EU RISK MANAGEMENT PLAN FOR LINVOSELTAMAB

RMP version to be assessed as part of this application:

RMP Version number: 1.0

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Rationale for submitting an updated RMP: Not applicable for the initial RMP.

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QPPV name[1]: Suzanne Green

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.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCMA	B-cell maturation antigen
BMI	Body mass index
bsAb	Bispecific antibody
CD3	Cluster of differentiation 3
CHO	Chinese hamster ovary
CI	Confidence intervals
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRS	Cytokine release syndrome
DL	Dose level
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DP	Drug product
ECIS	European Cancer Information System
EEA	European Economic Area
EPAR	European public assessment report
EPd	Elotuzumab, pomalidomide, and dexamethasone
EU	European Union
EURD	European Union reference dates
GLP	Good laboratory practice
FIH	First-in-human
FLC	Free light chains
HBV	Hepatitis B virus
HCP	Healthcare professional

Abbreviation	Definition
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICANS	Immune effector cell-associated neurotoxicity syndrome
IMiD	Immunomodulatory imide drugs
INN	International non-proprietary name
IARC	International Agency for Research on Cancer
ICH	International Council for Harmonization
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IMWG	International Myeloma Working Group
IRC	Independent review committee
IRR	Infusion related reaction
IV	Intravenous
IVIG	Intravenous gamma globulin infusions
mAb	Monoclonal antibody
MAH	Marketing authorisation holder
MAR	Melanoma associated retinopathy
MedDRA	Medical Dictionary of Regulatory Affairs
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
QT	The time from the start of the Q wave to the end of the T wave, time taken for ventricular depolarisation and repolarisation
QW	Weekly dosing
Q2W	Dosing every 2 weeks
PBRER/PSUR	Periodic benefit risk evaluation report/ Periodic safety update report
PFS	Progression free survival

Abbreviation	Definition
PK	Pharmacokinetics
PI	Proteasome inhibitor
PIL	Patient information leaflet
PT	MedDRA Preferred term
RMP	Risk management plan
RP2D	Recommended phase 2 dose
RP2DR	Recommended phase 2 dose regimen
RR	Relative risk
SC	Subcutaneous
SEER	Surveillance, Epidemiology and End Results
SMM	Smouldering multiple myeloma
SmPC	Summary of product characteristics
SOC	System organ class
TCR	T-cell receptor
TLS	Tumour lysis syndrome
TTO	Time to onset
ULN	Upper limit of normal
US	United States
VGPR	Very good partial response

PART I PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) (INN or common name)	Linvoseltamab
Pharmacotherapeutic group(s) (ATC Code)	Monoclonal antibodies and antibody drug conjugates
Marketing Authorisation Holder or Applicant	Regeneron Ireland DAC
Medicinal products to which this RMP refers	Linvoseltamab
Invented name(s) in the EEA	LYNOZYFIC
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Human (Ig) G4-based anti BCMA x anti CD3 bsAb
	Summary of mode of action: Linvoseltamab is a recombinant human (Ig) G4-based bsAb that binds to CD3 (a T cell antigen associated with the T cell receptor complex) and BCMA (a single pass type III transmembrane protein restricted to plasma cells and some mature or activated B cells) which is expressed on the surface of malignant MM B-lineage cells.
	Important information about its composition: Linvoseltamab is produced by recombinant DNA technology in CHO cell suspension culture.
Hyperlink to the Product Information	Module 1.3.1 SmPC
Indication(s) in the EEA	Current: Not applicable
	Proposed: Linvoseltamab is indicated as a monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy.
Dosage in the EEA	Current: Not applicable

<table>
<tr><td></td><td>Proposed:

Recommended posology:

<table>
<tr><th>Dosing schedule</th><th>Day[a]</th><th colspan="2">Linvoseltamab dose</th></tr>
<tr><td rowspan="3">Step-up dosing schedule</td><td>Week 1 Day 1</td><td>Step-up treatment dose 1</td><td>5 mg</td></tr>
<tr><td>Week 2 Day 1</td><td>Step-up treatment dose 2</td><td>25 mg</td></tr>
<tr><td>Week 3 Day 1</td><td>First full treatment dose</td><td>200 mg</td></tr>
<tr><td>Weekly dosing Schedule</td><td>Week 4 to Week 13 for 10 treatment doses</td><td>Full treatment doses</td><td>200 mg</td></tr>
<tr><td>Every 2 weeks dosing Schedule</td><td>Week 14 and every 2 weeks thereafter</td><td>Full treatment doses</td><td>200 mg</td></tr>
<tr><td colspan="4">Patients who have received at least 17 doses of 200 mg and have confirmed response of very good partial response (VGPR) or better per international myeloma working group (IMWG) criteria at or after Week 24 [b].</td></tr>
<tr><td>Every 4 weeks dosing schedule</td><td>At week 24 or after and every 4 weeks thereafter</td><td>Treatment doses</td><td>200 mg</td></tr>
<tr><td colspan="4">[a] Weekly doses should be at least 5 days apart.

[b] Patients who have not achieved VGPR or better at Week 24 should continue receiving linvoseltamab every 2 weeks.</td></tr>
</table>

Dosage recommendations for pretreatment medications, restarting therapy after a dose delay, and for the management of adverse reactions are provided in Section 4.2 of the SmPC.</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>Current: Not applicable</td></tr>
<tr><td>Proposed:
Linvoseltamab is available as a concentrate for solution for infusion.</td></tr>
</table>

	Linvoseltamab 5 mg concentrate for solution for infusion Each vial contains 5 mg of linvoseltamab in 2.5 mL at a concentration of 2 mg/mL. Linvoseltamab 200 mg concentrate for solution for infusion Each vial contains 200 mg of linvoseltamab in 10 mL at a concentration of 20 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)

Multiple myeloma is a malignancy associated with the clonal proliferation of plasma cells and commonly presents with organ impairment such as renal dysfunction, bone infiltration by malignant plasma cells, hypercalcemia, and hematopoietic suppression (Kazandjian, 2016).

Incidence

Multiple myeloma is the third most commonly occurring haematological malignancy in the world with an estimated 176,404 new cases diagnosed in 2020 and world-age-standardized incidence estimated at 1.8 per 100,000 (Ferlay, 2020)(Huang, 2022).

Data on the incidence of MM in the EU-27 is generated by the ECIS, with results computed from aggregated data submitted by population-based European cancer registries. In 2020, the overall incidence of MM in the EU-27 countries was 35,842 new cases and the age-adjusted incidence proportion was estimated as 7.5 per 100,000 persons (ECIS, 2020). Across all EU and EEA countries, the IARC identified the highest three country-specific crude incidence proportions in 2020 in France (10.7), Norway (10.3) and Italy (9.5), and the lowest in Bulgaria (2.5), Hungary (4.5) and Romania (4.6) (Ferlay, 2020).

Prevalence

In the EU-27 countries, the 5-year limited-duration prevalence of MM as of 2020 was estimated at 97,268 cases, or 21.9 per 100,000 (UICC, 2020). Across all EU and EEA countries, the associated country-specific prevalence proportion estimates were highest in Norway (29.9), France (28.3), Iceland (26.7), and lowest in Bulgaria (6.5), Romania (11.9), and Hungary (12.1) (Ferlay, 2020).

Demographic Characteristics of the Population in the Authorized/Proposed Indication

Age: In the ECIS, the EU (2013)-age-standardized incidence was higher for persons aged 65 or older (28.2 per 100,000) compared to persons younger than 65 (2.5 per 100,000) (ECIS, 2020). Similarly, the SEER program, which covers approximately 95% of the US population, estimated that more than 60% of MM cases were diagnosed in persons 65 years or older with a median age at diagnosis of 69 years (SEER, 2023).

Sex: MM occurs more frequently in men than in women. The world-age-standardized incidence rates were 2.2 per 100,000 in men and 1.5 per 100,000 in women (Sung, 2021). In the ECIS EU-27 data, EU (2013)-age-standardized incidence rate was also higher in men than women (9.7 vs 5.9 per 100,000) (ECIS, 2020).

Racial and/or ethnic origin: MM is more frequently diagnosed in Black persons compared to White persons or persons of other races and ethnicities. From the most recent assessment conducted by the applicant in the SEER program, the age-adjusted incidence rate in the US from 2015 to 2019 was higher for Black persons at 14.3 per 100,000 compared to White (8.5 per

100,000), Asian/Hawaiian/Pacific Islander (4.1 per 100,000), and American Indian/Alaska Native (3.8 per 100,000) persons (SEER, 2021).

Risk factors: A family history of haematological malignancy may indicate an increased risk for MM. In a population-based case-control study in the US, persons having a first degree relative with a history of MM had an increased risk of MM (OR:3.7, 95% CI: 1.2-2.0) compared to persons with no family history (Brown, 1999). In European case-control studies, MM risk was also elevated (OR:1.29, 95% CI: 1.08-1.54) in persons with a family history of any haematolymphoid cancer (Schinasi, 2016) and in persons who had a first degree relative with MM (RR: 2.1, 95% CI: 1.6-2.9), MGUS (RR: 2.1, 95% CI: 1.5–3.1), or acute lymphoblastic leukaemia (RR: 2.1, 95% CI:1.0-4.2) (Kristinsson, 2009).

Additional factors may be associated with increased MM risk. Higher country-specific incidence was associated with a higher prevalence of physical inactivity, overweight, obesity, and diabetes (Huang, 2022). In a US prospective cohort study, increasing BMI categories were significantly associated with higher mortality risk (p-value for trend: <0.002) among MM patients (Calle, 2003). The risk of MM also increased with increasing BMI in men (RR: 1.11, 95% CI: 1.05-1.18) and women (RR: 1.11, 95% CI: 1.07-1.15) in a meta-analysis of 10 studies across North America, Europe, Australia, and Asia-Pacific (Renehan, 2008).

Main Treatment Options

Significant advances have been made in the treatment of MM. The treatment options approved in the EU include the following:

- Stem cell transplant (usually autologous but allogenic is a later-line option),
- IMiDs such as thalidomide, lenalidomide, and pomalidomide,
- PIs, such as bortezomib, ixazomib, and carfilzomib,
- Nuclear export inhibitor therapy (selinexor),
- Chemotherapeutic agents (melphalan, vincristine, cyclophosphamide, etoposide, bendamustine, and doxorubicin),
- Corticosteroids (dexamethasone, methylprednisone, and prednisone)
- Histone deacetylase inhibitors (panobinostat),
- Monoclonal antibodies (daratumumab, isatuximab, elotuzumab, and belantamab mafodotin),
- Bispecific antibody (teclistamab, talquetamab, and elranatamab),
- CAR T-cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel).

Due to the modest monotherapy activity of all agents except CAR-Ts and bispecific antibodies, early line treatment often utilizes combinations including 2 to 4 active drugs including IMiDs, PIs, CD38 antibodies, corticosteroids (such as dexamethasone), and/or alkylating agents.

When a patient has failed an anti-CD38 antibody, a PI, and an IMiD (particularly when a patient is refractory to the latter 2 agents), the opportunities for treatment are limited.

Therapies have recently been approved in the EU for treatment of patients with myeloma who have failed an anti-CD38 antibody, a PI, and an IMiD. For triple-class refractory patients, Sd (Selinexor dexamethasone) is recommended, if available (ESMO-EHA guidelines 2021) (Dimopoulos, 2021).

Despite advances in the initial management of MM and benefits of combination therapy in first line and for relapsed/refractory disease, and the various drugs available, relapse remains a persistent clinical problem and unmet medical need. Due to the number of therapeutic options and combinations available to treating physicians and patients, there is no single algorithm for the therapy of relapsed and refractory multiple myeloma. In US and European guidelines, treatment approaches depend on patient fitness and risk of toxicities (Dimopoulos, 2021)(NCCN, 2023). For triple-class refractory MM, OS remains poor at approximately 12 months (Mateos, 2022).

