27 February 2025
EMA/141656/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynozyfic

International non-proprietary name: linvoseltamab

Procedure No. EMEA/H/C/006370/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMR	Analytical measurement range
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUCt	Area under the concentration-time curve under specified time period
BCMA	B cell maturation antigen
BMPC	Bone marrow plasma cell
BOR	Best overall response
bsAb	Bispecific antibody
CAR	Chimeric antigen receptor
Cavg	Average concentration
CAVGAVG	The weekly average of the Cavg up until the last dose for efficacy endpoints; or until the event or last dose (if censored) for safety endpoints (mg/L)
CAVGWK14	Cavg at week14 (mg/L)
CAVGWKE	Cavg at the week of the event or final dose if censored (mg/L)
CD	Cluster of differentiation
CI	Confidence interval
Cmax	Maximum (peak) concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough concentration at predose before the next dose
CYP	Cytochrome P450
DL	Dose level
DLT	Dose-limiting toxicity
DOR	Duration of response
DS	Disease symptoms
ECG	Electrocardiogram
EMP	Extramedullary plasmacytoma
EOI	End of infusion
E-R	Exposure-response
FAS	Full analysis set
Fc	Fragment crystallisable
FDS	Formulated Drug Substance
FIH	First-in-human
FLC	Free light chain
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
IgG	Immunoglobulin G
IMiD	Immunomodulatory agents
IRC	Independent review committee
IRR	Infusion related reaction
ISS	International Staging System
ITT	Intent-to-treat
IV	Intravenous

IVIG	Intravenous immunoglobulin
KM	Kaplan-Meier
LLOQ	Lower limit of quantitation
LS	Least squares
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MM	Multiple myeloma
MRD	Minimal residual disease
NCS	Not clinically significant
NE	Not evaluable
NDMM	Newly diagnosed multiple myeloma
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic
PF	Physical functioning
PFS	Progression-free survival
PI	Proteasome inhibitor
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PRO	Patient-reported outcome
PT	Preferred term
QoL	Quality-of-life
QW	Once weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
RRMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
sBCMA	Soluble B cell maturation antigen
sCR	Stringent complete response
SD	Standard deviation
SOC	System organ class
TCE	Triple-class exposed
TEAE	Treatment-emergent adverse event
TLS	Tumour lysis syndrome
TSE	Treatment side effects
TTE	Time to event
TTR	Time to response
VGPR	Very good partial response
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Regeneron Ireland Designated Activity Company submitted on 11 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for LYNOZYFIC, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 May 2023.

The applicant applied for the following indication: as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0153/2022 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active Substance status

The applicant requested the active substance linvoseltamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 January 2023	EMA/SA/0000114572	Rune Kjeken and Johanna Lähteenvuo
20 July 2023	EMA/SA/0000139600	Martin Walter, Vilma Petrikaite

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Drug product analytical comparability strategy to support the proposed commercial presentations.
- Comparability approach to establish a proposed commercial shelf-life.
- Microbial study approach to support in-use stability.
- Validation of FDS manufacturing process in multiple single-use bioreactor (SUB) suites/process areas at the same facility
- Need for developmental and reproductive toxicology studies
- Regulatory strategy to pursue a conditional marketing authorisation based on the results of the phase1/2 study 1826; design of the phase 3 study 2245 including the patient population, control arm, primary and secondary endpoints, stratification factors, reported outcomes capturing pain symptoms, statistical considerations and interim analysis; adequacy of study 2245 to support conversion of the conditional marketing authorisation to standard

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paolo Gasparini Co-Rapporteur: Edward Laane

The application was received by the EMA on	11 January 2024
The procedure started on	1 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 April 2024
The CHMP Co-Rapporteur's first Assessment Report (Critique) was circulated to all CHMP and PRAC members on	6 May 2024
The PRAC Rapporteur's first Assessment Report was circulated to all	7 May 2024

PRAC and CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on>	16 May 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 May 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 January 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	19 February 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to LYNOZYFIC on	26 February 2025
The CHMP adopted a report on similarity of Lynozyfic product with Talvey, Carvykti, Abecma, Farydak, Blenrep, Ninlaro and Kyprolis on (see Appendix on similarity)	26 February 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 February 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is pursuing a conditional marketing authorisation (MA) for linvoseltamab as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma (RR MM) who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

2.1.2. Epidemiology

Multiple myeloma (MM) is a chronic and incurable malignancy characterised by the proliferation of neoplastic plasma cells in the bone marrow. MM accounts for, approximately, 1-2% of all cancers, being one of the most common forms of haematologic malignancy (Siegel RL et al, CA Cancer J Clin. 2024).

The crude annual incidence rate for MM in Europe is approximately 5.44-6.0 per 100.000 (see e.g. Sant M et al, Blood 2010), yet prevalence is higher, reflecting both natural history and improvement in survival (43.2 per 100.000, ECIS - European Cancer Information System 2024). In 2014, an EU population-based study reported that the 5-year survival rates for MM increased from 29.8% in 1997-1999 to 39.6% in 2006-2008 (Sant M et al, Lancet Oncol. 2014), reflecting the impact of novel treatments introduced in clinical practice.

With a median age at diagnosis comprised between 65 and 74 years, a significant fraction of patients with MM consists of older adults, with subjects aged ≤ 50 years being just 10% of the whole MM population (Kyle RA et al, Mayo Clin Proc. 2003).

MM is slightly more frequent in males than in females, and the incidence in subjects with African American ethnicity is higher compared to Caucasians or Asians (Shirley MH, et al, Br J Haematol. 2013; Giaquinto AN et al, CA Cancer J Clin. 2022). Despite familial cases having been reported, most MM cases are sporadic.

2.1.3. Biologic features

MM is biologically heterogenous: presence of cytogenetic (e.g. t(4;14), t(14;16), t(14;20), del17p, gain 1q, MYC rearrangements), morphological (i.e. plasmablastic aspect) and immunophenotypic alterations (e.g. CD28+/CD117- plasma cells), extramedullary disease (EMD) and type of monoclonal protein (e.g. IgD MM) have all been variably associated with more aggressive clinical behaviour and shorter survival.

B cell maturation antigen (BCMA) is a member of the tumour necrosis factor receptor (TNFR) superfamily that is able to bind both the B cell activating factor (BAFF) and, with higher affinity, the proliferation-inducing ligand (APRIL) (Rennert P, et al, Exp Med. 2000). BCMA is selectively expressed by mature B cells and plays a pivotal role in the survival of long-term bone marrow plasma cells (Novak AJ et al, Blood 2004; O'Connor BP et al, J Exp Med. 2004). As self-regulating control mechanism, BCMA con be removed from cell surface by γ-secretase–mediated shedding, resulting in increased concentration of soluble BCMA (sBCMA). Binding to APRIL and BAFF, sBCMA reduces the activation of membrane-bound BCMA (Laurent SA et al, Nat Commun 2015).

BCMA is overexpressed in MM plasma cells, and increased expression of both BCMA and sBCMA have been associated with MM progression (Tai Y-T et al, Blood. 2016; Sanchez E et al, Clin Cancer Res. 2016). Activation of BCMA in MM leads to the upregulation of the NF-κB pathway, resulting in the expression of pro-oncogenic genes related to survival, angiogenesis, cell growth, cell-cell and cell-matrix adhesion and immunosuppression (Sanchez E et al, Clin Cancer Res 2016).

BCMA is the target of several drugs currently approved in the EU, including two anti-BCMA CAR T cell ATMPs (Abecma and Carvykti) and two bispecific CD3/BCMA monoclonal antibodies (Tecvayli and Elrexfio).

2.1.4. Clinical presentation, diagnosis and prognosis

As a reflection of its complex biological background, MM is also clinically heterogeneous. Patients can present with signs/symptoms related to either direct infiltration of tissues by MM plasma cells or the consequences of the deposition in organs and tissues of monoclonal immunoglobulins (Igs) or Ig fragments produced by MM plasma cells.

Progressive bone marrow infiltration by MM plasma cells leads to impaired blood cell production, most commonly resulting in normocytic, normochromic anaemia. Anaemia was, in fact, reported in ~70% of patients with newly diagnosed MM (NDMM), and nearly all patients are expected to develop anaemia at some point during the course of the disease (Kyle RA et al, Mayo Clin Proc. 2003). Leukopenia and thrombocytopenia can also be present, especially in advanced settings of disease.

Bone involvement in the form of osteolytic lesions is typical of MM and can result in pathologic fractures. Clinically relevant bone involvement was reported in ~25% of patients with MM (Kyle RA et al, Mayo Clin Proc. 2003), and bone pain is a major determinant of MM patients' quality of life. Osteolytic lesions mainly result from bone reabsorption due to increased osteolytic activity and osteoblasts suppression, which are mediated by the dysregulation of the RANKL/OPG ratio promoted by neoplastic plasma cells. Increased osteoclastic activity in MM is also the main cause of hypercalcaemia, which can be found in ~30% of patients at diagnosis. Severe hypercalcaemia and spinal cord compression from plasmacytoma and/or bone fragments due to pathologic fracture can be serious complications of MM.

Hypercalcaemia and deposition of Ig or Ig fragments (i.e. light chains) in renal tissues both contribute to the development of progressive kidney failure. In normal conditions, Ig light chains are freely filtered by the renal glomerulus and reabsorbed by cells of the proximal tubule. High concentrations of monoclonal light chains, as observed in MM, however, result in binding with uromodulin (a protein secreted by renal cells) and formation of intratubular casts. High urinary calcium concentrations further promote cast formation. Light chain cast nephropathy can be detected in up to 50% of subjects with NDMM (Kyle RA et al, Mayo Clin Proc. 2003, Winearls CG Kidney Int. 1995).

Due to suppressed levels of normal immunoglobulins (immunoparesis) and impaired lymphocyte/plasma cell function, patients with MM are at higher risk of severe/life-threatening infections. A seven-fold higher risk of infection compared to controls has been reported in MM, in particular during the first year following diagnosis (Blimark C et al, Haematologica. 2015). Subjects with MM are especially prone to infections caused by encapsulated bacteria and viruses.

