blood creatine phosphokinase MB increased, Troponin T increased, Immune-mediated myocarditis, Troponin I increased, Heart injury, Giant cell myocarditis, Pericarditis, Myocardial necrosis marker increased, Bradyarrhythmia, Ventricular asystole, Adams-Stokes syndrome, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular dissociation, Atrioventricular node dysfunction, Bundle branch block left, Bundle branch block right, Conduction disorder, Defect conduction intraventricular, Paroxysmal atrioventricular block, Sinus arrhythmia, Sinus bradycardia, Sinus node dysfunction, Arrhythmia, Arrhythmia supraventricular, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Junctional ectopic tachycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Tachyarrhythmia, Cardiac fibrillation, Torsade de pointes,

Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia, Ventricular pre-excitation, Ejection fraction decreased.

- Immune-mediated nephritis

Nephropathy toxic, Renal failure, Renal impairment, Nephritis, Autoimmune nephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome, Acute kidney injury, Nephritic syndrome, Hypercreatinemia, Blood creatinine abnormal, Blood creatinine increased, Blood urea abnormal, Blood urea increased, Blood urea nitrogen/creatinine ratio increased, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Creatinine urine abnormal, Creatinine urine decreased, Immune-mediated nephritis, Renal injury, Immune-mediated renal disorder.

- Immune related ocular toxicity

Iritis, Uveitis, Cyclitis, Iridocyclitis, Conjunctivitis, Scleritis, Episcleritis, Blepharitis, Ocular toxicity, Immune-mediated uveitis, Ophthalmoplegia.

- Immune-mediated arthritis

Arthritis, Autoimmune arthritis, Caplan's syndrome, Diffuse idiopathic skeletal hyperostosis, Felty's syndrome, Laryngeal rheumatoid arthritis, Palindromic rheumatism, Periarthritis, Polyarthritis, Rheumatoid arthritis, Immune-mediated arthritis, Oligoarthritis.

- Immune-mediated upper gastrointestinal disease

Stomatitis, Stomatitis haemorrhagic, Stomatitis necrotising, Duodenitis, Immune-mediated gastritis, Gastritis, Mouth ulceration, Aphthous ulcer, Oral mucosa erosion, Pharyngeal ulceration, Pharyngeal inflammation, Pharyngeal erosion, Behcet's syndrome, Palatal ulcer, Tongue ulceration, Glossitis, Immune-mediated oesophagitis.

- Immune-mediated pancytopenia/binary cytopenia

Aplastic anaemia, Autoimmune aplastic anaemia, Bicytopenia, Bone marrow failure, Cytopenia, Febrile bone marrow aplasia, Full blood count decreased, Gelatinous transformation of the bone marrow, Pancytopenia, Panmyelopathy, Autoimmune pancytopenia, Immune-mediated cytopenia, Myelosuppression.

- Immune-mediated meningoencephalitis/encephalitis

Arachnoiditis, Central nervous system immune reconstitution inflammatory response, Central nervous system inflammation, Encephalitis, Encephalitis autoimmune, Encephalitis brain stem, Encephalomyelitis, Ependymitis, Meningitis, Meningitis aseptic, Meningitis noninfective, Noninfective encephalitis, Noninfective encephalomyelitis, Pachymeningitis, Limbic encephalitis, Immune-mediated encephalitis.

- Immune-mediated Guillain-Barre syndrome/demyelination

Acute motor axonal neuropathy, Acute motor-sensory axonal neuropathy, Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy, Acute disseminated encephalomyelitis, Acute haemorrhagic leukoencephalitis, Autoimmune demyelinating disease, Clinically isolated syndrome, Concentric sclerosis, Demyelination, Encephalitis periaxialis diffusa, Expanded disability status scale score decreased, Expanded disability status scale score increased, Leukoencephalomyelitis, Leukoencephalopathy, Lewis-Sumner syndrome, Marburg's variant multiple sclerosis, Multiple sclerosis, Multiple sclerosis relapse, Multiple sclerosis relapse prophylaxis, Myelitis transverse, Neuromyelitis optica pseudo relapse, Neuromyelitis optica spectrum disorder, Neuropathy, ataxia, retinitis pigmentosa syndrome, Noninfectious myelitis, Optic neuritis, Primary progressive

multiple sclerosis, Progressive multifocal leukoencephalopathy, Progressive multiple sclerosis, Progressive relapsing multiple sclerosis, Relapsing multiple sclerosis, Relapsing-remitting multiple sclerosis, Secondary progressive multiple sclerosis, Toxic leukoencephalopathy, Tumefactive multiple sclerosis, Immune-mediated neuropathy, Neuritis, Optic perineuritis, Axonal and demyelinating polyneuropathy, Immune-mediated encephalopathy, Immune-mediated neurological disorder.