Natural History of Indicated Condition in the Untreated Population Including Mortality and Morbidity

Multiple myeloma is a clonal disorder that may be preceded by premalignant clonal abnormalities. MGUS and SMM are two of the predominant premalignant conditions that can progress to MM through a series of genetic modifications to symptomatic MM (Munshi, 2019).

A diagnosis of MGUS typically precedes a MM diagnosis (Landgren, 2009). Among residents of a county in Minnesota, US, aged 50 years and older, MGUS was present in 3.2% of the residents (Kyle, 2006), which eventually progressed to MM in 7% of them. The risk of progression to MM in patients with MGUS was 23.8 times higher compared to an age, sex, and calendar-year matched control population (Kyle, 2018). The elevated risk observed was driven by non-IgM MGUS (non-IgM: RR: 27.5; CI 22.2 -33.7; IgM MGUS: RR: 0.0 [0.0- 6.5]) (Kyle, 2018). Risk of progression from MGUS is influenced by the type and serum level of monoclonal protein, and abnormal serum free light chain ratios (Kyle, 2010) (Rajkumar, 2005). Progression risk was found to be significantly higher (HR: 3.5, 95% CI: 2.3-5.5) with abnormal serum free light chain ratio (<0.26 or >1.65) compared to normal levels (0.26-1.65) (Kyle, 2018) (Rajkumar, 2005). At 20 years, the progression risk in the presence of abnormal serum level of monoclonal protein (≥15 g/l), IgA or IgM MGUS, and abnormal serum free light chain ratio was estimated at 58% (Kyle, 2010) (Rajkumar, 2005). In the presence of two, one, and none of the risk factors, the risk was estimated at 37%, 21%, and 5% respectively.

Similarly, among 276 patients with SMM diagnosed from 1970-1995 in the Mayo Clinic, US, approximately 57% developed symptomatic MM within up to 26 years of follow-up. The risk of progression to MM was greatest in the first 5 years and was estimated at 10% per year. For the next 5 years afterwards the annual risk was 3%, and 1% annually in the next 10 years (Kyle, 2007).

The 5-year relative survival of patients with MM reported in the RARECARE database was 35.3% (34.8% to 35.7%) (Gatta, 2017). In Poland, the 5-year survival rate was 48.3% in 2013 (Waszczuk-Gajda, 2023). Survival decreases in patients with early relapse (Kastritis, 2020) (Majithia, 2016) and in patients in later treatment lines (Braunlin, 2021) (Leleu, 2023).With each subsequent therapy, PFS shortens, and by the time patients are refractory to several classes of therapies, the median OS is less than 1 year (Gandhi, 2019) (Hemminki, 2021).

Important Co-Morbidities

Using data from the Swedish Cancer Registry of patients diagnosed from January 1990 to December 2013, 13,656 patients were identified and diagnosed with MM out of whom 54.2% had at least one comorbidity at the time of diagnosis (Sverrisdóttir, 2021). Hypertension (20.4%), other cancer (11.3%), arrhythmia (11.3%), and chronic ischemic heart disease (9.2%) were the most frequently occurring comorbidities. In a separate study in Finland, approximately 38% of MM patients diagnosed between Jan 2005 and Dec 2016 had at least one comorbidity (Toppila, 2022). Overall, the most common comorbidities at the time of diagnosis were malignancies including lymphoma and metastatic solid tumour (excluding malignant neoplasm of skin) (13.9%), renal disease (7.9%), diabetes without chronic complication (6.2%), congestive heart failure (5.7%), and chronic pulmonary disease (4.8%). Similarly, in the Danish Multiple Myeloma Registry containing MM cases diagnosed from 2005 to 2012, one or more comorbidities were identified in 40.9% of patients and any malignancies (13.5%), cerebrovascular disease (7.3%), chronic pulmonary disease (6.7%), moderate and severe renal disease (6.0%), congestive heart failure (5.8%), and myocardial infarction (5.4%) were the most prevalent comorbidities at the time of diagnosis (Gregersen, 2017).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

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

Key safety finding	**Relevance to human use**
Toxicity	
Repeat-dose toxicology: A 5-Week Intravenous Infusion Toxicity and Toxicokinetic Study in Cynomolgus Monkeys With a 12-Week Dose-Free Recovery Phase (GLP). Once weekly IV administration of up to 10 mg/kg linvoseltamab for 5 weeks (total of 5 doses) was well tolerated and resulted in an effects profile consistent with its intended pharmacology as a CD3 bsAb targeting BCMA, including clinical pathology changes consistent with an inflammatory response. Other non-adverse effects, which were relatively mild and reversible, included: • Transient clinical observations (emesis and faecal changes) • Decreases in circulating B-cell lineage lymphocytes. • Increased T cell cellularity and decreased CD20+ B cell and CD138+ plasma cell cellularity. • Microscopic immune cell infiltrates and/or inflammation in multiple tissues	Due to the mechanism of action of linvoseltamab treatment may result in pronounced hypogammaglobulinemia which may result in immunosuppression increasing the risk of infections. Adverse event reports from the clinical trial were analysed for a clinical correlate of the inflammatory response observed in animals in the 12-week toxicology study but a signal was not observed.

Repeat-dose toxicology: A 14-Week Intravenous Injection Toxicity and Toxicokinetic Study in Sexually Mature Cynomolgus Monkeys with a 13-Week Recovery Phase (GLP). Once weekly IV administration of ≥1 mg/kg linvoseltamab resulted in an apparent progression of the pharmacologically mediated inflammatory response observed in the 5-week study. The progressing inflammatory response contributed to declining general condition of some animals, as characterized by decreasing body weight and body condition scores. These declines necessitated the early sacrifice of animals across all dose groups and early cessation of dosing for the 20 mg/kg group at week 9 and for the 1 and 5 mg/kg groups at week 14. Major linvoseltamab-related changes included: • Pharmacologically anticipated decreases in BCMA-expressing B cells and plasma cells, and immunoglobulin concentrations. • Significant weight loss (≥15-20%) with corresponding observations of inappetence and liquid faeces. • A systemic inflammatory response characterized by clinical pathology changes and multi-organ immune cell infiltrates. • Microscopic evidence of minimal-to-moderate inflammation in multiple organs, including peritonitis and pleuritis (corresponding with macroscopic organ adhesions), which are considered to be associated with the observed decline in body weight and condition of animals across this study. • In some animals sacrificed early, positive bacterial cultures were obtained from abdominal swabs and/or blood samples; however, a relationship between potential opportunistic infections (due to elimination of B cells and plasma cells) and the observed treatment effects could not be determined. In general, the severity of these observed findings was dose-related and was observed to have reduced severity at the end of the 13-week dose-free recovery period. Based on the early sacrifice of animals across all groups, a NOAEL could not be determined in this study.	
Reproductive and development toxicity	The effects of linvoseltamab on reproduction and embryo-foetal development are unknown.

Reproductive and developmental toxicology studies are not warranted based on the known target-related effects on lymphocyte depletion, as well as the median MM diagnosis at >70 years of age.	
Genotoxicity No standard genotoxicity studies were conducted as these are not generally applicable to biological pharmaceuticals as large proteins cannot diffuse into cells and interact with DNA or chromosomal material (ICH S9).	Linvoseltamab is not expected to be genotoxic.
Carcinogenicity No standard carcinogenicity studies were conducted as these are generally not applicable to therapies for advanced cancer indication (ICH S9).	Linvoseltamab is not expected to be carcinogenic.
Safety pharmacology	
Cardiovascular system (including potential for QT interval prolongation No cardiovascular effects were identified in the 5-week intravenous Infusion toxicity and toxicokinetic study in Cynomolgus monkeys with a 12-Week Dose-Free Recovery Phase.	Based on non-clinical data, linvoseltamab is not expected to directly affect cardiovascular function or induce QT prolongation.
Nervous system No neurological effects were identified in the 5-week intravenous Infusion toxicity and toxicokinetic study in Cynomolgus monkeys with a 12-Week Dose-Free Recovery Phase.	Based on non-clinical data, linvoseltamab is not expected to directly affect nervous system function however neurotoxicity including ICANS is a known potential toxicity with bispecific antibodies that engage T cells.
Respiratory No respiratory system effects were identified in the 5-week intravenous Infusion toxicity and toxicokinetic study in Cynomolgus monkeys with a 12-Week Dose-Free Recovery Phase.	Based on non-clinical data, linvoseltamab is not expected to directly affect the respiratory system.
Other toxicity related information or data	
Tissue cross-reactivity Tissue Cross-Reactivity Studies of REGN5458 in Normal Human and Cynomolgus Monkey Tissues: Linvoseltamab staining was limited to plasma membrane and cytoplasmic staining of various normal human and monkey tissues and cytoplasmic staining of various human and monkey foetal tissues, consistent with reported	No unanticipated cross-reactivity of linvoseltamab was observed in either study.

expression of BCMA primarily by plasma cells, and CD3 by T cells.	
Immunogenicity **<u>Single-dose PK (non-GLP)</u>** Pharmacokinetic Evaluation of Total REGN5458 in Female Cynomolgus Monkeys Following a Single Intravenous Injection of REGN5458: ADA was apparent (precipitous decline in the concentration-time profiles) in 20% of animals (3 of 5 in the 1 mg/kg group). Pharmacokinetic & Pharmacodynamic Evaluation of Total REGN5458 in Male Cynomolgus Monkeys Following a Single Intravenous Dose of REGN5458: ADA was apparent in 11% of animals (1 of 3 in the 5 mg/kg group). Based on visual inspection of the concentration-time profiles, 1 of 9 drug-treated animals (11%; 1 of 3 animals in the 5 mg/kg group) demonstrated concentration-time profiles that demonstrated profiles impacted with ADA. **<u>Repeat-dose toxicology</u>**: A 5-Week Intravenous Infusion Toxicity and Toxicokinetic Study in Cynomolgus Monkeys With a 12-Week Dose-Free Recovery Phase. Approximately 40% (7 of 18) of recovery animals were deemed to have ADA-impacted linvoseltamab concentrations.	The relationship between immunogenicity in animals and humans is not well established and results in animals are not expected to be predictive of the human immunogenic response. The appearance of ADA did not adversely affect the ability to characterize the PK or toxicology profile of linvoseltamab and is not predictive of immunogenicity in humans.

<u>Summary of non-clinical safety concern</u>

Important identified risks

- None

Important potential risks

- None

Missing information:

- None

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

S111.1 Overview of Development

The safety of linvoseltamab (REGN5458) in patients with relapsed and refractory multiple myeloma is supported by 1 ongoing study (Study R5458-ONC-1826). The primary safety database for evaluating safety profile of linvoseltamab at the recommended dose will consist of pooled safety data from all patients who were administered the 200 mg full dose in Study 1826, including

those in Phase 1 (n=12) and Phase 2 (n=105) for a total of 117, referred to as the "All 200 mg patients".

Study R5854-ONC-1826 is a phase 1/2, open label, FIH study of the safety, tolerability, antitumour activity and PK of linvoseltamab in patients with relapsed or refractory multiple myeloma who have exhausted all therapeutic options that are expected to provide meaningful clinical benefit.

The Phase 1 portion of the study followed a modified 3 + 3 (4+3) dose escalation design with a 28-day DLT observation period to assess the safety of linvoseltamab and to select 1 or more RP2DRs of linvoseltamab IV as a monotherapy. There were 9 DLs in the Phase 1 portion. Doses were delivered QW for 16 doses, then Q2W thereafter. The treatment period for each patient enrolled to DL1 through the first 5 patients in DL6 was 40 weeks, with 12 Q2W doses planned. The treatment period was revised to a variable duration for all patients in Phase 1 regardless of DL, with treatment continuing until progression or any other criterion of study drug discontinuation was met. At the time of data cutoff, 73 patients had been treated and enrollment in Phase 1 was complete.