According to the International Myeloma Working Group (IMMG) criteria (Rajkumar SV et al, Lancet Oncol. 2014), MM diagnosis requires the presence of clonal bone marrow plasma cells ≥10% or biopsy-proven plasmacytoma, plus at least one of the following:

- anaemia (haemoglobin <10 g/dL or >2 g/dL below normal)
- hypercalcemia (serum calcium >11 mg/dL)
- renal insufficiency (estimated or measured creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
- one or more osteolytic lesions (i.e. ≥5 mm in size) on skeletal radiography, magnetic resonance imaging (MRI), computed tomography (CT), or combined positron emission tomography/computed tomography (PET/CT

- presence of a biomarker associated with near inevitable progression to end-organ damage (i.e. ≥60% clonal plasma cells in the bone marrow, and/or involved/uninvolved free-light chains [FLC] ratio ≥100 with involved FLC levels ≥100 mg/L, and/or more than one focal lesion involving bone or bone marrow on MRI)

Although in the majority of patients monoclonal immunoglobulins produced by MM plasma cells (i.e. M protein) can be detected in serum and/or urine, in ~20% of patients only light chains are observed (i.e. light chain myeloma) because of lacking or reduced expression of the immunoglobulin heavy chains. Approximately 3% of MM patients have no immunofixation-detectable M protein in serum of urine: this condition is known as non-secretory MM.

A recent systematic literature review showed that more than 90 factors have been statistically associated to R/R MM prognosis/response in at least one study. Worse survival was significantly associated with high disease stage, older age, increasing prior lines of therapy, suboptimal response to treatment, high-risk cytogenetics, elevated LDH levels, presence of extramedullary disease and reduced performance status (PS). Response rates were influenced by disease stage, age, number of prior lines of therapy, cytogenetics, and PS (Kumar S et al, Hemasphere 2023).

In clinical practice, the "International Staging System" (ISS, Greipp PR et al, JCO 2005) and the "Revised ISS" (R-ISS, Palumbo A, et al, JCO 2015) are routinely used to stratify patients according to prognosis. The ISS stratify patients in 3 distinct risk groups based on serum beta-2 microglobulin and serum albumin levels; the R-ISS further integrates ISS results with prognostic information from serum LDH levels and cytogenetics.

2.1.5. Management

MM is characterised by a chronic, relapsing/remitting behaviour with progressive increased resistance to active compounds.

Novel treatments introduced in the last 20 years have improved life expectancy for patients with MM, and the estimated 5-year survival rate now exceeds 50% (Cancer.net 2020). However, despite significant therapeutic advances, approximately 10% of patients die within 1 year of diagnosis, and early deaths due to disease progression or treatment toxicity are still a clinically relevant issue, with 6% and 24% of patients experiencing fatal events before or during their first-line treatment, respectively (Mohty M et al, Eur J Haematol. 2019).

Real-world data also suggest that approximately 40% and 62% of patients are not able to proceed to 2nd and 3rd line treatment, respectively (Raab Ms et al, Br J Haematol 2016; Yong K et al, Br J Haematol 2016).

Several compounds are approved in the EU for the treatment of MM, yet immunomodulators (IMiDs, e.g. lenalidomide, thalidomide and pomalidomide), proteasome inhibitors (PIs, e.g. bortezomib, carfilzomib and ixazomib) and anti-CD38 monoclonal antibodies (anti-CD38 mAbs, e.g. daratumumab, isatuximab) form the backbone of most regimens indicated for the treatment of NDMM and R/R MM.

The choice of frontline treatment is based on transplant eligibility: younger and fitter patients usually receive 1 to 4 cycles of induction therapy to reduce the burden of disease before transplant. The EHA-ESMO clinical practice guidelines for the treatment of MM (Dimopoulos MA et al, Ann Oncol 2021) recommend VRd (bortezomib, lenalidomide and dexamethasone) or Dara-VTD (daratumumab, bortezomib, thalidomide and dexamethasone) as first option induction regimens. Following induction, responders receive further consolidation with intravenous (iv) melphalan (200 mg/m^2) followed by autologous stem cell transplant (ASCT). Lenalidomide maintenance is recommended after ASCT to

prolong responses, while the role of additional treatment cycles as post-transplant consolidation is still unclear.

For older and/or frailer subjects who are not deemed eligible for ASCT the EHA-ESMO guidelines recommend as initial treatment multi-drug combinations such as Dara-RD (daratumumab, lenalidomide and dexamethasone), Dara-VMP (daratumumab, bortezomib, melphalan and prednisone) or VRd. VMP (bortezomib, melphalan and prednisone) and Rd (lenalidomide and dexamethasone) are considered as possible alternatives when first-choice regimens are not available.

The treatment of subjects with relapsed or refractory disease is less standardised. Several agents/combinations have been approved for the treatment of R/R MM and can be used sequentially with the aim of reducing the risk of cross-resistance and maximising clinical benefit in terms of disease control. Several factors such as age, comorbidities, PS, persisting toxicity from previous treatments, prior exposures, type and depth of response to previous lines of treatment, available treatment options and type of progression (e.g. biochemical relapse vs. clinical relapse) guide treatment choice in R/R MM. As a general rule, responses become shorter and their clinical relevance is reduced with increasing lines of therapy.

Real-world data showed that outcomes for subjects with MM who are "tripe-class refractory" (TCR, i.e. patients whose disease is refractory to at least one IMiD, one PI and one anti-CD38 mAb) are unsatisfactory: the ORR in this setting did not exceed 30%, the median PFS was approximately 3 to 5 months and the median OS was less than 1 year (see e.g. Gandhi UH et al, Leukemia 2019; Moreau P et al, Blood 2021). Recent data, however, hinted to some improvement in the life expectancy of these patients, with a median survival from development of TCR status of 25.5 months. The impact of novel therapies on survival improvements in TCR patients has not been definitely clarified, yet it was highlighted that the time to TCR status development could be of prognostic significance in this setting, since patients who took longer to become TCR had a longer median OS (see Danis R et al, Blood 2023 Supplement 1).

Several products are currently authorised in the EU for the treatment of "triple-class exposed" (TCE) patients[1].

Abecma (idecaptagene vicleucel) and Carvykti (ciltacaptagene autoleucel) are chimeric antigen receptor (CAR) T cell advanced medicinal products (ATMPs) targeting BCMA. CAR T cell (CARTs) products are manufactured from autologous T lymphocytes using a viral vector to transduce into T cells the DNA sequence codifying specific CARs. Abecma is indicated for the treatment of adult patients with relapsed and refractory MM (RR MM) who have received at least two prior therapies, including an IMiD, a PI and an anti-CD38 mAb and have demonstrated disease progression on the last therapy. Carvykti is indicated for the treatment of adult patients with RR MM who have received at least one prior therapy, including an IMiD and a PI, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

In the TCE populations therapy with CAR T cell (CARTs) products resulted in high ORRs (70 to 85%) and clinically relevant response durations (from 11 to more than 30 months). The main toxicities with anti-BCMA CARTs are cytokine release syndrome (CRS), which occurred in approximately 80-90% of patients in clinical study (Grade ≥3 ~5%), neurologic adverse reactions, including immune effector cell-associated neurotoxicity syndrome (ICANS), occurring in approximately 15% of patients (Grade ≥3 ~3%) and prolonged/recurrent cytopenias. Movement and neurocognitive toxicity with signs and symptoms of parkinsonism have been reported with CARTs targeting BCMA.

[1] All efficacy and safety data in this section are from registrational studies as reported in products' EPARs and SmPCs.

Three bispecific monoclonal antibodies are currently approved as monotherapy for the treatment of adult patients with RR MM who have received at least three prior therapies, including an IMiD, a PU, and an anti-CD38 mAb and have demonstrated disease progression on the last therapy. Tecvayli (teclistamab) and Elrexfio (elrantamab) are bispecific mAbs targeting CD3 on T cells and BCMA on MM plasma cells, Talvey (talquetamab) targets CD3 on T cells and GPRC5D on MM plasma cells.

Nexpovio (selinexor) is a selective inhibitor of nuclear export (SINE) that specifically blocks exportin 1 (XPO1). Nexpovio is indicated in combination with dexamethasone for the treatment of MM in adult patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy.

Pepaxti (melphalan flufenamide) is a peptide conjugated alkylating drug that is indicated, in combination with dexamethasone, for the treatment of adult patients with MM who have received at least three prior lines of therapies, whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 mAb, and who have demonstrated disease progression on or after the last therapy.

2.2. About the product

Linvoseltamab is a human IgG4-based bispecific antibody that binds to CD3, a T cell antigen associated with the T cell receptor complex, and BCMA, which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. Simultaneous engagement of both arms of linvoseltamab results in formation of a synapse between the T cell and the BCMA-expressing cell, resulting in T cell activation and generation of polyclonal cytotoxic T cell response, which results in redirected lysis of the targeted cells, including malignant multiple myeloma B-lineage cells. This effect occurs without regard to T cell receptor specificity or reliance on MHC Class 1 molecules on the surface of antigen presenting cells.

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant has initiated a Phase 3 study, R5458-ONC-2245 (Study 2245) [LINKER-MM3], to provide additional safety and efficacy data to confirm the positive benefit/risk of linvoseltamab in RRMM. Study 2245 is an open-label phase 3, randomised, active controlled study designed to evaluate the efficacy and safety of linvoseltamab monotherapy versus elotuzumab plus pomalidomide and low-dose dexamethasone (EPd) in participants with RRMM who have received 1 to 4 prior lines of therapy including a proteasome inhibitor and lenalidomide. The primary endpoint is progression free survival (PFS) as per IMWG response criteria (Kumar, 2016), determined by an IRC.

- Unmet medical needs will be addressed

  Despite advances in the initial management of MM and benefits of combination therapy in first line and for relapsed/refractory disease, relapse remains a persistent clinical problem. Irrespective of the order in which available therapies are administered across lines of treatment, when a patient has failed an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent, the opportunities for treatment can be classified into 3 categories:

- Non T-cell engaging products (selinexor/dexamethasone and melphalan flufenamide)
- Autologous BCMA targeting CAR-T therapies (idecabtagene vicleucel and ciltacabtagene autoleucel)
- Bispecific antibodies (teclistamab, elranatamab and talquetamab)

Indirect unadjusted comparisons of the clinical activity of linvoseltamab to other therapies approved in the EU are limited by important differences in the respective patient populations. However, when comparing linvoseltamab with non-T-cell engaging products (selinexor/dexamethasone and melphalan flufenamide), linvoseltamab shows efficacy benefit with higher ORR, CR rates and median DOR (71%, 50% and 29 months respectively):

- The selective inhibitor of nuclear export Selinexor (NEXPOVIO) CMA was based on the single-arm STORM study that reported ORR of 25.3% and median duration of response of 3.8 months in 83 patients with penta-refractory MM (Chari, 2019).
- The lipophilic derivative of the antineoplastic agent, melphan, known as melphan flufenamide was approved in 2022 based on the single-arm HORIZON study that reported ORR of 28.8% and median duration of response of 7.6 months in 157 patients with RRMM.