- Immune-mediated rhabdomyolysis/myopathy

Muscle necrosis, Myoglobin blood increased, Myoglobin blood present, Myoglobin urine present, Myoglobinaemia, Myoglobinuria, Myopathy, Myopathy toxic, Rhabdomyolysis, Thyrotoxic myopathy

- Immune-mediated hemolytic anemia

Acid haemolysin test positive, Autoimmune anaemia, Autoimmune haemolytic anaemia, Haemolysis, Haemolytic anaemia, Haemolytic uraemic syndrome

- Immune-mediated vasculitis

Anti-neutrophil cytoplasmic antibody positive vasculitis, Aortitis, Arteritis, Arteritis coronary
Behcet's syndrome, Capillaritis, Central nervous system vasculitis, Cerebral arteritis, Chronic pigmented purpura, Cogan's syndrome, Cutaneous vasculitis, Diffuse vasculitis, Erythema induratum, Granulomatosis with polyangiitis, Haemorrhagic vasculitis, Henoch-Schonlein purpura, Henoch-Schonlein purpura nephritis, Hypersensitivity vasculitis, Langerhans' cell histiocytosis, MAGIC syndrome, Microscopic polyangiitis, Nodular vasculitis, Ocular vasculitis, Polyarteritis nodosa, Pseudovasculitis, Pulmonary vasculitis, Renal arteritis, Renal vasculitis, Retinal vasculitis, Rheumatoid vasculitis, Segmented hyalinising vasculitis, Takayasu's arteritis, Thromboangiitis obliterans, Urticarial vasculitis, Vaccination site vasculitis, Vascular purpura, Vasculitic rash, Vasculitis, Vasculitis gastrointestinal, Vasculitis necrotising, Reactive capillary endothelial proliferation, Giant cell arteritis.

Important potential risk: reproductive and developmental toxicity

Potential mechanisms:

Based on literature assessment, the PD-1/PD-L1 signalling pathway plays a role in pregnancy by maintaining maternal immune tolerance to the foetus, so blocking the PD-L1 signalling pathway may disrupt the tolerance of the mother to the foetus and increase the risk of miscarriage. Human IgG4 is known to cross the placental barrier, and sugemalimab is a recombinant fully humanised IgG4 anti-PD-L1 mAb and may therefore be transported to the developing foetus via the maternal body. Based on the current understanding of the mechanism of action of these drugs, the PD-1/PD-L1 blocking antibody has potential reproductive and developmental toxicity.

Evidence source(s) and strength of evidence:

Reproductive and developmental toxicity studies have not been conducted with sugemalimab but based on the mechanism of action of PD-1/PD-L1, it may be inferred that sugemalimab has the potential to cause reproductive and developmental toxicity.

Reproductive and developmental toxicity has also been listed as an important potential risk for other anti PD 1/PD-L1 products.

Characterisation of the risk:

No safety data have been obtained from patients exposed during pregnancy.

Risk factors and risk groups:

Exposure during pregnancy.

Preventability:

Women of childbearing potential must be advised to avoid pregnancy during treatment with sugemalimab. Female patients of childbearing potential receiving sugemalimab should use reliable contraception methods during treatment and for at least 4 months after the last dose of sugemalimab (SmPC Section 4.6). A decision should be made whether to discontinue breast-feeding or to discontinue sugemalimab treatment, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (SmPC Section 4.6).

Compliance with these recommendations may limit exposure during pregnancy and thereby prevent any potential malformations or other abnormalities that may result from foetal exposure.

Impact on the risk benefit balance of the product:

Routine pharmacovigilance activities will continuously monitor safety data on exposure during pregnancy. The company will continuously assess the impact of this risk on the risk-benefit balance of sugemalimab. Routine risk minimisation actions are considered adequate to inform patients of this potential risk.

Public health impact:

The number of pregnant women exposed to sugemalimab is expected to be minimal and no major impact is expected on public health.

Reproductive and developmental toxicity is a major complication of pregnancy with significant maternal and foetal/infant effects. Although the nature and severity of reproductive and developmental toxicity events cannot be predicted based on available data, the occurrence of such events is expected to have a major impact on individual patients.

MedDRA search strategy:

PTs of Maternal drugs affecting foetus and Paternal drugs affecting foetus.

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Important identified and potential risks, together with missing information, are summarised in Table Part II: Module SVIII.1.

Table Part II: Module SVIII.1: Summary of safety concerns

Important identified risks	Immune-mediated adverse reactions
Important potential risks	Reproductive and developmental toxicity
Missing information	None

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

At present, adverse reaction reporting, signal detection, and routine pharmacovigilance activities are planned. There are no plans for additional monitoring activities.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary table of additional pharmacovigilance activities

Ongoing and planned additional pharmacovigilance activities studies are summarised in Table Part III:1.