The Phase 2 portion evaluated the anti-tumour activity, safety, PK properties, PRO, biomarker, and immunogenicity (ADA) responses in patients treated with linvoseltamab IV monotherapy.

- Cohort 1: Step-up regimen of 5 mg initial dose at week 1, 25 mg intermediate dose at week 2, and a full dose of 50 mg full dose at week 3 and until disease progression or another discontinuation criterion was met. Patients who progressed could dose-escalate to 200 mg after minimum of 4 weeks of treatment or maximal of 12 full doses). Enrollment is complete: 104 patients have been enrolled and treated.
- Cohort 2: Step-up regimen of 5 mg initial dose at week 1, 25 mg intermediate dose at week 2, and a full dose of 200 mg full dose at week 3 and thereafter until disease progression or another discontinuation criterion was met. Additionally, patients in Cohort 2 who had received linvoseltamab for at least 24 weeks and also had achieved a response of VGPR or better could transition to Q4W administration of linvoseltamab. Enrollment is complete: 105 patients have been enrolled and treated.

The RMP includes data from 117 subjects from the combination of Phase 1 (dose escalation) and Phase 2 (expansion) who received 200 mg linvoseltamab. This allowed for almost all patients in Phase 2 Expansion Cohort 2 (200 mg full dose), as well as all study patients, to have the opportunity for a minimum of 13 months duration of response (median follow-up was 14 months).

S111.2 Clinical Trial Exposure

Study R5458-ONC-1826

The safety profile is primarily characterized by the database of all 117 patients with relapsed or refractory multiple myeloma treated at the registrational dosing regimen (5/25/200 mg).

Exposure to linvoseltamab in all clinical trials population is summarized in Tables SIII.1 through SIII.4 for all patients by duration, by age group and gender, by dose, and by variable stratifications relevant to the product (ethnic origin and race).

Table Part II: Module SIII.1: Duration of Exposure

Duration of exposure	Number of Patients exposed (N = 117)	Cumulative exposure (Patient months)
≤3 months	39 (33.3%)	61.3
≤6 months	48 (41.0%)	102.1
≤9 months	53 (45.3%)	137.0
≤12 months	57 (48.7%)	181.3
≤15 months	72 (61.5%)	389.0
≤18 months	93 (79.5%)	728.8
≤21 months	106 (90.6%)	977.9
≤24 months	111 (94.9%)	1086.6
≤27 months	112(95.7%)	1112.4
≤30 months	113 (96.6%)	1142.1
Total	117 (100%)	1280.2

Source: Study R5854-ONC-1826
Data cutoff date = 06 Jan 2024

Table Part II: Module SIII.2: Age Group and Gender

Age group	Number of Patients Exposed (N = 117)		Cumulative exposure (Patient months)	
	M	F	M	F
<30 years	0	0	0	0
30-54 years	7 (6.0%)	7 (6.0%)	41.1	98.0
55-64 years	16 (13.7%)	14 (12.0%)	139.2	235.6
65-74 years	22 (18.8%)	20 (17.1%)	220.1	238.5
75-84 years	19 (16.2%)	11 (9.4%)	177.3	115.0
>=85 years	0	1 (0.9%)	0	15.3
Total	64 (54.7%)	53 (45.3%)	577.8	702.4

M=Male, F=Female
Source: Study R5854-ONC-1826
Data cutoff date = 06 Jan 2024

Table Part II: Module SIII.3: Exposure by Dose for All Clinical Subjects

Dose of exposure	Number of Patients Exposed (N = 117)	Cumulative exposure (Patient months)
Dose level (5 mg/25 mg/200 mg)	117	1280.2

Source: Study R5854-ONC-1826
Data cutoff date = 06 Jan 2024

Table Part II: Module SIII.4: Special Populations

Ethnic origin	Number of Patients Exposed (N = 117)	Cumulative Exposure (Patient-months)
Hispanic or Latino	4 (3.4%)	22.6
Not Hispanic or Latino	107 (91.5%)	1191.6
Not reported	6 (5.1%)	66.0
Total	117	1280.2
Race		
Asian	10 (8.5%)	95.4
Black or African American	20 (17.1%)	224.1
Not reported	3 (2.6%)	20.7
Other	1 (0.9%)	0.5
White	83 (70.9%)	939.5
Total	117	1280.2

Source: Study R5854-ONC-1826
Data cutoff date = 06 Jan 2024

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

Important exclusion criteria in pivotal clinical trials across the development programme:

Criterion 1	**Pregnant or breastfeeding women and sexually active men and women of childbearing potential who were unwilling to use highly effective contraception prior to the initial dose/start of the first treatment, during the study and up to 6 months after the last dose.**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant women and breastfeeding women should normally be excluded from clinical trials. No reproductive and developmental toxicology studies have been conducted with linvoseltamab.

	Pregnant women were excluded to avoid potential harm to an unborn foetus. Linvoseltamab, like other monoclonal antibodies may be secreted in breast milk. The safety of exposure to a newborn through breast milk is unknown.
Considered to be missing data (Yes/No)	No
Rationale (if not included as missing information)	No additional pharmacovigilance activities to further characterise the risk are feasible. The risk is addressed through labelling (Section 4.6 of the SmPC).
Criterion 2	**Uncontrolled infection with HIV, HBV, or HCV infection; or other uncontrolled infection (such as CMV).**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with uncontrolled HIV, HBV, HCV, or other infections from clinical trials on anticancer therapy because of the potential to increase the risk of severe adverse events in these patients which may confound the interpretation of safety.
Considered to be missing data (Yes/No)	No
Rationale (if not included as missing information)	It is consistent with standard of care not to treat patients with active infections. Serious Infections are an important identified risk. The risk is addressed through labelling (Section 4.2 and 4.4 of the SmPC). The treating physician would be expected to weigh the benefit and risk for each individual patient.
Criterion 3	**Evidence of significant concurrent disease or medical condition, including but not limited to significant cardiac conditions, including cardiac ejection fraction <40%, NYHA class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmias, and unstable angina and/or significant pulmonary disease (eg, prior history or ongoing complicated interstitial lung disease; obstructive pulmonary disease and history of symptomatic bronchospasm).**

Reason for being an exclusion criterion	It is common clinical practice not to include patients with significant concurrent disease or medical conditions that could interfere with the conduct of the study or put the patient at significant risk.
Considered to be missing data (Yes/No)	No
Rationale (if not included as missing information)	No cardiovascular effects were identified in the 5-week intravenous infusion toxicity and toxicokinetic study in cynomolgus monkeys with a 12-week dose-free recovery phase. No signal for cardiovascular disease was identified in the clinical trial. There is a risk of CRS, hypoxia, tachycardia, and hypotension with linvoseltamab therefore an adequate cardiovascular function is required. The treating physician would be expected to assess the benefit/risk balance for each individual patient.
Criterion 4	**Known MM brain lesions or meningeal involvement** **History of neurodegenerative condition, CNS movement disorder, or patients with a history of seizure within 12 months prior to study enrollment.**
Reason for being an exclusion criterion	Neurologic toxicities have been reported with bispecific T cell therapies. Therefore, inclusion of patients with known CNS involvement or a history of neurologic conditions may confound analysis of neurologic toxicity and may increase risk to patients with these types of underlying conditions.
Considered to be missing data (Yes/No)	No
Rationale (if not included as missing information)	Immune effector cell associated neurotoxicity syndrome is considered an identified risk. The risk is addressed through labelling (Section 4.2 and 4.4 of the SmPC). The treating physician is expected to weigh the benefit and risks for an individual patient.

Criterion 5	**Another malignancy in the past 5 years, except for non-melanoma skin cancer that has undergone potentially curative therapy or in situ cancer, or any other tumour that has been deemed to be effectively treated with definitive local control and with curative intent.**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with other active malignancies from clinical trials to allow a minimal interval of time since prior therapies, in order to avoid overlapping toxicities from anticancer therapies.
Considered to be missing data (Yes/No)	No
Rationale (if not included as missing information)	It is relatively rare for patients to have overlapping malignancies. If there are co-existing malignancies, it is standard practice to treat the most urgent malignancy and to hold treatment for other malignancies that may interfere with the treatment of the most urgent malignancy. The treating physician would be expected to weigh the benefit-risk for individual patients and to prioritise cancer therapies accordingly. It is not expected that the safety profile would differ in patients with active malignancies.
Criterion 6	**Has known allergy or hypersensitivity to components of linvoseltamab.**
Reason for being an exclusion criterion	Possible confounding of safety data.
Considered to be missing data (Yes/No)	No
Rationale (if not included as missing information)	Linvoseltamab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. See Section 4.3 of the SmPC.

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

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

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 clinical development programme.
Breastfeeding women	Not included in clinical development programme.
Patients with hepatic impairment	Participants were required to have adequate hepatic function to participate in the study, including total bilirubin ≤1.5 x ULN, transaminase (ALT, AST) ≤2.5 x ULN, and ALP ≤2.5 x ULN. Patients with baseline moderate and severe hepatic impairment were not exposed in the clinical development programme.
Patients with renal impairment	Participants were required to have adequate renal function to participate in the study, namely serum creatinine clearance by Cockcroft-Gault >30 mL/min. This inclusion criterion resulted in very limited exposure of patients with baseline severe renal impairment in the clinical development programme.
Patients with cardiovascular impairment	Participants with the following cardiovascular conditions were excluded from the study: cardiac ejection fraction <40%, NYHA class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmias or unstable angina.
Immunocompromised patients	Not applicable.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	The studies did not exclude patients based on ethnicity or race (Table Part II: Module SIII.4).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

Not applicable as linvoseltamab is not yet authorized in any country.

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

Potential for misuse for illegal purposes

Based on the molecular structure, pharmacokinetics, and known mechanism of action of linvoseltamab, it is unlikely that linvoseltamab has any potential for misuse for illegal purposes. Additionally, linvoseltamab will be administered in a controlled clinical setting by healthcare professionals.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The important identified and potential risks with linvoseltamab have been determined based on the observations in preclinical toxicology, or clinical studies with linvoseltamab, risks reported with T cell engaging immunotherapies as well as risks generally associated with mAb therapies.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks not included in the list of safety concerns in the RMP	
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	The followings risks (ADRs) although frequently reported are considered to have minimal clinical impact: Decreased appetite Diarrhoea Nausea Vomiting Constipation Cough Dyspnoea Nasal congestion Fatigue Oedema Pyrexia Chills Motor dysfunction Insomnia Infusion related reactions

	Rash Hypertension Musculoskeletal pain Headache Pain Weight decreased
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	Not Applicable
Known risks that require no further characterisation and are followed up via routine pharmacovigilance and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU member state where the product is authorized)	The following risks are considered fully characterized and where appropriate risk minimisation messaging (including monitoring and management) is included in the current SmPC/PIL: Neutropenia including febrile neutropenia Hypogammaglobulinemia Anaemia Thrombocytopenia Lymphopenia Hypophosphataemia Blood creatinine increased Hyperuricaemia Transaminase elevation Encephalopathy (excluding ICANS)
Known risks that do not impact the risk benefit profile	Not Applicable
Other reasons for considering the risks not important	Not Applicable

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

Safety concerns for inclusion in the RMP	**Risk benefit impact**
Important identified risks	