Indirect comparison of linvoseltamab's efficacy against approved BCMA targeting CAR-T, as measured by ORR/CR and projected DOR are within range of CAR-T efficacy.

- BCMA CAR-T, idecabtagene vicleucel (ABECMA) CMA approval was based on the single arm KarMMa study that showed ORR/sCR = 73.4%/32.8% and mDOR = 10.6 months in 128 MM patients who had received a median of 6 prior lines of therapy. Twelve additional patients underwent leukapheresis but did not receive idecabtagene vicleucel, lowering the IRC assessed ORR/sCR rate to 67.1%/30% (n=140).
- BCMA CAR-T, ciltacabtagene autoleucel (CARVYKTI) CMA approval was based on the CARTITUDE-1 study which showed ORR/sCR = 97.9%/82.5%. Sixteen additional patients underwent leukapheresis but did not receive ciltacabtagene autoleucel, lowering the IRC assessed ORR/sCR rate to 84.1%/70.8% (n=113) (CARVYKTI SmPC).

These CAR-T therapies may not be suitable for all patients due to their potential to cause severe safety events, limited data on relatively younger patient, and complexity of the treatment (limited availability in specialised treatment centres, delay in treatment related to the manufacturing process, need for bridging therapy). Unlike CAR-T, linvoseltamab is an off-the shelf option, enabling easier and more reliable patient access.

Compared with the approved BCMAxCD3 bispecific antibodies, teclistamab (TECVAYLI SmPC), and elranatamab (ELREXFIO SmPC), and with the GPRC5DxCD3 bispecific antibody talquetamab, linvoseltamab shows a comparable efficacy/safety profile.

Overall, these cross-study comparisons indicate that the efficacy and safety results of linvoseltamab:

- Compares favourably to other approved therapies which currently present limited efficacy, and/or have important safety concerns, or limited availability.
- Is in line with the other bi-specific antibody that are approved under CMA and have not established their benefit/risk with comprehensive data.

Given the treatment options available the efficacy and safety data for linvoseltamab indicate it is a suitable treatment option to fulfil an unmet medical need.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Based on the above considerations, the applicant believes that the available data support a premise that immediate access for patients with RRMM who have received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody would be beneficial.

2.4. Quality aspects

2.4.1. Introduction

Linvoseltamab is a human IgG4-based bispecific antibody that binds to human cluster of differentiation 3 (CD3), and human B cell maturation antigen (BCMA), resulting in T cell activation, proliferation, and T cell-induced cell lysis of malignant multiple myeloma B cells.

The finished product (FP) is presented as concentrate for solution for infusion containing 5 mg or 200 mg of Linvoseltamab as active substance (AS). Other ingredients are histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

Linvoseltamab finished product is intended for intravenous infusion after dilution in 0.9% sodium chloride solution and is available in packs of one vial:

- 2.5 mL of concentrate in a 5 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and a 20 mm aluminium seal cap with a white flip-off button, for the 5 mg presentation;

- 10 mL of concentrate in a 20 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and a 20 mm aluminium seal cap with a blue flip-off button, for the 200 mg presentation.

2.4.2. Active Substance

2.4.2.1. General Information

Linvoseltamab is a human IgG4-based bispecific antibody that binds to human cluster of differentiation 3 (CD3) and human B cell maturation antigen (BCMA). In terms of structure, linvoseltamab is a heterotetrameric protein containing two identical human kappa (κ) light chains, each covalently linked to one of two unique human gamma (γ) heavy chains. The amino acid sequence of the Fc region has been modified to reduce effector functions and to stabilise the IgG4 hinge region. Annotated amino acid sequences of heavy and light chains are provided.

The predicted molecular weight (MW) of linvoseltamab is approximately 146 kDa.

The mode of action includes bridging of BCMA-expressing cells with CD3+ T cells, resulting in T cell-mediated killing of BCMA-expressing cells.

The provided general information for the bispecific antibody is adequate.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturers

Linvoseltamab AS is manufactured at Regeneron Pharmaceuticals, Inc. 81 Columbia Turnpike, Rensselaer, New York 12144, United States.

The GMP compliance for the AS and FDS manufacturing sites involved was demonstrated.

Description of manufacturing process and process controls

Batch and Scale Definition

The scale of the FDS manufacturing process is defined by the size of the production bioreactor. Material from a single cell culture production bioreactor is harvested and purified to comprise a single lot of active substance. Each lot of linvoseltamab FDS receives a unique lot number which provides traceability to the manufacture.

Linvoseltamab FDS is expressed in Chinese hamster ovary (CHO) cells. The cell culture process starts with the thawing of single vial of the Working Cell Bank (WCB) followed by several expansion steps. The production bioreactor is operated in fed-batch mode. At the end of the production bioreactor step, samples of the unprocessed bulk are tested according to defined in-process controls. Production is performed up to the maximum limit of in vitro cell age (LIVCA). Process parameters, manufacturing or in-process controls and monitors for the cell culture process are provided in a tabulated format.

Purification of linvoseltamab is achieved through a series of chromatography, filtration, and viral inactivation and removal steps. The AS is adjusted to the target concentration and the material is classified as FDS. The filtered FDS is aseptically dispensed into the containers and stored at the proposed storage conditions.

The description of the manufacturing process steps is accompanied by flow charts indicating the process parameters and process controls. Hold times between process steps are provided. For the individual process steps, tables summarising conditions and process control classification are provided. Manufacturing or in-process limit/set points/ranges are indicated. For the chromatography steps, the procedure and buffers used at each cycle step are provided. Overall, the process parameters and in-process controls in combination with the other control measures appear sufficient to ensure consistent quality of linvoseltamab FDS.

Reprocessing is not part of the standard manufacturing process with the exception of refiltration of FDS. A post-approval change management protocol (PACMP) is provided to introduce refiltration of FDS and is considered appropriate. A commitment has been made to submit a variation if changes to the protocol itself will be made.

The linvoseltamab AS manufacturing process has been adequately described and is considered acceptable.

Control of Materials

Raw materials used for the cell culture and purification process are listed together with their quality standard (non-compendial, Ph. Eur., USP, NF, JP) and their intended use. There are no materials of animal origin used during the manufacture of linvoseltamab, except for the CHO production cells.

For non-compendial raw materials, general descriptions are provided with regards to their quality assurance. All non-compendial raw materials are tested by the vendor using their established specification and by the applicant's manufacturing site for appearance and identity. The provided general specification for all non-compendial materials in the Module 3 documentation is sufficiently detailed.

Cell culture media and feed solutions are proprietary to Regeneron. The applicant confirmed that there is a quality agreement in place with the suppliers to notify Regeneron if there are any changes in the proprietary media. Module 3 includes adequate information on the qualitative composition of cell culture media and feed solutions, and their quality control.

Source, history and generation of the cell substrate

The applicant has described the origin of the nucleotide sequences coding for the protein in sufficient detail. Schematic representations of the expression plasmids and a schematic of the genomic integration structure are provided.

Cell banking system, characterisation and testing

A master cell bank (MCB)/WCB system has been established by the applicant. Cell banks are stored at separate storage sites at or below -135°C.

The MCB was created from three vials of the source cell line. Cells were expanded harvested, resuspended and transferred to cryovials and frozen under controlled conditions

The WCB was created from a single vial of the MCB and the cells followed the same process.

The MCB and WCB were tested in accordance with ICH Q5D and ICH Q5A. The results of the testing and the testing strategy are acceptable.

Genetic stability of the production cell line was established by a limit of in vitro cell age (LIVCA).

A protocol for the establishment of future WCBs is provided. Any change to the protocol for the establishment of future WCBs should be notified via variation.

Controls of Critical Steps

The applicant has satisfactorily described the control strategy for linvoseltamab FDS production. The in-process control and monitoring programme strategy is part of the overall control strategy and relies on process knowledge gained from manufacturing process development and characterisation, historical and production experience and product knowledge.

Definitions for the process control strategy and how this is controlled, are provided. The definitions and control strategies are considered appropriate.

Tabulated summaries for in-process controls and monitors are provided for each process step. Overall, the control strategy is deemed adequate.

The microbial control approach is to minimise microbial contamination of product by controlling the facilities, utilities, raw materials, personnel, equipment, and manufacturing processes. The approach is supported.

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process.

Process validation and/or evaluation

Performance of the AS and FDS manufacturing process was verified at commercial site and scale using consecutive process validation batches.

The process validation results support the control strategy and the manufacturing process is able to consistently produce FDS with the desired quality.

The approach to setting acceptance criteria is acceptable.

Impurity clearance

The applicant has validated the removal of process-related impurities and has demonstrated that all process-related impurities were cleared to low levels during manufacturing.

Product-related impurities were evaluated during process validation studies and the methods used for the analysis of product-related impurities are validated

Hold times

Hold time limits were established and are considered acceptable.

Equipment sanitisation and storage

Equipment and reusable materials are cleaned and stored post-use.

Resin and filter lifetime

The applicant has provided protocols for the commercial scale validation plans. Resin reuse and maximum planned cycles have been established based on small-scale studies.

Data from historical manufacturing experience demonstrate consistent filter performance through several filter reuse cycles. The applicant confirms that the data from the at-scale lifetime studies will be provided through the appropriate post authorisation procedure, when available.

Medium, feed, and buffer validation

Preparation of buffers and media is validated at production scale. Validation studies demonstrate that the preparation process consistently delivers solutions that meet preparation requirements.

Shipping validation

The FDS shipping validation was successfully completed. To support linvoseltamab FDS shipping, reference is also made to prior knowledge obtained from similar products shipped at a similar setting.

Overall, the active substance manufacturing process has been validated adequately. Consistency in production has been shown. The purification process consistently produces linvoseltamab AS of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Two production processes were developed for linvoseltamab.

Changes have been introduced during the development of the manufacturing process and comparability studies have been carried out demonstrating that, apart from some expected differences, the change did not have a significant influence on the quality of the product. Overall, the comparability study is in line with the requirements of ICH Q5E guideline.

For release testing, small differences were observed, which were adequately explained and justified, and are not expected to impact safety, efficacy or pharmacokinetics. Based on release data, batches from different processes are considered comparable.

Stability data generated were used to assess comparability and the differences observed are duly justified. Overall, comparability between pre- and post-change material has been demonstrated.

Characterisation

Elucidation of Structure and other Characteristics

Linvoseltamab was extensively characterised. Characterisation studies were conducted using commercial scale and process material.

The information provided for the characterisation of the mode of action is considered sufficient.