Table Part III:1: Ongoing and planned additional pharmacovigilance activities

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

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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

Risk Minimisation Plan

V.1 Routine risk minimisation measures

Table Part V:1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Immune-mediated adverse reactions	**Routine risk communication:** *SmPC Section 4.2* *SmPC Section 4.4* *SmPC Section 4.5* *SmPC Section 4.8* *PL Section 2* *PL Section 4* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for sugemalimab dose modification (withhold or permanent discontinuation) in the event of immune-mediated adverse reactions are included in the SmPC Sections 4.2. Instructions to monitor for the relevant clinical signs and symptoms is provided in the SmPC Section 4.4. Recommendations for liver, kidney and thyroid function monitoring prior to/at start of treatment and periodically during treatment with sugemalimab, and monitoring for pneumonitis, severe skin reactions, colitis, hyperglycaemia/diabetes, adrenal insufficiency/hypophysitis, myositis, myocarditis, pancreatitis, changes in thyroid function, pituitary function and hormone levels, and serum amylase or lipase are included in the SmPC Section 4.4. Recommendations to ensure that adequate evaluations have been conducted to confirm the aetiology (e.g., suspected pneumonitis should be confirmed with radiographic imaging to exclude other causes) and exclude other causes are presented in the SmPC Section 4.4. Advice regarding treatment (including insulin for diabetes mellitus, hormone replacement therapy for hypothyroidism and hypophysitis, symptomatic treatment for hyperthyroidism, and corticosteroids [or other systemic immunosuppressants if the adverse reaction cannot be controlled with corticosteroids] with tapering on improvement for other immune-mediated adverse reactions) is provided in the SmPC Section 4.4 and 4.5. A warning for the patient to talk to a doctor or nurse prior to being given sugemalimab if they have an autoimmune disease, immunosuppressive treatment, live-virus vaccine administration, medical history of lung disease, chronic viral infection, HIV infection, active or untreated CNS metastases, liver damage, kidney damage is included in the PL Section 2. Skin, lung, gut, pancreas, liver, hormone gland, endocrine, muscle, heart and circulatory, as well as infusion-related reactions are included as possible side effects in the PL Section 4.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription.
Reproductive and developmental toxicity	**Routine risk communication:** *SmPC Section 4.6* *PL Section 2* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation to not use sugemalimab during pregnancy or in women of childbearing potential not using contraception is provided in SmPC Section 4.6. Instruction that female patients of childbearing potential receiving sugemalimab should use reliable contraception methods during treatment and for at least 4 months after the last dose of sugemalimab is included in the SmPC Section 4.6. Description that a decision should be made whether to discontinue breast-feeding or to discontinue sugemalimab treatment, taking into account the benefit of breast-feeding for the child and the benefit of sugemalimab therapy for the woman is included in the SmPC Section 4.6. A precaution for the patient to talk to the doctor if they are pregnant, think they may be pregnant or are planning to have a baby is included in the PL Section 2. Instruction to use reliable method of birth control to avoid becoming pregnant while being treated and for at least 4 months after the last dose of sugemalimab is included in the PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** Restricted medical prescription.

V.2 Additional risk minimisation measures

Patient Cards

Besides routine risk minimisation activities as described in Part V.1, a Patient Card (PC), is considered to be necessary for the important identified risk of immune-mediated adverse reactions.

Objectives:

To raise awareness of patients on immune-mediated adverse reactions, focusing on the key elements to alert patients to the relevant symptoms and the importance of seeking medical advice.

Rationale for the additional risk minimisation activity:

Immune-mediated adverse reactions may occur during immunotherapy or following its discontinuation and may involve any tissue or organ. Different signs and symptoms may present depending on the organ involved. Immune-mediated adverse reactions can be mild, moderate or severe in intensity, ranging from asymptomatic to life-threatening, or leading to death. Early diagnosis and appropriate management are essential to minimise any consequences of immune-mediated adverse reactions.

Target audience and planned distribution path:

The target audience is patients. The PC will be provided for each packaging unit of Cejemly.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The PC will be assessed by routine pharmacovigilance and reported in the periodic safety update reports (PSURs), including the evaluation of post-marketing reports of immune-mediated adverse reactions to assess trends indicating delays in recognising symptoms or seeking medical attention.

V.3 Summary of risk minimisation measures

Table Part V:2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-mediated adverse reactions	**Routine risk minimisation measures:** *SmPC Section 4.2* *SmPC Section 4.4* *SmPC Section 4.5* *SmPC Section 4.8* *PL Section 2* PL Section 4 Restricted medical prescription. **Additional risk minimisation measures:** Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None proposed.* **Additional pharmacovigilance activities**: *None proposed.*
Reproductive and developmental toxicity	**Routine risk minimisation measures:** *SmPC Section 4.6* *PL Section 2* *Restricted medical prescription.* **Additional risk minimisation measures:** *None proposed.*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None proposed.* **Additional pharmacovigilance activities**: *None proposed.*

Part VI: Summary of the risk management plan

SUMMARY OF RISK MANAGEMENT PLAN FOR Cejemly (SUGEMALIMAB)

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

Cejemly's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Cejemly should be used.