1.8.2 Risk Management Plan

Safety concerns for inclusion in the RMP	Risk benefit impact
Cytokine release syndrome	Cytokine release syndrome is a known class effect associated with T-cell redirector therapy including bispecific antibodies that bind to CD3. While CRS may be life-threatening or fatal, the majority of CRS events in the clinical trial were grade 1 (41/117 patients [35.0%]) or grade 2 (12/117 patients [10.3%]) with 1/117 patients (0.9%) experiencing grade 3 CRS. All events of CRS were effectively managed with available treatments. All CRS events had recovered/resolved in the clinical trial. The risk of CRS is mitigated by the use of step-up dosing and pretreatment medicinal products. Detailed guidance for how to manage and mitigate this risk is provided in the SmPC Section 4.2 and Section 4.4 and reflects the guidance followed by investigators in the clinical trial. A patient card is included as an additional risk minimisation measure to further mitigate the risk of CRS, by increasing patient and caregiver awareness of signs and symptoms requiring medical attention and ensuring prompt recognition and presentation to healthcare professionals in case of CRS. Overall, the benefit-risk balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with linvoseltamab and the primarily low-grade severity of CRS observed in the clinical trial.
Neurologic toxicity including immune effector cell associated neurotoxicity syndrome (ICANS)	Immune effector cell associated neurotoxicity syndrome is a known class effect associated with T-cell redirector therapies. The sponsor conducted an internal adjudication of potential ICANS events. All TEAEs were screened with the Sponsor Screening List, and the resulting retrieval set was adjudicated by 2 Sponsor physicians to determine events meeting the ASTCT definition of ICANS (Lee, 2019). Events determined to not meet the definition were then assessed to determine whether they represented any other neurotoxicity of linvoseltamab. In the clinical trial, 9/117 (7.7%) patients experienced at least one event that was adjudicated as ICANS for a total of 10 events. 3/117 (2.6%) patients experienced grade 3 events, 3/117 (2.6%) experienced grade 2 events, and 3/117 (2.6%) experienced grade 1 events. There were no grade 4 or 5 events. The majority of adjudicated ICANS events (90%) had resolved in the clinical trial. Detailed guidance for how to manage and mitigate ICANS is provided in the SmPC Section 4.2, Section 4.4, and Section 4.7.

1.8.2 Risk Management Plan

Safety concerns for inclusion in the RMP	Risk benefit impact
	A patient card is included as an additional risk minimisation measure to further mitigate the risk of ICANS, by increasing patient and caregiver awareness of signs and symptoms requiring medical attention and ensuring prompt recognition and presentation to healthcare professionals in case of CRS. Overall, the benefit-risk balance is positive for the product considering the severity of the indication, the demonstrated efficacy for patients treated with linvoseltamab, and the primarily low-grade severity of ICANS observed in clinical trial.
Serious Infections	Based on the mechanism of action, treatment with linvoseltamab may result in pronounced B-cell depletion and hypogammaglobulinemia. The expected primary pharmacology of B-cell depletion can result in increased risk of infections including opportunistic infections and viral infections including HBV reactivation. Myeloma patients are at high risk of infection due to immunodeficiency (B-cell dysfunction and hypogammaglobulinemia that are associated with the underlying malignancy), cumulative immunosuppression from previous lines of therapy, neutropenia, advanced age, renal impairment, and other organ dysfunctions. The incidence of infections in this refractory and relapsing population is expected to be high. In addition, because the clinical programme for linvoseltamab spans the duration of the COVID-19 pandemic, most patients were at background risk of COVID-19 infection. Serious infections and opportunistic infections were seen with linvoseltamab in the clinical trial: 50/117 (42.7%) patients experienced serious infections and 12/117 (10.3%) experienced opportunistic infections. Overall, 89.7% of patients experiencing infections had recovered in the clinical trial. 11/117 (9.4%) patients had a fatal infection. The SmPC Section 4.2 and Section 4.4 provide information on how to manage the risk of infection. Overall, the benefit-risk balance is positive for the product considering the severity of the proposed indication and the demonstrated efficacy for patients treated with linvoseltamab.
Important potential risk	None
Missing information	**Risk-benefit impact**

Safety concerns for inclusion in the RMP	Risk benefit impact
Long-term safety	There are limited data available on the long-term safety (ie, >2 years) of linvoseltamab.

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

Important identified risks

Cytokine release syndrome

Neurologic toxicity including Immune effector cell associated neurotoxicity syndrome (ICANS)

Serious Infections

Important potential risks

None

Missing information

Long-term safety

MedDRA version 26.1 was used to classify the clinical trial AE information that is summarised in this section.

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

Important identified risk: Cytokine release syndrome	
Potential mechanism	Linvoseltamab targets the CD3 receptor on T cells and BCMA on B cells and subsequently promotes T-cell activation and causes cytokines to be released, which may result in CRS. The increase in multiple cytokines, in particular IL-10, IL-6, and IL-2R, was noted during step-up dosing and the first cycle of linvoseltamab.
Evidence source and strength of evidence	Cytokine release syndrome is a known class effect associated with T-cell redirector therapy including bispecific antibodies that bind to CD3. Cytokine release syndrome has been reported in subjects treated in the linvoseltamab clinical trial and was identified as an adverse reaction. The risk for CRS and information regarding this adverse reaction are described in the SmPC for linvoseltamab.

	Based on the strength of evidence from the clinical trial data and information from the literature, CRS is considered an important identified risk for linvoseltamab.
Characterisation of risk	<u>CRS</u> Clinical signs and symptoms of CRS may include but are not limited to fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal or hepatic failure, and disseminated intravascular coagulation. In the clinical trial, for patients receiving 200 mg linvoseltamab, 54/117 (46.2%) experienced an event of CRS. The most frequent severity of CRS experienced by most patients was grade 1 (41/117 [35.0%]) or grade 2 (12/117 [10.3%]) with 1/117 (0.9%) patients experiencing grade 3 events. There were no grade 4 or 5 events. In the clinical trial, for patients receiving 200 mg linvoseltamab, CRS occurrence was highest following the initial dose (45/117 [38.5%]), with fewer patients experiencing CRS following the intermediate dose (19/113 [16.8%]), fewer again after the first full dose (11/111 [9.9%]), and still fewer experiencing CRS following the third full dose and beyond (2/99 [2.0%]). Patients who did not experience any grade CRS during the first 3 doses did not develop new onset grade ≥2 CRS at dose 4 or beyond, with the exception of 1 patient who had grade 2 CRS with dose 7, which was treated with tocilizumab. Patients who received tocilizumab to treat CRS tended to have lower recurrence of CRS than those who did not receive tocilizumab. The most common signs and symptoms of CRS (>5% of patients) were typical of CRS: Pyrexia (52/117 [44.4%] patients), Chills (11/117 [9.4%] patients), Hypoxia (9/117 [7.7%] patients), Tachycardia (8/117 [6.8%] patients), and hypotension (6/117 [5.1%] patients). The median (range) time to onset of any grade CRS from end of infusion was 11.04 hours (-1.1 to 183.6). The median duration of CRS events was 15.63 hours. There were no CRS events leading to discontinuation. When evaluating CRS leading to dose delays/interruptions, 7/117 (6.0%) patients had dose delays/interruption due to CRS including 1/117 (0.9%) patient with grade ≥3 CRS. In total, 5/117 (4.3%) had dose reductions due to CRS including 1/117 (0.9%) with grade ≥3 CRS. Dose reductions occurred when a patient repeated or reduced a step-up dose during the first few weeks of treatment (prior to

	reaching the full dose) as a result of early toxicity (usually CRS or ICANS) or when a patient resumed treatment with step-up dosing after a prolonged treatment delay. All patients with 200 mg linvoseltamab with dose reduction returned to the planned full dose. Overall, 23/117 (19.7%) had recurrent CRS. All recurrent CRS events were grade 1 (21/23 [91.3%] patients) or grade 2 (2/23 [8.7%] patients). There were no recurrent CRS events of grade ≥3. All patients had recurrent events of the same or lower severity as the initial CRS except for 1 patient who had initial CRS of grade 1 and recurrent CRS of grade 2. Overall, 29/117 (24.8%) patients received treatment for CRS after the infusion of linvoseltamab. The most common treatments were tocilizumab (22/117 [18.8%] patients) and corticosteroids (13/117 [11.1%]). Only, 1/17 (5.9%) patient who received tocilizumab to treat a first episode of CRS experienced recurrence. All CRS events had recovered/resolved in the clinical trial. <u>IRR</u> IRR may be clinically indistinguishable from manifestations of CRS. CRS was defined in the protocol as occurring ≥6 hours from the start of the infusion or >2 hours after completion of the infusion (whichever was later). An acute IRR is defined as any AE that occurs less than 6 hours from the start of infusion, or within 2 hours after completion of the infusion (whichever is later). In the clinical trial, for patients receiving 200 mg linvoseltamab, 10/117 (8.5%) patients experienced an event of IRR; 3/117 (2.6%) patients experienced grade 1, 5/117 (4.3%) patients experienced grade 2, and 2/117 (1.7%) patients experienced grade 3 IRR events. There were no grade 4 or 5 events. IRR occurrence was highest following the initial dose 6/117 (5.1%) with fewer patients experiencing IRR following the intermediate dose (3/113 [2.7%]), first full dose (2/111 [1.8%]) and third full dose and beyond (1/99 [1.0%]). The signs and symptoms of IRR reported by >1 patient were: Pyrexia (6/117 [5.1%]), Chills (4/117 [3.4%]), and Hypertension and Hypotension (2/117 [1.7%] each). All IRR events had recovered/resolved in the clinical trial.
Risk factors and risk groups	The risk factors for CRS/IRR are not fully identified; however, active infection may increase the severity of CRS. Active infection was an exclusionary criterion in the clinical trial. The incidence

	and severity of CRS might be related to both tumour type and tumour burden.
Preventability	Specific guidance in the SmPC Sections 4.2 and 4.4 is provided to minimise and manage the risk of CRS and/or IRR. Linvoseltamab should be initiated using step-up dosing, and pretreatment medicinal products (dexamethasone, antihistamine, and paracetamol) should be administered prior to each dose during the step-up phase. All patients should be monitored for signs and symptoms of CRS and/or IRR during administration and after infusion. All patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur. For the first step-up treatment dose of linvoseltamab, all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion. For the second step-up treatment dose of linvoseltamab and subsequent doses, patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion: • For the second step-up treatment dose of linvoseltamab if the patient experienced CRS and/or IRR with the first step-up treatment dose. • For a subsequent dose if the patient experienced grade 2 CRS and/or IRR with the prior dose. Patients that experience a first grade 3 CRS event at any time should be hospitalised for 24 hours after receiving the next dose. If CRS and/or IRR is suspected, linvoseltamab should be withheld, the patient immediately evaluated for hospitalisation, and the CRS and/or IRR managed per current practice guidelines and by severity including supportive therapy (which may include intensive care) for CRS. Linvoseltamab should be withheld until CRS resolves and the next dose should be modified. Linvoseltamab should be discontinued for recurrent Grade 3 and Grade 4 CRS and/or IRR. IRR may be clinically indistinguishable from manifestations of CRS. For IRR, the rate of infusion should be interrupted or slowed, or linvoseltamab permanently discontinued based on the severity of the reaction. Section Part IV:V.2 of the RMP includes an additional risk minimisation measure (ie, patient card) to further mitigate the risk of CRS.