For the primary structure characterisation, the applicant has presented relevant data to support the identity of the linvoseltamab FDS and the results are in compliance with the theoretical sequences.

The structure and profiles of linvoseltamab were determined, confirmed and the results are acceptable and as expected for a monoclonal antibody.

Overall, the AS has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG4-based antibody. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised. In summary, the characterisation is considered appropriate for this type of molecule.

Impurities

Clearance of product-related impurities has been demonstrated during process validation. Process-related impurities were sufficiently cleared below the limit of detection during process validation.

For extractables and leachables, a risk assessment program in accordance with ICH Q3D guideline was performed and resulted in a low risk. Residual solvents were sufficiently cleared by the manufacturing process. A microbial control program is in place and the adventitious agents testing program and viral risk mitigation is described.

Overall, product and process-related impurities are sufficiently cleared or controlled during the manufacturing process.

2.4.2.3. Specification

The acceptance criteria have been established based on experience with manufactured lots, development data, safety considerations, clinical experience, and stability data. For release and stability, specification acceptance criteria were also supported by statistical evaluations.

Specifications are provided for release and in-process controls. Batches used for specification setting are considered representative. For each attribute included in the specification, information has been provided. The set of release and in-process parameters tested complies with ICH Q6B, Ph. Eur. general monograph (2031), and EMA/CHMP/BWP/532517/2008.

For the compendial methods reference has been made to the respective Ph. Eur monographs.

Overall, linvoseltamab FDS specifications and in-process control limits are considered adequate.

Analytical Procedures

For the in-house analytical methods, the descriptions are sufficiently detailed and acceptable. For compendial methods, the applicant refers to USP/Ph. Eur./JP, as applicable.

The information provided is considered sufficient.

Validation of analytical procedures

According to the tabulated validation summaries, analytical methods have been sufficiently validated and are suitable for their intended use. The characteristics mentioned in the current ICH Q2 guideline have been considered for method validation.

Batch analyses

Batch analyses data are provided for linvoseltamab AS and FDS lots used during non-clinical and clinical development and used during process validation.

All results comply with the specifications valid at time of testing. All of the results are consistent from batch to batch and the process can be considered under control.

Reference Standards or Materials

No international reference standard is available for linvoseltamab since it is a new molecular entity. An appropriate description of reference standards used throughout the development of linvoseltamab has been provided. In addition, method description and qualification/validation of the methods used in the qualification of the linvoseltamab reference standards are provided.

The primary linvoseltamab reference standard was prepared from AS batch that was produced using the current manufacturing process. The primary reference standard is used to qualify new primary and working reference standards. Once a working reference standard is in use, the primary reference standard will not be used for release and stability testing anymore. Qualification results are provided. The current primary reference standard has been tested and all acceptance criteria were met.

A working reference standard has not (yet) been established. However, a protocol for the qualification of future primary and working reference standards is provided. For qualification, reference standards will be extensively tested using release and additional characterisation tests. This approach is considered appropriate. According to ICH Q6B guideline, a two-tiered reference standard system is envisaged. A working reference standard is currently being qualified and will be implemented via an appropriate post authorisation procedure, as applicable.

Container Closure System

A description of the container closure system has been given together with a drawing of the container closure components (with dimensions). The container closure system meets the criteria outlined in the Ph.Eur. 3.2.2.1 Plastic Containers for Aqueous Solutions for Infusion and is supplied ready-to-use (sterilised by irradiated) by the supplier. An overview of components and their specifications is provided. No animal-derived materials are used in the manufacturing of the bottles of closures.

Extractables and leachables study were performed and no leachables of toxicological concern originating from the container closure system were identified. A commitment has been made to continue the leachables study until the end of shelf-life (REC).

Protection of the AS by the container closure system from external stress were evaluated. Photostability studies according to ICH Q1B guideline were conducted. Overall, suitability of the container closure system was demonstrated.

2.4.2.4. Stability

The design of the registration stability studies is in line with ICH Q5C guideline. Stability specifications are identical to the release specifications. Overall, the selected stability assays have been justified and are considered adequate.

All batches were stored in container closures representative of the commercial container closure system.

At the recommended storage condition, all results were within specifications and no significant trending has been observed.

The provided stability data currently support the proposed shelf-life at the recommended storage condition for linvoseltamab FDS. The stability program of linvoseltamab FDS also includes photostability, freeze/thaw stability, and forced degradation studies.

The photostability study has been conducted in line with ICH Q1B guideline. Based on the results of the photostability study, light exposure should be limited during storage and handling of linvoseltamab. This aspect is also covered by the accompanying SmPC: "*Keep the vial in the outer carton to protect from light.*"

A commitment to complete the currently ongoing stability studies is provided. In addition, at least one commercial batch of linvoseltamab FDS will be placed in the long-term stability program at per year during production years.

2.4.3. Finished Medicinal Product

2 . 4 . 3 . 1 . Description of the product and Pharmaceutical Development

Description and Composition of the Drug Product

The finished product (FP) is presented as concentrate for solution for infusion containing 5 mg or 200 mg of linvoseltamab as active substance (AS). Other ingredients are histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

The product is available in two presentations: 5 mg (2 mg/ml) and 200 mg presentation (20 mg/ml).

Both FP presentations are filled into a Type I glass vial, with a grey chlorobutyl stopper with coating and a 20 mm aluminium seal cap with a white or blue flip-off button.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur standards. There are no novel excipients or excipients of human or animal origin used in the finished product formulation.

There are no overages included in the formula; however, a slight overfill is included to ensure that there is adequate volume in the vial to provide the required dose.

Pharmaceutical development

The FDS consists of purified protein in an aqueous buffered solution. FDS is then diluted to the final concentration, filled into a glass vial, and administered as liquid finished product (FP). After dilution, the FDS and FP excipient concentrations remain the same. The choice of the FP formulation and its components were adequately justified and supported by the results of various studies.

Manufacturing process development

The FP manufacturing process is a standard aseptic filling process. During development, some changes to the manufacturing process were applied. All those changes were addressed by appropriate comparability studies. The results of the comparability studies are found acceptable.

Product contact material

The single-use disposable materials used in the FP manufacturing process, which come into contact with product were analysed. The choice of the filters, their characteristics, performances and compatibility were sufficiently addressed and justified.

The extractable assessments and leachable studies performed for the FP filling process indicate no leachables of toxicological concern associated with the manufacturing process of FP.

The description and choice of the container was acceptable and adequately justified. Results from the extractables and leachables study currently evidenced no leachable of toxicological concern. However, the long-term study is still ongoing. The applicant committed to provide post approval, additional results of the ongoing leachables study via a post authorisation procedure (REC).

Compatibility

Lynozyfic should be administered as an intravenous (IV) infusion through a dedicated infusion line. Compatibility with intravenous materials as well as in-use stability were investigated, using different linvoseltamab concentrations. No significant changes in the main attributes were observed. Lynozyfic is compatible with polyvinyl chloride (PVC) non-di-ethylhexylphthalate (non-DEHP), polyolefin (PO), or ethyl vinyl acetate (EVA) infusion bags. The microbial challenge and in-use stability studies support the recommended storage conditions:

"Once prepared, administer diluted solution immediately. Chemical and physical in-use stability has been demonstrated for the diluted infusion solution as follows:
- up to 8 hours at room temperature (20 to 25°C) from preparation to the start of the infusion
- up to 48 hours under refrigeration at 2 to 8 °C from preparation to the start of the infusion.
From microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior use are responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions."

All results are in good agreement with previous in-use studies performed and are within acceptance limit of long-term stability of DP in container. The quality and in-use stability of linvoseltamab is sufficiently shown and acceptably justified.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

During the assessment, a major objection was raised regarding the GMP compliance of a site involved in the manufacture of the FP. This issue was adequately addressed by the applicant and the site was confirmed to be GMP compliant to perform the manufacturing activities intended for Lynozyfic.

For all the sites involved, proof of GMP compliance was provided.

Description of manufacturing process and process controls

Batch formula and batch size ranges for the two FP presentations were provided and based on the results of the process validation and process development studies.

The FP manufacturing process is standard for monoclonal antibodies. The manufacturing process is adequately described with a sufficient level of detail. For each process step, conditions and classifications are provided. Process parameter ranges are supported by manufacturing process development. Critical operations in manufacture are defined and validated.

Control of critical steps

Critical steps and points at which process controls, intermediate tests and final FP controls are conducted are identified. The in-process controls, test methods, acceptance limits and testing frequency at each step in the manufacturing, sterilising and packaging processes are defined, and considered appropriate and adequate to assure batch quality and unit-to-unit consistency. Controls of critical steps are adequately described and supported by validation data.

Process validation

The validation process for every step was described. Consecutive PPQ batches were produced and assessed.

Overall, the collection and evaluation of in-process and release testing product quality data from the PPQ lots demonstrate that the process operates within the defined process parameters and is capable of consistently producing product that meets pre-determined quality acceptance criteria. The FP manufacturing process is consistent throughout the different steps (thawing, filtration and filling) at the scale presented in the validation documentation.

Media fill simulations

The validation of aseptic processing is performed and overall the designs and results of the validation studies for media fills can be considered acceptable.

Shipping validation

The shipping validation is acceptable and confirm that the shipping process is capable.

As conclusion, the manufacturing process has been adequately validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

2.4.3.3. Product specification

Release and end-of-shelf-life specifications for both FP presentations are provided. An appropriate testing panel is in place to ensure the quality of each batch of linvoseltamab FP given in tabulated form including test parameters, acceptance criteria and methods for release and shelf-life.

Overall, specifications for release and shelf-life are clearly identified. The specification acceptance criteria are both clinically justified and will ensure consistent product quality from the commercial manufacturing process.

Analytical procedures

The description of analytical procedures used specific for FP is provided, where mainly Ph. Eur. methods are used with reference provided and confirmation that procedures are carried out according to the monographs.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Overall, analytical methods are considered validated.

Batch analyses

The release data for commercial FP batches presented are within the specifications and confirm the consistency of the manufacturing process.

Characterisation of impurities

Analytical methods used to test process-related impurities were qualified and determined to be suitable for use. The impurity clearance performance was evaluated during process performance qualification and clearance data is provided.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for Marketing Authorisation Holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Results from confirmatory testing were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Container Closure System

The commercial FP primary container closure system (CCS) consists of either a 5 mL or 20 mL Type I glass vial and 20 mm elastomeric stopper with FluroTec film and cured silicone coating, with white or blue cap.

Overall, description and suitability of the primary CCS is found acceptable.