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

I. The medicine and what it is used for

- ✓ Cejemly is authorised for in combination with platinum-based chemotherapy indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising epidermal growth factor receptor (EGFR) mutations, or anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1) or rearranged during transfection (RET) genomic tumour aberrations; and as monotherapy indicated for the treatment of patients with unresectable, stage III non-small cell lung cancer (NSCLC) who have not developed disease progression after receiving platinum-based concurrent or sequential chemoradiotherapy (see SmPC for the full indication). It contains sugemalimab as the active substance and it is given by intravenous infusion.

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

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

Important risks of Cejemly, together with measures to minimise such risks and the proposed data collection to learn more about Cejemly's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

In the case of Cejemly, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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

II.A List of important risks and missing information

Important risks of Cejemly are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cejemly. 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).

Table Part VI:1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Immune-mediated adverse reactions
Important potential risks	Reproductive and developmental toxicity
Missing information	None

II.B Summary of important risks

Important identified risk: immune-mediated adverse reactions	
Evidence for linking the risk to the medicine	Immune-mediated adverse reactions may occur during immunotherapy or following its discontinuation and may involve any tissues and organs. Different symptoms or signs may present depending on the organ involved. Immune-mediated adverse reactions can be mild, moderate, or severe in severity, ranging from asymptomatic to life-threatening or leading to death. Some serious immune-mediated adverse reactions may have a relatively large impact on the quality of life of patients, but most immune-mediated adverse reactions resolve after active intervention and treatment, with no significant impact on quality of life expected in the future. Other anti-programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) products have confirmed the occurrence of immune-mediated adverse reactions, which have been listed as important identified or potential risks in these products.
Risk factors and risk groups	Specific risk factors or risk groups have not been identified.
Risk minimisation measures	**Routine risk minimisation measures** *SmPC Section 4.2* *SmPC Section 4.4* *SmPC Section 4.5* *SmPC Section 4.8*

Important identified risk: immune-mediated adverse reactions	
	PL Section 2 *PL Section 4* *Restricted medical prescription.* **Additional risk minimisation measures** Patient card.

Important potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	Reproductive and developmental toxicity studies have not been conducted with sugemalimab but based on the mechanism of action of PD-1/PD-L1, it may be inferred that sugemalimab has the potential to cause reproductive and developmental toxicity. Reproductive and developmental toxicity has also been listed as an important potential risk for other anti PD-1/PD-L1 products.
Risk factors and risk groups	Exposure during pregnancy.
Risk minimisation measures	**Routine risk minimisation measures** *SmPC Section 4.6* *PL Section 2* *Restricted medical prescription.* **Additional risk minimisation measures:** *None proposed.*

II.C Post-authorisation development plan

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

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

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

There are no studies required for Cejemly.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimization activities

Key Safety Messages of Additional Risk Minimisation Measures:
Prior to the launch of Cejemly in each Member State, the Marketing Authorisation Holder must agree about the content and format of the Patient Card, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The Patient Card is aimed at increasing the awareness of patients about signs and symptoms relevant to the early recognition/identification of the potential immune-related adverse reactions adverse reactions and prompt them about when to seek medical attention. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is being treated with Cejemly. The Patient Card is designed to be carried by the patient at all times and presented to any HCPs who may help them.

The Marketing Authorisation Holder shall ensure that in each Member State where Cejemly is marketed, all HCPs and patients/carers who are expected to prescribe and use Cejemly have access to/are provided with the Patient Card disseminated through HCPs.

The Patient Card Will Contain the Following Key Elements:

- Description of the main signs or symptoms of immune-related adverse reactions (e.g., pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis and other immune-related adverse reactions) and IRRs, and the importance of notifying their treating physician immediately if symptoms occur.
- The importance of not attempting to self-treat any symptoms without consulting their HCP first.
- The importance of carrying the Patient Card at all times and to show it at all medical visits to HCPs other than the prescriber (e.g., emergency HCPs).
- A warning message to inform HCPs treating the patient at any time, including in emergency conditions, that the patient is being treated with Cejemly.
- A reminder that all known or suspected adverse drug reactions can also be reported to local regulatory authorities.
- The contact details of their Cejemly prescriber.
- The Patient Card reminds patients about key symptoms that need to be reported immediately to the physician.

Annex 7 - Other supporting data (including referenced material)

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