Impact on the risks benefit balance of the product	Cytokine release syndrome is a known class effect associated with T-cell redirector therapy including bispecific antibodies that bind to CD3. While CRS may be life threatening or fatal, the majority of CRS events in the clinical trial were grade 1 (35.0% of patients), grade 2 (10.3% of patients). All events of CRS were effectively managed with available treatments recommended for management of CRS and there were no grade 4 or 5 events. The risk of CRS is mitigated by the use of step-up dosing and pretreatment medicinal products. The SmPC Section 4.2 and Section 4.4 and PIL Section 2 and Section 3 provide information on how to manage the risk of CRS. A patient card is included as an additional risk minimisation measure to further mitigate the risk of CRS by increasing patient and caregiver awareness of signs and symptoms requiring medical attention and to ensure prompt recognition and presentation to healthcare professionals in case of CRS. Overall, the risk benefit balance is positive for linvoseltamab considering the severity of the proposed indication, the demonstrated efficacy for patients treated with linvoseltamab and the primarily low-grade severity of CRS observed in the clinical trial.
Public health impact	Linvoseltamab will be administered in a controlled clinical setting by healthcare professionals. No public health impact is anticipated.
Annex MedDRA Term	Cytokine release syndrome (PT) Infusion related reactions (PT)
Important identified risk: Neurologic toxicity including immune effector cell associated neurotoxicity syndrome (ICANS)	
Potential mechanism	Immune effector cell associated neurotoxicity syndrome has been reported with T-cell redirectors, however the precise mechanism is unclear.
Evidence source and strength of evidence	Immune effector cell associated neurotoxicity syndrome is a known class effect associated with bispecific T-cell redirectors. ICANS has been reported and adjudicated by the sponsor in participants treated with linvoseltamab in the clinical trial and ICANS were identified as adverse reactions. The risk for ICANS is described in the SmPC for linvoseltamab.

	Based on the known class effect and the evidence from clinical trial data, ICANS is considered an important identified risk for linvoseltamab.
Characterisation of the risks	Immune effector cell associated neurotoxicity syndrome is considered a class effect associated with bispecific T-cell engaging agents. Events of ICANS were adjudicated by the sponsor based on pre-specified criteria. In the clinical trial, for patients receiving 200 mg linvoseltamab, 9/117 (7.7%) patients experienced at least one event that was adjudicated as ICANS for a total of 10 events. 3/117 (2.6%) patients experienced grade 3 events, 3/117 (2.6%) experienced grade 2 events, and 3/117 (2.6%) experienced grade 1 events. There were no grade 4 or 5 events. 7 of 10 events adjudicated as ICANS were coded to the PT of Immune effector cell-associated neurotoxicity syndrome, followed by Depressed level of consciousness, Encephalopathy, and Toxic encephalopathy (1/117 [0.9%] each). In the 9 patients who experienced adjudicated ICANS, the median time to onset was 1.0 day (range: 1 to 4 days). The median duration of adjudicated ICANS was 2.0 days (range: 1 to 11 days). 8/117 (6.8%) experienced ICANS concurrently with CRS. All events started on the same day as CRS or soon after the onset of CRS. Of the 9 patients who experienced adjudicated ICANS, 1/9 (11.1%) experienced recurrent ICANS (on day 2 after 5 mg dose on day 1). 1/117 (0.9%) patient discontinued treatment due to ICANS. When evaluating ICANS leading to dose delays/interruptions, 2/117 (1.7%) had dose delays/interruptions due to ICANS. 1/117 (0.9%) had a dose reduction due to ICANS. Dose reductions occurred when a patient reduced a step-up dose during the first few weeks of treatment (prior to reaching the full dose) as a result of early toxicity (usually CRS or ICANS) or when a patient resumed treatment with step-up dosing after a prolonged treatment delay. For patients receiving 200 mg linvoseltamab, all those with dose reduction returned to the planned full dose except for the patient who discontinued treatment due to ICANS who did not reach full dose. The majority of adjudicated ICANS events (90%) had resolved in the clinical trial.
Risk factors and risk groups	Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological adverse events.

Preventability	Specific guidance in the SmPC Sections 4.2, 4.4 and 4.7 is provided to minimise and manage the risk of ICANS. All patients should be monitored for signs and symptoms of ICANS during treatment. For the first step-up treatment dose of linvoseltamab, all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion. For the second step-up treatment dose of linvoseltamab and subsequent doses, patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion: • For the second step-up treatment dose of linvoseltamab if the patient experienced ICANS with the first step-up treatment dose. • For a subsequent dose if the patient experienced grade 2 ICANS with the prior dose. Patients that experience a first grade 3 ICANS event at any time should be hospitalised for 24 hours after receiving the next dose. At the first sign of ICANS, linvoseltamab treatment should be withheld, consultation with a neurologist and other specialists for further evaluation should be considered and the ICANS managed by severity including the provision of supportive therapy, (which may include intensive care for severe or life-threatening ICANS). Linvoseltamab should be withheld until ICANS resolves and the next dose should be modified or linvoseltamab should be permanently discontinued based on severity. Linvoseltamab should be permanently discontinued for recurrent grade 3 and grade 4 ICANS. Patients are advised to refrain from driving or using heavy or potentially dangerous machines for 24 hours after completion of each of the step-up doses and if new neurological symptoms develop until symptoms resolve. Section Part IV:V.2 of the RMP includes additional risk minimisation measures (ie, a patient card) to further mitigate the risk of ICANS.
Impact on the risk benefit of the product	ICANS is a known class effect associated with bispecific T cell engaging agents. While ICANS may be life threatening or fatal, most ICANS events in the clinical trial were grade 1, grade 2, or grade 3. ICANS events were effectively managed with available treatments.

	The SmPC Section 4.2, Section 4.4, and Section 4.7, and PIL Section 2 and Section 3 provide information on how to manage the risk of ICANS. Additional risk minimisation measures to further mitigate the risk of ICANS includes a patient card to increase patient and caregiver awareness of signs and symptoms requiring medical attention and to ensure prompt recognition and presentation to healthcare professional for evaluation of potential ICANS. Overall, the risk-benefit balance is positive for linvoseltamab considering the severity of the proposed indication, the demonstrated efficacy for patients treated with linvoseltamab, and the low-grade severity of ICANS observed in the clinical trial.
Public health impact	Linvoseltamab will be administered in a controlled clinical setting by healthcare professionals. No public health impact is anticipated.
Annex 1 MedDRA Term	Nervous system disorders and psychiatric disorders (SOC)
Important identified risk: Serious Infections	
Potential mechanisms	Multiple myeloma is a bone marrow disorder of immune system cells (plasma cells) with impaired immune function resulting in infection. BCMA is expressed in B cell lineage. Linvoseltamab is expected to reduce B cells, which may lead to hypogammaglobulinemia.
Evidence source and strength of evidence	Infections, especially serious infections, are consistent with the known risk among MM patients treated with BCMAxCD3 bispecific antibodies due to its mechanism of action that results to pronounced B-cell depletion and hypogammaglobulinaemia. Serious infections, including life threatening or fatal events, have been reported for subjects treated with linvoseltamab in the clinical trial. Serious Infections are considered an important identified risk due to the frequency, seriousness and severity of infections observed during clinical trial. The risks for infections and information regarding this adverse reaction are described in the SmPC and PIL for linvoseltamab.
Characterisation of risk	In the clinical trial, for patients receiving 200 mg linvoseltamab, 87/117 (74.4%) patients experienced at least one TEAE of infection. The most common infections by PT (≥10%) were: Upper respiratory tract infection (22/117 [18.8%]), COVID-19 (20/117 [17.1%]), and Pneumonia (19/117 [16.2%]).

	Overall, 50/117 (42.7%) patients experienced serious infections. The most common serious infections (>3 patients) were Pneumonia (15/117 [12.8%]), COVID-19 (8/117 [6.8%], and COVID-19 pneumonia and PJP (each 5/117 [4.3%]) and 42/117 (35.9%) patients had grade 3 or 4 infections and 11/117 (9.4%) had grade 5 infections. Overall, 11/117 (9.4%) had a fatal infection. These were COVID-19 pneumonia (3/117 [2.6%]), Septic shock (2/117 [1.7%]), and Escherichia sepsis, Haemophilus sepsis, PJP, pneumonia influenzal, progressive multifocal leukoencephalopathy, and pseudomonal sepsis (1/117 [0.9%] patients each). Of these, 5/11 were within 30 days of the last dose. Regarding the relationship between disease activity and fatal infection, 7 out of 11 fatal infection cases had progressive or stable disease; the remaining were in VGPR or partial response, and none were in CR. Analysis of incidence of fatal infections by 3-month windows (ie 0-3 months of treatment, 3-6 months of treatment, etc) shows a higher incidence of fatal infections in the first 6 months of treatment, and especially the first 3 months (6.0%) of treatment, than over subsequent time (for example 3 to 6 months incidence was 2.4% and 6 to 9 months incidence was 1.4%). Almost two-thirds of infection-related deaths occur in the first 3 months; suggesting a baseline susceptibility. In all patients receiving 200 mg linvoseltamab, it appears that over time, as patients developed CR, their risk of infection and serious infection diminished in general. 11/117 (9.4%) patients discontinued the study due to infection; 9 of these patients had grade 5 infections. 55/117 (47.0%) patients had dose delays/interruptions due to infections mostly of grade 3/4 infections (31/117 [26.5%] patients). 7/117 (6.0%) patients had dose reductions due to infections, they were all grade 3/4 infections. Dose reductions occurred when a patient reduced a step-up dose during the first few weeks of treatment (prior to reaching the full dose) as a result of early toxicity (usually CRS or ICANS) or when a patient resumed treatment with step-up dosing after a prolonged treatment delay. In the clinical trial, for patients receiving 200 mg linvoseltamab, 12/117 (10.3%) patients experienced opportunistic infections. 6/117 (5.1%) patients experienced CMV infections, 5/117 (4.3%) patients experienced Pneumocystis infections, and 1/117 (0.9%) patient experienced PML; 1 patient with CMV also experienced Candida infections (Oesophageal candidiasis) and Herpes viral infections (Ophthalmic herpes simplex). Overall, 7/117 (6.0%) patients experienced serious opportunistic infection: PJP in 5

	patients with Pneumocystis infections, CMV infection reactivation in 1 patient, and PML in 1 patient. 7/117 (6.0%) had grade 3 or 4 opportunistic infections and 2/117 (1.7%) patients had a grade 5 opportunistic infections. The fatal opportunistic infections were PJP and PML. Overall, 89.7% of patients experiencing infections had recovered in the clinical trial.
Risk factors and risk groups	Patients with MM are susceptible to infections due to immunosuppression related to their underlying disease. Patients with MM are at risk of infection due to the overproduction of ineffective monoclonal antibodies from the underlying disease, which causes immune dysfunction. In addition, age, functional status, and medical frailty of the patient may be a risk factor. Studies have shown that hospitalized patients, those with poor functional status or comorbid conditions, and older adults are more likely to develop infection complications. Another risk factor is the concomitant use of other immunosuppressive medications with synergistic adverse immunologic effects. The use of multiple chemotherapy and immunosuppressive treatments (eg, corticosteroids) and neutropenia as a complication of the treatments, increases the risks of infection. In addition, B-cell aplasia and subsequent hypogammaglobulinemia are on target, off tumour toxicities for linvoseltamab, which could result in increased susceptibility to infection including reactivation of latent hepatitis B infection. In addition, patients with haematological malignancies who have COVID-19 have worse mortality outcomes than the general population with COVID-19.
Preventability	Specific guidance in the SmPC Sections 4.2 and 4.4 is provided to minimise and manage the risk of infections. Patients should be monitored for signs and symptoms of infection and immunoglobulin levels prior to and during treatment with linvoseltamab, treated appropriately and prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines, and IVIG according to guidelines. Linvoseltamab should be withheld in patients with active infections or permanently discontinued based on the severity of the infection. Prophylactic treatment per local institutional guidelines for PJP and herpes simplex and zoster viruses is recommended for all patients. Prophylactic antimicrobials and anti-virals, including prophylaxis against CMV, should be administered according to local institutional guidelines. Vaccination for seasonal influenza, COVID-19, haemophilus influenza, and pneumococcus should be administered for all patients according to local institutional guidelines. Hypogammaglobulinemia has been reported in patients receiving

	linvoseltamab. Immunoglobulin levels should be monitored during linvoseltamab treatment and hypogammaglobulinemia should be treated according to local institutional guidelines.
Impact on the risk benefit balance of the product	Infections including serious and opportunistic infections have been reported in the linvoseltamab clinical trial. Linvoseltamab is expected to reduce B cells which may lead to hypogammaglobulinaemia resulting in the increase of serious infection including HBV reactivation. Multiple myeloma is a bone marrow disorder of immune system cells (plasma cells) with impaired immune function, thus the incidence of serious infection in this refractory and relapsing population is expected to be high. Recent preclinical experiments (Limnander, 2023) demonstrate that BCMAxCD3 therapeutics leave the memory B cell compartment intact, a difference between these and anti-CD20 therapeutics. Thus, linvoseltamab treatment may be able to restore immunocompetency through its effect of reducing tumour burden in the marrow while leaving critical parts of the immune system intact. The SmPC Section 4.2 and Section 4.4 and PIL Section 2 provide information on how to manage the risk of infection. Overall, the risks-benefit balance is positive for the product considering the severity of the proposed indication, the ability to manage infections and the demonstrated efficacy for patients treated with linvoseltamab.
Public heath impact	All usage will be well controlled by the healthcare professional. No public health impact is anticipated.
Annex 1 MedDRA Term	Infections and Infestations (SOC)

SVII.3.2 Presentation of the Missing Information

Missing Information: Long-term safety
Evidence source: There are limited data available on the long-term safety (ie, >2 years) of linvoseltamab.
Population in need of further characterization: A risk associated with long-term use cannot be defined based on available evidence but long term-safety data may be available at a later date.