Photostability studies demonstrated that the marketing pack designated for use with the FP CCS offers additional protection from light exposure during the transportation of labelled FP.

2.4.3.4. Stability of the product

Stability studies are executed according to ICH Q5C recommended long-term and accelerated storage conditions, maintained by qualified controlled temperature chambers.

The test articles of the 5 mg and 200 mg FP are packaged in USP/EP, Type I clear 5 mL and 20 mL borosilicate glass vials.

To date all results of long-term stability presented for commercial FP batches are within stability specification.

Long-term stability studies with liquid FP are performed with vials in inverted position only as worst-case condition for study container closure system (CCS) leachables impact. No leachables of toxicological concern have been observed through 12 months. All accelerated and stressed stability studies were performed in upright position only to study FP degradation profile.

In-use stability/photostability

In-use stability study was provided and the in-use conditions (according to SmPC) are adequately justified.

Based on the results of the photostability assessment, the additional storage precaution "protect from light" is warranted for in-use infusion solution.

Post-approval stability protocol

A minimum of one batch of each FP presentation will be placed on long-term stability at the recommended storage condition of 5°C every year that manufacturing of such batches occurs. The lot(s) will be tested in accordance with the analysis plan provided according to end-of-shelf-life specifications using validated methods. Stability protocol and commitment for the continuing/annual stability monitoring programme is provided. The stability protocol is generally acceptable.

The provided stability data currently support the proposed shelf-life at the recommended storage condition for linvoseltamab FP.

2.4.3.5. Adventitious agents

TSE compliance

Compliance with the TSE guideline has been sufficiently demonstrated.

Virus safety

The cells used for production of linvoseltamab have been extensively screened for viruses. The purification process of linvoseltamab includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated.

Viral clearance was evaluated through spiking studies at an external contract research organisation (CRO). Purified virus was intentionally added (spiked) into the process stream so that reduction by the process could be determined. The designated manufacturing steps were challenged with the selected viruses, and each step was evaluated individually at least twice to fully assess the ability of that step to remove and/or inactivate viruses.

In summary, the virus safety of linvoseltamab is sufficiently demonstrated.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Linvoseltamab is a human IgG4-based bispecific antibody that binds to human cluster of differentiation 3 (CD3), and human B cell maturation antigen (BCMA). Upon simultaneously binding to the CD3 component of the T cell receptor complex and BCMA, T cells and B cells are bridged - resulting in T cell activation, proliferation, and T cell-induced cell lysis of malignant multiple myeloma B cells.

Linvoseltamab will be commercially supplied as an aqueous buffered solution in sterile, single-use glass vials in two FP presentations: 5mg (2 mg/mL) and 200mg (20 mg/mL) concentrate for solution for infusion. It is intended for intravenous infusion after dilution in 0.9% sodium chloride solution.

During the assessment, the major objection raised regarding the GMP compliance of the finished product manufacturer site was adequately solved and it was confirmed that the site is GMP-compliant. A commitment has been made to provide the results of the ongoing leachable studies for the CCS, once available (REC).

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1 - The Applicant should provide the results of the ongoing leachable studies for the CCS, once available (REC).

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical development program was designed to evaluate the *in vitro* and *in vivo* pharmacology, PK, and toxicology profiles of linvoseltamab.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro studies

R5458-PH-18025-SR-01V1

By means of SPR-Biacore technology, REGN5458 was found to bind specifically to recombinant monomeric human BCMA protein (hBCMA.mmH, KD 437pM) with high affinity and to Cynomolgus monkey BCMA protein with lower affinity. No binding was detected for dimeric rat or mouse BCMA. Linvoseltamab also bound monomeric MfBCMA (MfBCMA.mmH) protein with lower affinity (KD = 24.6nM), with no detectable binding to dimeric rat or mouse BCMA proteins. Overall, data indicate that linvoseltamab bound human and Cynomolgus monkey BCMA, but not rat or mouse BCMA. No similar assay was performed for recombinant CD3.

R5458-PH-18026-SR-01V1

In a T cell binding test, Linvoseltamab bound to human and Cynomolgus monkey primary T cells with similar EC50 values, ranging between 120-193nM. In an evaluation of Jurkat T cell binding, linvoseltamab bound to both Jurkat/NFAT-Luc (endogenous hCD3 expression) and Jurkat/NFAT-Luc/MfCD3 (engineered to stably express Cynomolgus monkey but not human CD3 with antibody binding capacity (ABC) ranging between 21171-24104 antibodies/cell.

In an evaluation of linvoseltamab binding to 2 human MM cell lines, NCI-H929 and MOLP-8, binding to NCI-H929 was observed with an ABC of 109007 antibodies/cell and EC50 of 200nM.

In an assessment of linvoseltamab binding to HEK293 cells engineered to express either human (HEK293/hBCMA) or Cynomolgus monkey (HEK293/MfBCMA) BCMA, linvoseltamab showed detectable binding to HEK293/hBCMA only. The lack of detectable binding to HEK293/MfBCMA cells may be due to the relatively lower binding affinity of linvoseltamab for Cynomolgus monkey BCMA and low levels of Cynomolgus monkey BCMA expression on the surface of these engineered cells.

R5458-PH-18065-SR-01V1

In the presence of autologous T cells, linvoseltamab mediated cytotoxicity of primary MM cells in a concentration-dependent manner in 7 out of 12 samples from newly diagnosed patients and in 1 out of 7 samples from patients with relapsed/refractory disease. The maximum percentage kill ranged from 63-88%. No correlation between killing activity and BCMA was seen, however, as cytotoxicity of was seen also in MOLP-8 cells, which express low levels of BCMA.

PH-17123

Binding data on IgG4P-PVA isotype variants show that:

The IgG4P-PVA antibodies did not bind to the high affinity FcγRI from human or Cynomolgus monkey, in comparison to the IgG4P control antibody which bound to human and monkey FcγRI with high affinity. With regards to human FcγRIIa, similar binding is observed for the variant H167 but not for R167 one (~12-fold weaker), in comparison to the IgG4P control antibody. Different results were seen for monkey FcγRIIa where similar binding was seen for both the IgG4P-PVA isotype variants and the IgG4P control antibody.

~10-20-fold weaker binding to human low-affinity FcγRIIb was seen with the IgG4P-PVA antibodies, while comparable affinity was seen for the monkey one. Only very weak binding to FcγRIIIa (V176 variant) was seen, while no binding was showed for FcγRIIIa (F176) and FcγRIIIb, in comparison to the IgG4P control antibody which showed binding for all three proteins. Binding to Cynomolgus monkey FcγRIIIa was ~10-20-fold lower.

R5458-PH-18027-SR-01V1

A series of in vitro assays in vitro cell-based assays were performed to evaluate the potential of linvoseltamab to mediate ADCC via engagement of NK effector cells and to mediate CDC in the presence of normal human serum (NHS).

The target cell lines in these assays consisted of HEK293 cells engineered to stably express hBCMA and Jurkat cells which endogenously express hCD3. To allow for simultaneous testing of an anti-CD20 positive control IgG1, target cells were also engineered to stably express hCD20. Cell-surface binding of linvoseltamab to HEK293/hBCMA/hCD20 and Jurkat/hCD20 and anti-CD20 IgG1 control to HEK293/hCD20, HEK293/hBCMA/hCD20, and Jurkat/hCD20 was confirmed by flow cytometry.

Binding of REGN5458 to cell-surface BCMA or CD3 did not elicit ADCC or CDC at concentrations ranging from 95fM to 100nM (ADCC) or 700fM to 750nM (CDC), in comparison to control anti-CD20 IgG1 confirming both the capacity of the NK effector cells and the NHS to induce ADCC and CDC, respectively. Moreover, no detectable levels of binding to C1q were seen. This is consistent with the minimal effector function activity of IG4-based antibodies, as stated by the applicant.

In this assay, linvoseltamab:hBCMA complexes did not demonstrate detectable levels of binding to C1q. This further confirms the lack of effector function due to the IgG4-derived IgG4P-PVA heavy chain Fc constant domain, which shows minimal binding to FcGRs (demonstrated in study PH-17123).

In vivo studies

In *in vivo* xenograft models, immediate treatment with REGN5458 of mice bearing both NCI-H929 and MOLP-8 xenografts at 0.4 and 4 mg resulted in significant tumour clearance in all mice by the end of the dosing regimen, in comparison to REGN5458 at 0.04 mg/kg. Serum Levels of IFN-γ and IL-2 are significantly elevated (data not shown in the AR).

REGN5458 serum trough concentration ranges at 0.04, 0.4, and 4 mg/kg were of 0.4-1.3, 3.8-13.9, and 33.6-139.8 µg/mL, and 0.4-1.4, 3.8-12.5, and 38.2-137.2 µg/mL during the dosing period, for NCI-H929 and MOLP-8 xenografts, respectively.

Mice co-implanted SC with xenografts of human PBMC and NCI-H929 cells on day 0 and administered IP PBS vehicle control, CD3-binding isotype control bsAb, or REGN5458 at 0.04, 0.4, or 4 mg/kg on day 5, treatment with REGN5458 at 0.4 and 4 mg/kg resulted in NCI-H929 tumour growth suppression

through the dosing period when compared to CD3-binding isotype control bsAb. REGN5458 at either 0.4 or 4 mg/kg resulted in mice that remained tumour-free through day 55, 4 weeks after the last dose. Treatment with REGN5458 at 4 mg/kg showed significantly higher efficacy compared to REGN5458 at 0.4 mg/kg, by day 19.

Treatment of mice bearing 5-day established NCI-H929 tumours with REGN5458 at 0.04, 0.4, and 4 mg/kg was associated with serum trough concentration ranges of 0.3-0.6, 3.5-8.6, and 34.8-122.4 µg/mL, respectively, during the dosing period.

The extent of depletion of plasma B and peripheral B cells in BM samples was assessed after a single IV dose (0.1, 1, or 5 mg/kg) of linvoseltamab to male Cynomolgus monkeys (Study R5458-PM-17155, see PK Section). Examination of BM samples on Day 8 revealed linvoseltamab-mediated BM plasma cell depletion at all dose levels. Analysis of samples on Day 28 revealed BM plasma cell depletion in 2 of 3 animals in the 5 mg/kg dose groups.

A toxicology study in Cynomolgus monkeys dosed once weekly for 5 weeks IV with 0.1, 1, or 10 mg/kg linvoseltamab evaluated B cell and circulating plasma cell levels (Study R5458-TX-17179, see Toxicology Section).

Marked decreases in B cells (CD20+) occurred at all dose levels during the dosing period and returned to baseline during the 12-week recovery period following dosing. Low and variable numbers of circulating plasma cells (CD138+) were observed across the control and linvoseltamab-treated groups throughout the study.