PART II: MODULE SVIIISUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Cytokine release syndrome Neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) Serious Infections
Important potential risks	None
Missing information	Long-term safety

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

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

The Applicant will closely monitor the important identified risks of CRS, ICANS, and Serious Infections in the PSUR.

For the risk of CRS, the Applicant will additionally analyse in detail the following issues in the PSUR:

1. TTO and severity (Grade) of the CRS events with regard to the first linvoseltamab dose, last dose, premedication, and event outcomes
2. CRS events occurring after treatment reinitiation (TTO with regard to the first linvoseltamab dose, last dose, severity, dosage, event outcome, premedication, length of the treatment interruption, and need for hospitalisation)
3. CRS events occurring in patients with significant comorbidities (TTO, severity, events and outcomes)

III.2 Additional Pharmacovigilance Activities

1.8.2 Risk Management Plan

Study R5458-ONC-1826

Safety concerns addressed: Long-term safety

Study short name and title:

Study R5458-ONC-1826: Phase 1/2 FIH Study of REGN-5458 (Anti-BCMA x Anti-CD3 Bispecific Antibody) in Patients with Relapsed or Refractory Multiple Myeloma

Rationale and study objectives:

Primary Phase 1: To assess safety, tolerability, and dose-limiting toxicities (DLTs) and to determine recommended Phase 2 dose regimen

Primary Phase 2: To assess anti-tumor activity of linvoseltamab

Study design:

Open-label, first-in-human study

Study population:

Phase 1: Participants with MM who have exhausted all therapeutic options and have progressed after 3 prior lines of therapy

Phase 2: Participants with MM who have progressed on or after 3 prior lines of therapy or are triple-refractory

Final report (Phase 2 200 mg cohort): Jan 2027

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III-1: On-Going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable.				
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				
Phase 1/2 first-in-human study in patients with RRMM – R5458-ONC-1826 Ongoing	Phase 1 • The primary objective is to assess the safety, tolerability, and dose-limiting toxicities (DLTs) and to determine one or more recommended Phase 2 dose regimens (RP2DRs) of linvoseltamab as monotherapy in patients with relapsed or refractory multiple myeloma Phase 2 • The primary objective is to assess the anti-tumor activity of linvoseltamab. Further characterization of safety and tolerability of linvoseltamab was evaluated as a secondary objective.	• Long-term safety	Final report (Phase 2, 200 mg)	Jan 2027
Category 3 - Required additional pharmacovigilance activities				
Not applicable.				

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table Part IV.1: Planned and on-Going Post Authorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of objectives	Efficacy and Safety uncertainties addressed	Milestones	Due Date (in DD/MM/YY format)
Efficacy studies which are conditions of the marketing authorisation				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
R5458-ONC-2245 (intended confirmatory trial for conversion to full approval)	The primary objective is to evaluate the efficacy and safety of monotherapy of linvoseltamab vs elotuzumab, pomalidomide, and dexamethasone	To further confirm clinical efficacy of linvoseltamab monotherapy. To evaluate clinical safety of linvoseltamab monotherapy, including monitoring, evaluation and characterization of: • CRS • Neurologic toxicity including ICANS • Serious infections	Protocol 1st global submission Interim report Final report	21 Dec 2022 To be confirmed Jun 2027

1.8.2 Risk Management Plan

Study Status	Summary of objectives	Efficacy and Safety uncertainties addressed	Milestones	Due Date (in DD/MM/YY format)
		Long-term safety		

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

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
Cytokine release syndrome	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PIL section 2 • PIL Section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Instructions that linvoseltamab should be administered by an HCP with access to emergency equipment and medical support to manage severe reactions like CRS and/or IRR is included in SmPC Section 4.2. • Instructions to use a step-up dosing schedule and to administer pretreatment medications (dexamethasone, antihistamine, and paracetamol) prior to each dose until tolerated to reduce the risk of CRS and/or IRR are provided in SmPC Sections 4.2 and 4.4. • Recommendations that all patients should be monitored for signs and symptoms of CRS and/or IRR during and after infusion as provided in SmPC Sections 4.2 and 4.4. • Instructions that all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours for the first step-up treatment dose after the end of infusion, for the second step-up treatment dose if the patient experienced CRS and/or IRR with the first step-up treatment dose and for a subsequent dose if the patient experienced grade 2 CRS and/or IRR with the prior dose as provided in SmPC Section 4.2 and 4.4. • Instructions that patients that experience a first grade 3 CRS event at any time should be hospitalised for 24 hours after receiving the next dose as provided in SmPC Section 4.4. • Recommendations for the management of CRS and/or IRR by severity including actions to be taken (withholding, decreasing dose and infusion rate, discontinuation, hospitalization, monitoring) and treatment (including supportive therapy for CRS, which may include

Safety concern	Routine risk minimisation activities
	intensive care for severe or life-threatening CRS) are provided in SmPC Section 4.2 and Section 4.4. • Recommendations to counsel patients to seek immediate medical attention should signs or symptoms of CRS occur are provided in SmPC Section 4.4. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals are provided in SmPC Section 4.4. • Patients should seek immediate medical treatment if symptoms of CRS develop as described in PIL Section 2. • Patients should be monitored for 24 hours after the 1st infusion and after 2nd dose if they experience CRS after the first dose as described in PIL Section 3. • Patients are advised to stay close to the treatment location with a caregiver during the 24-hour monitoring period as described in PIL Section 3. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in PIL Section 2. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. • The design of the packaging has been chosen to appropriately differentiate between the product strengths to ensure the medicine is used correctly during the step-up dosing. Step-up dosing is designed to mitigate the severity of CRS.
Neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS)	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PIL Section 2 • PIL Section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for all patients to be monitored for signs and symptoms of ICANS. as provided in SmPC Section 4.2. • Instructions that all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours for the first step-up treatment dose after the end of infusion, for the second step-up treatment dose if the patient experienced ICANS

Safety concern	Routine risk minimisation activities
	with the first step-up treatment dose and for a subsequent dose if the patient experienced grade 2 ICANS with the prior dose as provided in SmPC Section 4.2 and Section 4.4. • Instructions that patients that experience a first grade 3 ICANS event at any time should be hospitalised for 24 hours after receiving the next dose as provided in SmPC Section 4.4. • Recommendations for the management of ICANS by severity including actions to be taken (withholding, discontinuation), and monitoring and treatment (including neurological consultation, corticosteroids, anti-seizure medicinal products and intensive care for severe or life-threatening ICANS) are provided in SmPC Section 4.2 and Section 4.4. • Recommendation to counsel patients to seek immediate medical attention should signs or symptoms of ICANS occur at any time is provided in SmPC Section 4.4. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals are provided in SmPC Section 4.4. • Recommendations for patients to be advised to refrain from driving or operating heavy or potentially dangerous machinery for 24 hours after completion of each of the step-up doses and if new neurological symptoms develop until symptoms resolve due to potential for ICANS is provided in SmPC Section 4.4 and Section 4.7 • Patients/carers should inform their doctor or nurse immediately if they have signs of ICANS as described in PIL Section 2. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in PIL Section 2. • Patients should be monitored for 24 hours after the 1st infusion and after the 2nd dose if they experience ICANS after the first dose as described in PIL Section 3. • Patients are advised to stay close to the treatment location with a caregiver during the 24-hour monitoring period as described in PIL Section 3. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM.
Serious Infections	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4

Safety concern	Routine risk minimisation activities
	• PIL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Prophylactic treatment per local institutional guidelines for PJP and herpes simplex and zoster viruses is recommended for all patients as described in SmPC Section 4.2 and 4.4. Prophylactic antimicrobials and anti-virals, including prophylaxis against CMV, should be administered according to local institutional guidelines. • Recommendations for the management of infections by severity including actions to be taken (withholding in patients with active infections and discontinuation) are provided in SmPC Section 4.2 and 4.4. • Recommendation to monitor patients for signs and symptoms of infection and immunoglobulin levels prior to and during treatment, to treat appropriately, and to administer prophylactic antimicrobials and IVIG according to guidelines is provided in SmPC Section 4.2 and 4.4. • Patients will be checked and treated for active infection before starting treatment with linvoseltamab as described in PIL Section 2. • Patients should inform their doctor or nurse immediately if they have signs and symptoms of an infection as described in PIL Section 2. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM.
Long-term safety	**Routine risk communication:** • None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** • None

V.2 Additional Risk Minimisation Measures

Additional Risk Minimisation Activity 1
Patient Card

1.8.2 Risk Management Plan

Important Identified Risks: Cytokine Release Syndrome and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS)	
Objective	To minimise the important identified risks of CRS and neurologic toxicity including ICANS by ensuring that patients are aware of the symptoms and know when to contact a healthcare professional.
Rationale for the additional risk minimisation activity	CRS and neurologic toxicity including ICANS can be serious if not detected and managed early. The additional risk minimisation activity is to facilitate early detection of CRS and neurologic toxicity including ICANS to ensure prompt medical intervention.
Target audience and planned distribution path	All patients who are receiving treatment with linvoseltamab. Patients will be given the Patient Card and instructed on the need to carry this card at all times and to show it whenever they are treated by a medical professional.
Plan to evaluate the effectiveness of the interventions and criteria for success	Effectiveness of the risk minimisation activity will be assessed using trends and outcome for the risks of CRS and neurologic toxicities including ICANS based on post-marketing reports. Assessment will be presented in the PBRER, and the additional risk minimisation measure will be considered effective if no negative trends or worsening of outcomes for these risks are identified.

Removal of Additional Risk Minimisation Activities

Not applicable.