2.5.2.2. Secondary pharmacodynamic studies

Secondary PD studies with linvoseltamab were not submitted.

2.5.2.3. Safety pharmacology programme

Safety pharmacology evaluations were integrated into a GLP-compliant repeat-dose toxicology study conducted in Cynomolgus monkeys using linvoseltamab (R5458-TX-17179, also see Repeat dose toxicity). These evaluations included measurement of cardiac conduction by Jacketed External Telemetry, as well as assessment of haemodynamics (heart rate and blood pressure), respiratory function (breaths/minute and pulse oximetry) and CNS function. At dosages up to 10 mg/kg/week (IV), the highest dose administered for 5 consecutive weeks, there were no drug-related respiratory, neurological, or cardiovascular changes evident.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug-drug interaction studies with linvoseltamab were submitted.

2.5.3. Pharmacokinetics

Two single IV dose PK studies were performed to characterise the PK profile of linvoseltamab, respectively in male Cynomolgus monkeys (R5458-PM-17155), and in female Cynomolgus monkeys (R5458-PM-17167), summarised in **Table 1**.

Table 1. Summary of mean pharmacokinetic parameters of total linvoseltamab In Cynomolgus monkey serum following a single intravenous injection of linvoseltamab to the in Cynomolgus monkey.

Study No. (Compliance)	Species/ Route	Dose (mg/kg)	N/Sex	t_{max} (h)	C_{max} (µg/mL)	C_{max}/ Dose ([µg/mL] / [mg/kg])	$t_{1/2}$ (day); (SD)	AUC_{inf} (day• [µg/mL])	AUC_{inf}/Dose (day•[µg/mL] / [mg/kg])	V_{ss} (mL/kg)	CL (mL/day/kg)
R5458 PM17155 (non-GLP)	Monkey / IV	0.1	3M	0.0833	2.66	26.6	5.17 (2.99)	12.2	122	62.7	8.58
	Monkey / IV	1	3M	0.0833	29.9	29.9	4.38 (2.61)	120	120	57.4	9.08
	Monkey / IV	5	3M	0.0833	142	28.4	4.45 (2.57)	601	120	58.5	8.38
R5458-PM-17167 (non-GLP)	Monkey / IV	0.01	5F	0.0700	0.218	21.8	9.21 (3.75)	1.48	148	82.9	7.13
	Monkey / IV	0.1	5F	0.0700	2.21	22.1	8.82 (3.00)	15.1	151	88.9	7.13
	Monkey / IV	1	5F	0.0700	20.7	20.7	8.43 (3.23)	131	131	84.6	8.06

ADA; Anti-drug antibody; AUC_{inf}, Area under the concentration-time curve from time zero extrapolated to infinity; C_{max}, Peak concentration, CL, Total body clearance; F, Female; GLP, Good Laboratory Practice; IV, Intravenous; M, Male; N, Number of animals; SD, Standard deviation; $t_{1/2}$, Elimination half-life (estimated in the elimination phase); t_{max}, Time to C_{max}; V_{ss}, Volume of distribution at steady state.
Note: Concentration values considered to be outliers (72-hour time points in all animals from 0.1 mg/kg and 1 mg/kg dose groups) and impacted by ADA (3 animals from the 1 mg/kg dose group) were excluded from mean concentration calculations and data analysis.

Non-compartmental analysis were conducted to establish the concentrations of total linvoseltamab in monkey serum (**Figure 1** and **Figure 2**).

Figure 1. Mean (+SD) Total linvoseltamab concentrations in serum vs time following a single intravenous injection of linvoseltamab in the male Cynomolgus monkey (R5458-PM-17155)

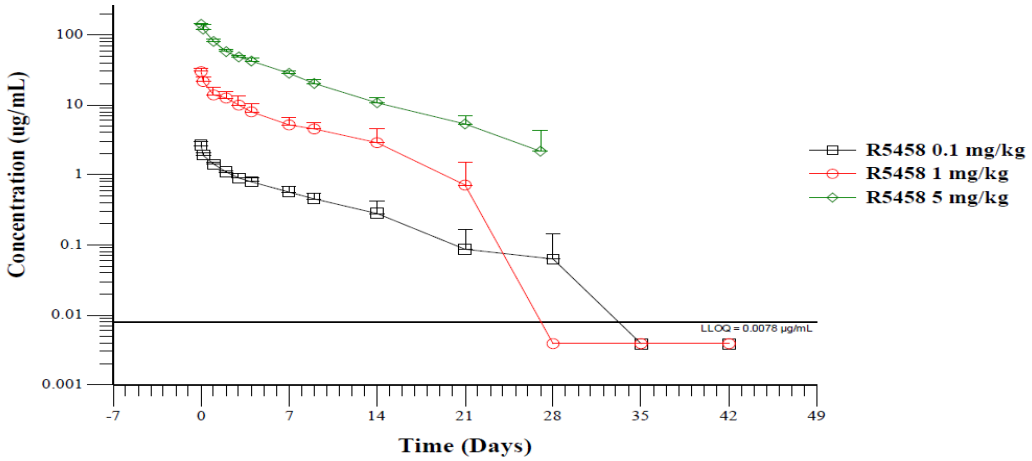
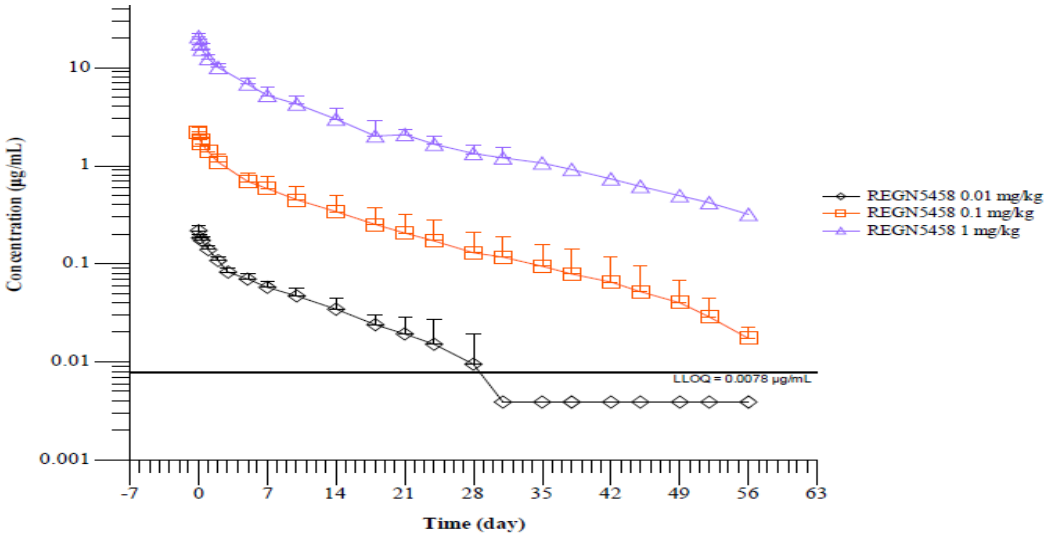


Figure 2. Mean (+SD) total linvoseltamab concentrations in serum vs time following intravenous injection of linvoseltamab in the female Cynomolgus monkey (R5458-PM-17167)



2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity studies were conducted. Based the results of the single-dose PK/PD study (R5458-PM-17155), the conduct of additional single dose studies in non-human primates (NHPs) were considered unnecessary to support the design and conduct of repeat-dose GLP toxicology studies.

2.5.4.2. Repeat dose toxicity

Two repeat dose toxicology studies were performed by the applicant, (Study R5458-TX-17179 and Study r5458-tx-20118). In the context of such studies, TK parameters, immunogenicity and safety pharmacology were evaluated.

Study R5458-TX-17179: A 5-Week Intravenous Infusion Toxicity and Toxicokinetic Study in Cynomolgus Monkeys With a 12-Week Dose-Free Recovery Phase

Male and female Cynomolgus monkeys, assigned to 4 groups, were administered once weekly for 5 weeks via intravenous infusion, according to the scheme below (**Table 2**). The potential toxicity of REGN5458 toxicokinetic profile were determined.

Table 2. Study R5458-TX-17179 Design: Group designation and dose levels

Group[a]	No. of Animals[b] Male	Female	Dose Level (mg/kg)	Dose Concentration (mg/mL)
1 (Control)	6	6	0	0
2 (Low)	6	6	0.1	0.1
3 (Mid)	6	6	1	1
4 (High)	6	6	10	10

a Group 1 was administered control article/placebo only. The control article/placebo was 10 mM Histidine pH 6.0, 10% sucrose, and 0.1% polysorbate 80.

b Animals designated for recovery sacrifice (three animals/sex/group in Groups 1 through 4) underwent 12 weeks of recovery following the dosing phase.

Noteworthy Findings: at the end of the 12-week dose-free recovery period effects occurred were fully or partially resolved and all animals survived to scheduled necropsy. For animals administered ≥0.1 mg/kg, clinical observations were limited to transient emesis/vomitus (associated with mildly elevated CRP and cytokines), and red or liquid faeces. Main treatment-related changes consisted of pharmacologically anticipated decreases in BCMA-expressing B cells and plasma cells, and globulins. Clinical pathology changes occurred are reflective of a pharmacologically mediated inflammatory/acute phase response, which included transient, minimal increases in cytokines and mild-to-moderate increases in CRP that were observed through the end of the dosing period, increased T cell cellularity and decreased $CD20^+$ B cell and $CD138^+$ plasma cell cellularity in lymphoid tissues. The high dose of 10mg/kg corresponds to mean Cmax and AUC values of 353 µg/mL and 1400 µg x day/mL, respectively, in males and 388 µg g/mL and 1630 µg x hr/mL, respectively, in females on Day 29 of the dosing phase.

Study R5458-TX-20118: A 9 or 14-Week Intravenous Injection Toxicity and Toxicokinetic Study in Sexually Mature Cynomolgus Monkeys with a 13-Week Recovery Phase (GLP)

Initially designed to evaluate the safety profile of linvoseltamab following once weekly dosing for up to 26 weeks, the study protocol was amended, and the study design (**Table 3**) was modified to a 9- or 14-week dosing period after several animals were electively euthanised due to deteriorating body condition, as described below, with a recovery period of 13 weeks.