V.3 Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cytokine release syndrome	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PIL section 2 • PIL Section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Instructions that linvoseltamab should be administered by an HCP with access to emergency equipment and medical support to manage severe reactions like CRS and/or IRR is included in SmPC Section 4.2. • Instructions to use a step-up dosing schedule and to administer pretreatment medications (dexamethasone, antihistamine, and paracetamol) prior to each dose until tolerated to reduce the risk of CRS and/or IRR are provided in SmPC Sections 4.2 and 4.4. • Recommendations for all patients to be monitored for signs and symptoms of CRS and/or IRR during and after infusion as provided in SmPC Sections 4.2 and 4.4. • Instructions that all patients should be instructed to remain with a caregiver	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	within close proximity of the qualified treatment centre for 24 hours for the first step-up treatment dose after the end of infusion, for the second step-up treatment dose if the patient experienced CRS and/or IRR with the first step-up treatment dose and for a subsequent dose if the patient experienced grade 2 CRS and/or IRR with the prior dose as provided in SmPC Section 4.2 and 4.4. • Recommendations for the management of CRS and/or IRR by severity including actions to be taken (withholding, decreasing dose and infusion rate, discontinuation, hospitalization, monitoring) and treatment (including supportive therapy for CRS which may include intensive care for severe or life-threatening CRS) are provided in SmPC Section 4.2 and 4.4. • Recommendations to counsel patients to seek immediate medical attention should signs or symptoms of CRS occur is provided in SmPC Section 4.4. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in SmPC Section 4.4. • Patients should seek immediate medical treatment	

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	if symptoms of CRS develop PIL Section 2. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in PIL Section 2. • Patients should be monitored during administration and for 24 hours after 1st infusion and after 2nd dose if they experience CRS and/or IRR, after the first dose as described in PIL Section 3. • Patients are advised to stay close to the qualified treatment location with a caregiver during the 24-hour monitoring period as described in PIL Section 3. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. • The design of the packaging has been chosen to appropriately differentiate between the product strengths to ensure the medicine is used correctly during step-up dosing. Step-up dosing is designed to mitigate the severity of CRS. **Additional risk minimisation measures:**	

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Patient card	
Neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS)	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PIL Section 2 • PIL Section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for all patients to be monitored for signs and symptoms of ICANS during treatment. as provided in SmPC Sections 4.2 and 4.4. • Instructions that all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours for the first step-up treatment dose after the end of infusion, for the second step-up treatment dose if the patient experienced ICANS with the first step-up treatment dose and for a subsequent dose if the patient experienced grade 2 ICANS with the prior dose as provided in SmPC Section 4.2 and 4.4. • Instructions that patients that experience a first grade 3 ICANS event at any time should be hospitalised for 24 hours after receiving the next dose as provided in SmPC Section 4.4. • Recommendations for the management of ICANS by	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	severity including actions to be taken (withholding, discontinuation), and monitoring and treatment (including neurological consultation, corticosteroids, anti-seizure medicinal products and intensive care for severe or life-threatening ICANS) are provided in SmPC Section 4.2 and 4.4. • Recommendation to counsel patients to seek immediate medical attention should signs or symptoms of ICANS occur at any time is provided in SmPC Section 4.4. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in SmPC Section 4.4. • Recommendations for patients to be advised to refrain from driving or operating heavy or potentially dangerous machines for 24 hours after completion of each of the step-up doses and if new neurological symptoms develop until symptoms resolve due to potential for ICANS is provided in SmPC Section 4.4 and Section 4.7. • Patients/carers should inform their doctor or nurse immediately if they have signs of ICANS as described in PIL Section 2. • Instructions that patients should be provided with the	

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in PIL Section 2. • Patients should be monitored during administration and for 24 hours after the 1st infusion and after the 2nd dose if they experience ICANS after the first dose as described in PIL Section 3. • Patients are advised to stay close to the treatment location with a caregiver during the 24-hour monitoring period as described in PIL Section 3. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. **Additional risk minimisation measures:** • Patient card	
Serious Infections	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PIL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risks**: • Prophylactic treatment per local institutional guidelines for PJP and herpes simplex and zoster viruses is	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	recommended for all patients as described in SmPC Section 4.2 and 4.4. Prophylactic antimicrobials and anti-virals, including prophylaxis against CMV, should be administered according to local institutional guidelines. • Recommendations for the management of infections by severity including actions to be taken (withholding linvoseltamab in patients with active infections and discontinuation) are provided in SmPC Section 4.2 and 4.4. • Recommendation to monitor patients for signs and symptoms of infection and immunoglobulin levels prior to and during treatment, to treat appropriately, and to administer prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines and IVIG according to guidelines is provided in SmPC Section 4.2 and 4.4. • Patients will be checked and treated for active infection before starting treatment with linvoseltamab as described in PIL Section 2. • Patients should inform their doctor or nurse immediately if they have signs and symptoms of an infection as described in PIL Section 2. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted	

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. **Additional risk minimisation measures:** • None	
Long-term safety	**Routine risk communication:** • None **Routine risk minimisation activities recommending specific clinical measures to address the risks**: • None **Other routine risk minimization measures beyond the Product Information:** • None **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Phase 1/2 first-in-human study in patients with RRMM – R5458-ONC-1826

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Linvoseltamab

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

Linvoseltamab’s SmPC and its package leaflet give essential information to healthcare professionals and patients on how linvoseltamab should be used.

This summary of the RMP for linvoseltamab 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 EPAR.

Important new concerns or changes to the current ones will be included in updates of {Invented Name}'s RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Linvoseltamab is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies including a proteosome inhibitor, an immunomodulatory agent, and an anti CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy. It contains linvoseltamab as the active substance and it is given by IV infusion.

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

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

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

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

- Specific information such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicines packaging.
- The authorized pack size – the amount of medicine in a pack is chosen to ensure that the medicine is used correctly.
- The medicines 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 PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

In the case of linvoseltamab, these measures are supplemented with additional risk minimisation measures for CRS and neurologic toxicity including ICANS as mentioned under relevant important risks (Section II:II.A).

- Patient Card.

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

If important information that may affect the safe use of linvoseltamab is not yet available, it is listed under missing information (Section II:II.A).

II.A List of Important Risks and Missing Information

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

Table II.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Cytokine release syndrome Neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) Serious Infections
Important potential risks	None
Missing information	Long-term safety

II.B Summary of Important Risks

Important identified risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine.	CRS is a known class effect associated with T cell redirector therapy bispecific antibodies that bind to CD3. CRS has been reported in subjects treated in the linvoseltamab clinical trial and was identified as an adverse reaction. The risk for CRS and

	information regarding this adverse reaction are described in the SmPC for linvoseltamab. Based on the strength of evidence from the clinical trial data and information from the literature, CRS is considered an important identified risk for linvoseltamab.
Risk factors and risk groups	The risk factors of CRS are not fully identified, however, active infection may increase the severity of CRS. Active infection was an exclusionary criterion in clinical trial. The incidence and severity of CRS might be related to both tumour type and tumour burden.
Risk minimisation measures	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PIL Section 2 • PIL Section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Instructions that linvoseltamab should be administered by an HCP with access to emergency equipment and medical support to manage severe reactions like CRS and/or IRR is included in SmPC Section 4.2. • Instructions to use a step-up dosing schedule and to administer pretreatment medications (dexamethasone, antihistamine, and paracetamol) prior to each dose until tolerated to reduce the risk of CRS and/or IRR are provided in SmPC Sections 4.2 and 4.4. • Recommendation that all patients should be monitored for signs and symptoms of potential CRS and/or IRR during and after infusion. as provided in SmPC Section 4.2 and 4.4. • Instructions that all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours for the first step-up treatment dose after the end of infusion, for the second step-up treatment dose if the patient experienced CRS and/or IRR with the first step-up treatment dose and for a subsequent dose if the patient experienced grade 2 CRS and/or IRR with the prior dose as provided in SmPC Section 4.2 and 4.4. • Instructions that patients that experience a first grade 3 CRS event at any time should be hospitalised for 24 hours after receiving the next dose as provided in SmPC Section 4.4.

	• Recommendations for the management of CRS and/or IRR by severity including actions to be taken (withholding, decreasing dose and infusion rate, discontinuation, hospitalization, monitoring) and treatment (including supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS) are provided in SmPC Section 4.2 and 4.4. • Recommendations to counsel patients to seek immediate medical attention should signs or symptoms of CRS occur is provided in SmPC Section 4.4. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in SmPC Section 4.4. • Patients should seek immediate medical treatment if symptoms of CRS develop as described in PIL Section 2. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in PIL Section 2. • Patients should be monitored during administration and for 24 hours after 1st infusion and after 2nd dose if they experience CRS and/or IRR, after the first dose, and if the patient has received linvoseltamab after experiencing grade 2 CRS with the prior dose as described in PIL Section 3. • Patients are advised to stay close to the treatment location with a caregiver during the 24-hour monitoring period as described in PIL Section 3. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. **Additional risk minimisation measures:** • Patient card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • None
Important identified risk: Neurologic toxicity including Immune effector cell-associated neurotoxicity syndrome (ICANS)	
Evidence for linking the risk to the medicine.	Neurologic toxicity including ICANS is a known class effect associated with bispecific T-cell redirectors. Neurotoxicity has been reported in subjects treated with linvoseltamab in the clinical trial and ICANS was identified as an adverse reaction. The risk of neurologic

	toxicity including ICANS and information regarding this adverse reaction is described in the SmPC for linvoseltamab. Based on the known class effect and the evidence from clinical trial data, neurologic toxicity including ICANS is considered an important identified risk for linvoseltamab.
Risk factors and risk groups	Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological adverse events.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PIL Section 2 • PIL Section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for all patients to be monitored for signs and symptoms of ICANS as provided in SmPC Sections 4.2 and 4.4. • Instructions that all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours for the first step-up treatment dose after the end of infusion, for the second step-up treatment dose if the patient experienced ICANS with the first step-up treatment dose and for a subsequent dose if the patient experienced grade 2 ICANS with the prior dose as provided in SmPC Section 4.2 and 4.4. • Instructions that patients that experience a first grade 3 ICANS event at any time should be hospitalised for 24 hours after receiving the next dose as provided in SmPC Section 4.4. • Recommendations for the management of ICANS by severity, including actions to be taken (withholding, discontinuation), and monitoring and treatment (including neurological consultation, anti-seizure medicinal products and intensive care for severe or life-threatening ICANS) are provided in SmPC Section 4.2 and 4.4. • Recommendation to counsel patients to seek immediate medical attention should signs or symptoms of ICANS occur at any time is provided in SmPC Section 4.4. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in SmPC Section 4.4.