Table 3. Study R5458-TX-20118 Design of the 9- or 14-week repeat-dose toxicology study

Group	Terminal Necropsy[a]		Recovery Necropsy[b]		Unscheduled Necropsy		Dose Level (mg/kg)
	Male	Female	Male	Female	Male	Female	
1 control	4	4	2	2	NA	NA	0
2	3	3	2	2	1	1	1
3	1	NA	1	1	4	5	5
4	3	3	2	NA	1	3	20

[a] Terminal necropsy was conducted on Day 64 (Group 4) or Day 95 (Groups 1, 2, and 3).
[b] Recovery necropsy was conducted on Day 154 (Group 4) or Day 183 (Groups 1, 2, and 3).
NA, Not applicable

Noteworthy Findings: because of the early sacrifice of animals across all groups, a NOAEL could not be determined in this study. Once weekly IV administration of ≥1 mg/kg linvoseltamab resulted in a worsening of the inflammatory response observed in the 5-week study. Decline of general conditions of

the animals 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. Main findings are related to activation of the immune system included multi-organ immune cell infiltrates progressing to occasional inflammation, including peritonitis and pleuritis, and variable changes in clinical pathology parameters. The observed inflammatory response and the associated macroscopic and microscopic inflammation, corresponding with clinical observations of inappetence and liquid faeces, were associated with the observed decline in body weight and condition of animals. In some animals sacrificed early, positive bacterial cultures were obtained from abdominal swabs and/or blood samples. In addition, a role for opportunistic infections could not be confirmed or ruled out based on the available data in this study. The observed inflammatory process was not completely resolved after the 13-week treatment free interval; however, as stated in the study report, the severity of the described findings was reduced suggesting the hypothesis for reversal.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted with linvoseltamab as antibodies are not expected to interact directly with DNA or other chromosomal material.

2.5.4.4. Carcinogenicity

As linvoseltamab is intended for use in patients with advanced malignancies, carcinogenicity studies were not conducted with linvoseltamab, consistent with ICH S9 guideline Nonclinical Evaluation of Anticancer Pharmaceuticals.

2.5.4.5. Reproductive and developmental toxicity

Standalone fertility studies were not conducted by the applicant as male and female fertility endpoints were evaluated in the 5-week study and specific immunotoxicology endpoints were evaluated in both the 5- and 9- or 14-week studies repeat dose toxicity studies.

Linvoseltamab-induces B cell/plasma cell cytopenia which can affect the offspring in pregnant women receiving treatment. This is known from other B cell targeting therapeutics as reported in the literature and in their product labelling. Moreover, antibodies can cross the placenta into the fetal circulation. Based on the above, in vivo studies are deemed not warranted because of the limited value to further understand or communicate the risk to patients with advanced cancer.

2.5.4.6. Toxicokinetic data

Study R5458-TX-17179

Mean Cmax and exposure (AUCtau) values increased in a dose-proportional manner during the treatment period. Dose-proportional exposure was maintained during the recovery periods.

An increased 1.8- to 2.4-fold of mean Ctrough concentrations, measured 1 week following each dose, from the first dose to the fifth dose, indicates accumulation of linvoseltamab during the treatment period.

By visual inspection of the individual concentration-time profiles ADA appeared to affect linvoseltamab concentrations in 13 of 36 (36%; 5 of 12, 5 of 12, and 3 of 12 animals in the 0.1, 1, and 10 mg/kg dose groups, respectively) linvoseltamab-treated animals. The concentration values considered to be impacted by ADA were excluded from mean concentration calculations and data analysis. The apparent

ADA response was dose independent. Concentrations were impacted by ADA in a greater number of males (10) than females (3).

With the exception of 6 animals (3 animals each in the 0.1 and 1 mg/kg dose groups), which were deemed to have ADA-impacted linvoseltamab concentrations, continuous exposure was maintained in 30 of 36 (83%; 9 of 12 animals in both the 0.1 and 1mg/kg dose groups, and in 12 of 12 animals at the highest administered dose of 10 mg/kg, which was denoted as the HNSTD during the 5-week treatment period) linvoseltamab-treated animals during the 5-week treatment period.

Through the end of the recovery period, concentrations of total linvoseltamab were detected in 2 of 18 (11%; 1 in each of the 0.1 and 1 mg/kg dose groups) recovery animals. At least 7 of the 18 recovery animals had linvoseltamab concentration values that were deemed to be affected by ADA, leading to the lack of detectable drug exposure.

Study R5458-TX 20118

The TK profile was characterised based on the parameters extrapolated from the repeat dose toxicity studies, following once weekly IV bolus injections of 20 mg/kg linvoseltamab for 9 weeks or control article, 1, or 5 mg/kg linvoseltamab for 14 weeks. There were no substantive differences in total linvoseltamab concentrations in serum between male and female animals; therefore, as indicated by the applicant, the data discussed in the dossier submitted were pooled and analysed as combined values.

92% of linvoseltamab treated animals maintained the exposure to total linvoseltamab during treatment periods.

50% of the animals shown detectable concentrations in the 13-week recovery period or until the time of early necropsy.

Concentration-time profiles of total linvoseltamab indicates dose-proportional increases in C_{max} and exposure (AUC_{tau}) that means linear kinetics and were characterised by a brief distribution phase followed by a single elimination phase throughout the 13-week recovery period. Steady state was achieved by the eighth dose.

Immunogenicity was observed in 47% of linvoseltamab treated animals exhibiting a positive ADA response, including 9 of 12, 4 of 12, and 4 of 12 animals in the 1, 5, and 20 mg/kg groups, respectively, suggesting a dose dependency in the generation of the ADA response. The drug tolerance limit of the assay was approximately 1300 µg/mL of linvoseltamab in neat monkey serum.

The concentration-time profiles, indicates a clear correlation between ADA response levels and an accelerated elimination of linvoseltamab.

For the 17 ADA-positive animals, 10 animals (6, 2, and 2 animals in the 1, 5, and 20 mg/kg dose groups) had a strong ADA response (>10-fold from mean prestudy counts), 2 animals in the 5 mg/kg dose group had moderate ADA responses (3- to 10-fold from mean prestudy counts), and the remaining 5 animals had low ADA responses (< 3-fold from mean prestudy counts). A slightly greater preponderance of sex-related ADA responses was observed, as more females than males (10 females versus 7 males) had anti-linvoseltamab responses.

Accumulation of linvoseltamab was observed following multiple dosing during the treatment period, as indicated by a 1.8- to 3.7-fold increases in Ctrough values across all dose groups in the 5-week and 9-

or 14-week studies. In the 9- or14-week study, steady state was achieved by approximately the eighth dose in all groups.

2.5.4.7. Local Tolerance

Local tolerability of the IV administration of linvoseltamab was investigated in the repeat-dose toxicology studies.

Mild or no findings at the injection site occurred during administration of linvoseltamab to the animals in repat dose toxicity studies, except for subcutaneous fibroplasia and/or minimal-to-mild mixed inflammatory or mononuclear cell infiltration. However, all findings were no more present at recovery necropsy.

2.5.4.8. Other toxicity studies

2 GLP tissue cross-reactivity studies were performed respectively in normal human and Cynomolgus monkey tissues (R5458-TX-17162) and selected fetal human and Cynomolgus monkey tissues (R5458-TX-21227). In these studies, linvoseltamab was applied to cryosections from panels of normal human and Cnomolgus monkey tissues (at least 3 donors and 3 animals per tissue, where available; at concentrations of 2 and 10 µg/mL) and selected fetal human and Cynomolgus monkey tissues (1-3 donors and at least 2 animals per tissue, as available; at concentrations of 2 and 5 µg/mL).

In both studies linvoseltamab staining was limited to the membrane and/or cytoplasm of mononuclear leukocytes in various human (adult and fetal) and monkey (adult and fetal) tissues, consistent with the known expression of BCMA by plasma cells and CD3 by T cells (Chetty, 1994) (Cho, 2018) (Nobari, 2022) (Madry, 1998) (Ryan, 2007).

No unanticipated cross-reactivity of linvoseltamab was observed in either study.

2.5.5. Ecotoxicity/environmental risk assessment

Linvoseltamab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), "Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment." Consequently, no studies as part of the Environmental Risk Assessment for linvoseltamab are required.

2.5.6. Discussion on non-clinical aspects

Linvoseltamab was shown to bind to both human and Cynomolgus monkey BCMA, while no binding was detected for dimeric rat or mouse BCMA. Moreover, it was able to bridge CD3 and BCMA expressed on effector and target cells, supporting its proposed mechanism of action of T cell activation and cytotoxicity.

Linvoseltamab mediated cytotoxicity was demonstrated both in vitro and in vivo. Cytotoxicity was seen against MM cell lines as well as normal autologous plasma cells, resulting from human primary T cell activation.

In cell-based in vitro assays, pre-treatment of T cells with dexamethasone slightly reduced the potency of linvoseltamab but did not affect the maximum percentage target cell kill, thus suggesting that the

proposed dexamethasone premedication regimen for mitigating cytokine release syndrome in patients receiving linvoseltamab will not impact on the product's efficacy.

Linvoseltamab has the capacity to mediate killing of primary MM cells from newly diagnosed and relapsed/refractory patients in the presence of autologous T cells. Some of the primary MM cells that could not be killed in the presence of autologous T cells with linvoseltamab have been produced with an IgG4-derived IgG4P-PVA heavy chain Fc constant domain. As stated by the applicant, the IgG4P-PVA isotype is not expected to mediate effector functions because its binding to the low affinity Fcγ receptors is drastically reduced by design. In vitro Biacore binding studies have shown that the IgG4P-PVA isotype has undetectable binding to recombinant soluble forms of FcγRI and FcγRIII, and equivalent or weaker binding to the FcγRII subtypes than IgG4P antibodies that do not contain P233VA235 mutations. This was confirmed by the lack of ADCC or CDC following binding to cell-surface BCMA or CD3. In addition, linvoseltamab:BCMA complexes did not demonstrate detectable levels of binding to C1q.

In vivo studies evaluating the efficacy of linvoseltamab show that twice weekly treatment over the course of approximately 3 weeks significantly reduces human MM tumour growth and results in tumour clearance at 0.4 and 4 mg/kg in mice co-implanted with hPBMC and either MOLP-8 or NCI-H929 MM cells, following both immediate treatment and after 5 days from implantation. Overall, linvoseltamab efficacy was demonstrated in the above-described xenograft models.

Linvoseltamab exhibits basically linear kinetics with deviations from linearity occurring only in some animals at low concentrations. Following administration of IV doses mean C_{max} and exposure (AUC_{inf}) increased dose-proportionally; total body clearance was dose independent across the dose groups and $t_{1/2}$, calculated during the terminal elimination phase, varied from 4 to 9 days.