	• Recommendations for patients to be advised to refrain from driving or operating heavy or potentially machines for 24 hours after completion of each of the step-up doses and if new neurological symptoms develop until symptoms resolve due to potential for ICANS is provided in SmPC Section 4.4 and Section 4.7. • Patients/carers should inform their doctor or nurse immediately if they have signs of ICANS as described in PIL Section 2. • Instructions that patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare professionals as described in PIL Section 2. • Patients should be monitored during administration and for 24 hours after the 1st infusion and after the 2nd dose if they experience ICANS after the first dose as described in PIL Section 3. • Patients are advised to stay close to the treatment location with a caregiver during the 24-hour monitoring period as described in PIL Section 3. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. **Additional risk minimisation measures** • Patient card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • None
Important identified risk: Serious Infections	
Evidence for linking the risk to the medicine	Based on the mechanism of action, treatment with linvoseltamab may result in pronounced B cell depletion and hypogammaglobulinaemia. The expected primary pharmacology of B cell depletion can result in increased risk of infections including opportunistic infections and viral infections including HBV reactivation. Myeloma patients are at high risk of infection due to immunodeficiency (B-cell dysfunction and hypogammaglobulinaemia that are associated with the underlying malignancy), cumulative immunosuppression from previous lines of therapy, neutropenia, advanced age, renal impairment, and other organ dysfunctions. The incidence of infections in this refractory and relapsing population is expected to be high. In addition, because the clinical programme for

	linvoseltamab spans the duration of the COVID-19 pandemic, most patients were at background risk of COVID-19 infection. In the clinical trial, infections including serious and opportunistic infections have been seen with linvoseltamab. Based on the known class effect and the evidence from clinical trial data, Serious Infections are considered an important identified risk for linvoseltamab.
Risk factors and risk groups	There are multiple factors that may increase the risk of infectious complications, patients with MM are at risk of infection due to the overproduction of ineffective mAbs from the underlying disease which causes immune dysfunction. Multiple myeloma patients have as much as a 15-fold increase in risk of infections particularly pneumonia. In addition, the functional status and medical fragility of the patient may be a risk factor. Studies have shown that hospitalised patients, those with poor functional status or comorbid conditions, and older adults are more likely to develop infection complications. Another risk factor is the concomitant use of other immunosuppressive medications with synergistic adverse immunologic effects. The use of multiple chemotherapy and immunosuppressive treatments (eg, corticosteroids) and neutropenia as a complication of the treatments, increases the risk of infection. In addition, B cell aplasia and subsequent hypogammaglobulinaemia are on target, off tumour toxicities for linvoseltamab which could result in increased susceptibility to infection including reactivation of latent hepatitis B infection.
Risk minimisation measures	**Routine risk minimisation activities:** • SmPC Section 4.2 • SmPC Section 4.4 • PIL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Prophylactic treatment per local institutional guidelines for PJP and herpes simplex and zoster viruses is recommended for all patients as described in SmPC Section 4.2 and 4.4. Prophylactic antimicrobials and anti-virals, including prophylaxis against CMV, should be administered according to local institutional guidelines. • Recommendations for the management of infections by severity including actions to be taken (withholding linvoseltamab in patients with active infections and discontinuation) are provided in SmPC Section 4.2 and 4.4. • Recommendation to monitor patients for signs and symptoms of infection and immunoglobulin levels prior to and during treatment, to treat appropriately, and to

	administer prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines and IVIG according to guidelines including prophylaxis for PJP and herpes viruses is provided in SmPC Section 4.4. • Patients will be checked and treated for active infection before starting treatment with linvoseltamab as described in SmPC Section 4.4 and PIL Section 2. • Patients should inform their doctor or nurse immediately if they have signs and symptoms of an infection as described in PIL Section 2. **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Linvoseltamab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • None
Missing Information: Long-Term Safety	
Risk minimisation measures	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Phase 1/2 first-in-human study in patients with RRMM – R5458-ONC-1826

II.C Post-Authorisation Development Plan

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

II.C.1.1 Study R5458-ONC-1826

Study R5458-ONC-1826 is a phase 1/2, open-label, FIH study of REGN5458 (anti-BCMA × anti-CD3 bispecific antibody) in patients with relapsed or refractory multiple myeloma to support conditional marketing authorization.

- Phase 1 primary objective is to assess the safety, tolerability, and dose-limiting toxicities (DLTs) and to determine 1 or more recommended phase 2 dose regimens

(RP2DRs) of linvoseltamab as monotherapy in patients with relapsed or refractory multiple myeloma.

- Phase 2 primary objective is to assess the anti-tumor activity of linvoseltamab. Further characterization of safety and tolerability of linvoseltamab was evaluated as a secondary objective.

II.C.1.2 Study R5458-ONC-2245

Study R5458-ONC-2245 is an open-label phase 3, randomized, active controlled study designed to evaluate the efficacy and safety of linvoseltamab monotherapy vs EPd in participants with relapsed/refractory multiple myeloma who have received 1 to 4 prior lines of therapy including a proteasome inhibitor and lenalidomide to support regular approval. Based on data generated from the ongoing phase 1/2 Study 1826, this phase 3 study will investigate full dose of 200 mg linvoseltamab (following a step-up dose of 5 and 25 mg). Eligible patients will be randomized in a 1:1 ratio to the investigational arm linvoseltamab monotherapy or the active control arm EPd. The primary endpoint is PFS as per IMWG response criteria (Kumar, 2016), determined by an IRC.

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

None

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

Not applicable.

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link / Milestone
Phase 1/2 first-in-human study in patients with RRMM – R5458-ONC-1826 Ongoing	Phase 1 • The primary objective is to assess the safety, tolerability, and dose-limiting toxicities (DLTs) and to determine one or more recommended Phase 2 dose regimens (RP2DRs) of linvoseltamab as monotherapy in patients with relapsed or refractory multiple myeloma Phase 2 • The primary objective is to assess the anti-tumor activity of linvoseltamab. Further characterization of safety and tolerability of linvoseltamab was evaluated as a secondary objective.	• Long-term safety	R5458-ONC-1826 Final study report submission: Jan 2027

ANNEX 3 PROTOCOLS FOR PROPOSED, ON-GOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Protocol R5458-ONC-1826

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 5 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Protocol R5458-ONC-2245

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Additional Risk Minimisation Measure 1

Patient Card

The MAH shall ensure that in each Member State where LYNOZYFIC is marketed, all patients/carers who are expected to use LYNOZYFIC have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS and neurologic toxicity including ICANS. The Patient Card also includes a warning message for the healthcare professionals treating the patient that the patient is receiving LYNOZYFIC, which may cause CRS or neurologic toxicity including ICANS.

The Patient Card will contain the following key messages:

- A description of the key signs and symptoms of CRS and ICANS.
- A description of when to seek urgent attention from the healthcare professional or seek emergency help, should signs or symptoms of CRS and ICANS present themselves.
- A reminder that for the first step-up treatment dose of LYNOZYFIC, all patients should be instructed to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion.
- A reminder for the second step-up treatment dose of LYNOZYFIC, or any subsequent doses, that the treating physician will inform the patient if it is considered necessary for them to remain with a caregiver within close proximity of the qualified treatment centre for 24 hours after the end of infusion.
- The prescribing physician’s contact details.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Braunlin M, Belani R, Buchanan J, Wheeling T, Kim C. Trends in the multiple myeloma treatment landscape and survival: a U.S. analysis using 2011-2019 oncology clinic electronic health record data. Leukemia & lymphoma. 2021;62(2):377-86.

Brown LM, Linet MS, Greenberg RS, Silverman DT, Hayes RB, Swanson GM, et al. Multiple myeloma and family history of cancer among blacks and whites in the U.S. Cancer. 1999;85(11):2385-90.

Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. The New England journal of medicine. 2003;348(17):1625-38.

Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†). Annals of oncology : official journal of the European Society for Medical Oncology. 2021;32(3):309-22.

ECIS. ECIS - European Cancer Information System European Commission2020 [cited 2023 Dec]. Available from: https://ecis.jrc.ec.europa.eu/

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today Lyon, France: International Agency for Research on Cancer; 2020 [updated Dec 2020; cited 2020 05 Jun]. Available from: http://gco.iarc.fr/today/home

Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-75.

Gatta G, Capocaccia R, Botta L, Mallone S, De Angelis R, Ardanaz E, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. The Lancet Oncology. 2017;18(8):1022-39.

Gregersen H, Vangsted AJ, Abildgaard N, Andersen NF, Pedersen RS, Frølund UC, et al. The impact of comorbidity on mortality in multiple myeloma: a Danish nationwide population-based study. Cancer Med. 2017;6(7):1807-16.

Hemminki K, Försti A, Houlston R, Sud A. Epidemiology, genetics and treatment of multiple myeloma and precursor diseases. International journal of cancer. 2021;149(12):1980-96.

Huang J, Chan SC, Lok V, Zhang L, Lucero-Prisno DE, 3rd, Xu W, et al. The epidemiological landscape of multiple myeloma: a global cancer registry estimate of disease burden, risk factors, and temporal trends. The Lancet Haematology. 2022;9(9):e670-e7.

Kastritis E, Roussou M, Eleutherakis-Papaiakovou E, Gavriatopoulou M, Migkou M, Gika D, et al. Early Relapse After Autologous Transplant Is Associated With Very Poor Survival and Identifies an Ultra-High-Risk Group of Patients With Myeloma. Clinical lymphoma, myeloma & leukemia. 2020;20(7):445-52.

Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Seminars in oncology. 2016;43(6):676-81.

Kristinsson SY, Björkholm M, Goldin LR, Blimark C, Mellqvist UH, Wahlin A, et al. Patterns of hematologic malignancies and solid tumors among 37,838 first-degree relatives of 13,896 patients with multiple myeloma in Sweden. International journal of cancer. 2009;125(9):2147-50.

Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17(8):e328-e46.

Kyle RA, Durie BGM, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia. 2010;24(6):1121-7.

Kyle RA, Larson DR, Therneau TM, Dispenzieri A, Kumar S, Cerhan JR, et al. Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. New England Journal of Medicine. 2018;378(3):241-9.

Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical Course and Prognosis of Smoldering (Asymptomatic) Multiple Myeloma. New England Journal of Medicine. 2007;356(25):2582-90.

Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of Monoclonal Gammopathy of Undetermined Significance. New England Journal of Medicine. 2006;354(13):1362-9.

Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412-7.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2019;25(4):625-38.

Leleu X, Gorsh B, Bessou A, Paka P, De Nascimento J, Colin X, et al. Survival outcomes for patients with multiple myeloma in France: A retrospective cohort study using the Système

National des Données de Santé national healthcare database. European journal of haematology. 2023;111(1):125-34.

Limnander A, Kaur N, Asrat S, Tasker C, Boyapati A, Ben LH, et al. A therapeutic strategy to target distinct sources of IgE and durably reverse allergy. Science translational medicine. 2023;15(726):eadf9561.

Majithia N, Rajkumar SV, Lacy MQ, Buadi FK, Dispenzieri A, Gertz MA, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. Leukemia. 2016;30(11):2208-13.

Mateos MV, Weisel K, De Stefano V, Goldschmidt H, Delforge M, Mohty M, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia. 2022;36(5):1371-6.

Munshi NC, Jagannath S, Avet-Loiseau H. Monoclonal Gammopathy May Be of Unpredictable Significance. JAMA Oncol. 2019;5(9):1302-3.

NCCN. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma v3.2023. 2023.

Rajkumar SV, Kyle RA, Therneau TM, Melton LJ, 3rd, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106(3):812-7.

Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet (London, England). 2008;371(9612):569-78.

Schinasi LH, Brown EE, Camp NJ, Wang SS, Hofmann JN, Chiu BC, et al. Multiple myeloma and family history of lymphohaematopoietic cancers: Results from the International Multiple Myeloma Consortium. Br J Haematol. 2016;175(1):87-101.

SEER. Cancer Stat Facts: Myeloma: National Cancer Institute; 2023 [cited 2023 Dec]. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html

SEER. SEER Stat Databases: SEER November 2021 Submission: National Cancer Institute; 2021 [cited 2023 Dec]. Available from: https://seer.cancer.gov/data-software/documentation/seerstat/nov2021/

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021;71(3):209-49.

Sverrisdóttir IS, Rögnvaldsson S, Thorsteinsdottir S, Gíslason GK, Aspelund T, Turesson I, et al. Comorbidities in multiple myeloma and implications on survival: A population-based study. European journal of haematology. 2021;106(6):774-82.

Toppila I, Kysenius K, Miettinen T, Lassenius MI, Lievonen J, Anttila P. Comorbidity characteristics of multiple myeloma patients diagnosed in Finland 2005-2016. Annals of hematology. 2022;101(11):2485-95.

UICC. GLOBOCAN 2020: New Global Cancer Data 2020 [cited 2023 Dec]. Available from: https://www.uicc.org/news/globocan-2020-new-global-cancer-data

Waszczuk-Gajda A, Szafraniec-Buryło S, Kraj L, Skwierawska K, Aleksandrowicz K, Basak GW, et al. Epidemiology of multiple myeloma in Poland in the years 2008-2017. Arch Med Sci. 2023;19(3):645-50.

ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable.

Approval/eSignature	[redacted] 12-Mar-2025 11:39:30 GMT+0000

Approval/eSignature	[redacted] 12-Mar-2025 12:08:43 GMT+0000

Approval/eSignature	[redacted] 12-Mar-2025 13:44:02 GMT+0000

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