ADA response occurred unevenly in both studies and across dose groups and genders.

The concentration-time profiles of linvoseltamab are characterised by a brief distribution phase followed by a linear beta elimination phase at concentrations adequate to saturate the target mediated elimination pathway and a nonlinear terminal elimination phase at the lower linvoseltamab concentrations.

Toxicology aspects of linvoseltamab were investigated in two repeat dose toxicity studies.

The first study was conducted in male and female monkeys once weekly for 5 weeks at doses of 0.1, 1, or 10 mg/kg IV infusion with a subsequent recovery period of 12. The subsequent toxicology study was initially programmed for 26 weeks of treatment but due to declining clinical condition that necessitated early sacrifice of a number of animals for welfare reasons, the study was stopped after 9 (total of 9 doses; 20 mg/kg group) or 14 weeks (total of 14 doses;1 and 5 mg/kg groups) via IV infusion with a subsequent recovery period of 13 weeks following the last dose.

In the 5-week study, linvoseltamab administration resulted in acute and/or transient effects (emesis, cytokine release, and faecal changes) occurring at initiation of treatment or during the dosing period. Inflammatory response, including increased CRP, were noted through the end of the dosing period and corresponded with microscopic changes of increased inflammatory cell infiltrates and/or inflammation in multiple tissues. However, most of the effects were fully or partially resolved at the end of the 12-week dose-free recovery period, and all animals survived to scheduled necropsy.

In the 9- or 14-week study, a NOAEL could not be determined. Clinical observations leading to early termination included persistent body-weight loss and decreased body-condition scores, correlated with inappetence, liquid faeces, and decreased activity. Elevated CRP and IL6 concentrations indicative of an ongoing inflammatory response correlated with pathology findings of multi-organ infiltrates with or without inflammation, including peritonitis and pleuritis with associated organ adhesions.

In some animals sacrificed early, positive bacterial cultures were obtained from abdominal swabs and/or blood samples, consistent with compromised immune surveillance due to the elimination of targeted B cells and plasma cells. The relationship between potential infections and the observed treatment effects was not definitively determined.

ADA response occurred across the studies, with a reduced systemic exposure and pharmacologic effect, more pronounced in groups that received ≤ 1 mg/kg.

No animal reproductive or developmental toxicity studies have been conducted with linvoseltamab. Linvoseltamab causes T cell activation and cytokine release; immune activation may compromise pregnancy maintenance. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, linvoseltamab has the potential to be transferred from the pregnant woman to the developing foetus. Linvoseltamab is therefore not recommended during pregnancy and in women of childbearing potential not using contraception. Based on its mechanism of action, linvoseltamab may cause foetal harm, including B cell and plasma cell lymphocytopenia, when administered to a pregnant patient.

ERA

The active substance is a bispecific antibody consisting of naturally occurring amino acids. Therefore, linvoseltamab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view linvoseltamab has been adequately characterised and is recommended for marketing authorisation.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study ID	Country/ Region	Study design	Study population	Dose Regimen	Primary Objective	Enrollment
R5458-ONC-1826 (Ongoing; Primary CSR)	US, UK, EU, South Korea	Phase 1/2 open-label, FIH study of the safety, tolerability, anti-tumor activity, and PK of linvoseltamab (anti-BCMA x anti-CD3 bispecific antibody)	**Phase 1** Patients with MM who have exhausted all therapeutic options that are expected to provide meaningful clinical benefit. In addition, each patient must have progressed after at least 3 prior lines of therapy, including an anti-CD38 antibody, a PI, and an IMiD OR progression on or after an anti-CD38 antibody and have double-refractory disease (to a PI and IMiD) or intolerance. **Phase 2** Patients must have progressed on or after 3 prior lines of therapy including a PI, IMiD, and anti-CD38 antibody, OR must be triple-refractory (defined as refractory to at least 1 PI, 1 IMiD, and an anti-CD38 monoclonal antibody).	**Phase 1** Dose escalation study to investigate linvoseltamab full dose from 3 mg (DL1) up to 800 mg (DL9) **Phase 2** Dose optimization study with 2 selected doses: Cohort 1: 5 mg/25 mg/50 mg Cohort 2: 5 mg/25 mg/200 mg	**Phase 1** To assess the safety, tolerability, DLTs and to determine one or more RP2DRs of linvoseltamab as monotherapy in patients with RRMM **Phase 2** To assess the anti-tumor activity of linvoseltamab separately in cohorts 1 and 2, as measured by ORR as determined by blinded IRC, as measured using the IMWG criteria.	*Planned Enrollment:* **Phase 1** Up to 83 **Phase 2 Cohort 1** ~104 **Phase 2 Cohort 2** ~104 *Currently Enrolled:* **Phase 1** 73 (complete) **Phase 2 Cohort 1** 104 (complete) **Phase 2 Cohort 2** 105 (complete)

2.6.2. Clinical pharmacology

Linvoseltamab clinical pharmacology was investigated in the clinical study R5458-ONC-1826 (referred to as Study 1826); a phase 1/2, open label, FIH study to assess the safety, tolerability, anti-tumour activity, PK, PD (biomarkers), and immunogenicity (ADA) of linvoseltamab in patients with RRMM.

Moreover, a population pharmacokinetics analysis of linvoseltamab in relapsed or refractory multiple myeloma has been developed with the main objectives to: 1) describe linvoseltamab PK in the RRMM population, accounting for relevant intrinsic and extrinsic covariates of exposure; 2) estimate post hoc exposure metrics, derived from individual Bayesian estimates, to enable comparison between subgroups and 3) simulate linvoseltamab exposure in the proposed registrational dose regimen of 5 mg Week 1 /25 mg Week 2 /200 mg Weekly treatment for 12 doses and then 200 mg Every other week for 5 doses after receiving at least twelve 200-mg doses. Thereafter: 1) Continued treatment with response less than VGPR: Every other week treatment, 200 mg or 2) Continued treatment with response that is VGPR or greater and have received at least seventeen 200-mg doses: Every 4 weeks treatment, 200 mg.

Population PK (PopPK) analysis

The developed population PK model (Report 23174) is based on 6995 PK observations from 281 patients from study ONC-1826 (73 patients from the phase 1 part of the study and 208 patients from the phase 2 part of the study) with the PK data cut-off: 07 Jun 2023. 46 post-dose linvoseltamab concentrations were below the limit of quantification (0.06%) and all BLQ PK observations were excluded from the analysis. Overall, there were 423 excluded observations of linvoseltamab in serum with the majority being pre-first dose concentration (260), followed by pre-dose end of infusion inversion (102), that result, in a percentage of excluded observation of 6%.

Concentrations of linvoseltamab in serum were well described by a two-compartment distribution model with parallel linear and nonlinear (Michaelis-Menten type) clearance processes. The final model

contains covariate effects for baseline WGT on CL and Q, sex on VC, and the structural covariates of time-varying albumin and IgG on CL and time-varying FLC on Vmax. The final parameter estimates are presented in **Table 4**.

Table 4. Final popPK model parameter estimates

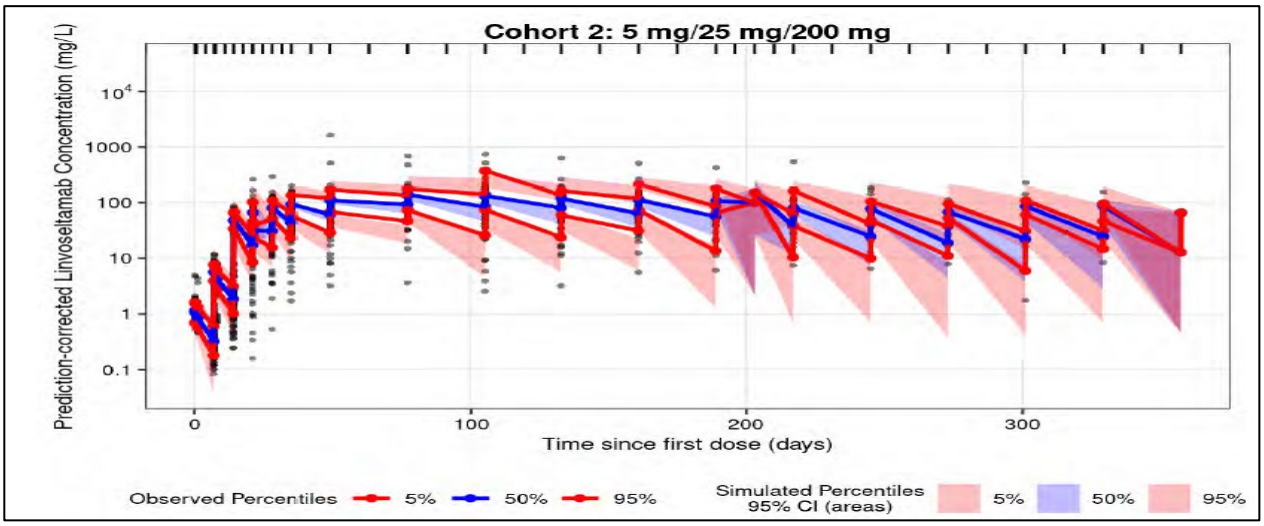
Parameter Label [Units]	Parameter Estimate (95% CI)	RSE (%) [shrinkage (%)]
CL [L/Day]	0.2022 (0.1769 — 0.2275)	6.39
VC [L]	4.125 (3.85 — 4.4)	3.407
Q [L/Day]	0.6721 (0.5856 — 0.7586)	6.565
VP [L]	3.029 (2.697 — 3.361)	5.586
Vmax [nmol/L/Day]	8.278 (5.105 — 11.45)	19.55
KM [nmol]	99.78 (63.4 — 136.2)	18.6
CL_IGG [-]	0.121 (0.08411 — 0.1579)	15.55
CL_IGG1 [-]	0.8354 (0.7631 — 0.9077)	4.418
CUT_IGG [g/L]	11.25 (10.26 — 12.24)	4.483
Albumin Effect on CL	-1.651 (-1.735 — -1.567)	2.586
FLC Effect on Vmax	0.03597 (0.02436 — 0.04758)	16.47
Proportional Error	0.2637 (0.2583 — 0.2691)	1.042
Additive Error	0.04502 (0.02564 — 0.0644)	21.96
Weight Baseline Effect on CL	0.8457 (0.5256 — 1.166)	19.31
Weight Baseline Effect on Q	1.891 (1.569 — 2.213)	8.694
Sex Effect on VC	-0.1606 (-0.2581 — -0.06311)	30.98
IIV on CL	0.2592 (0.1942 — 0.3242)	12.79 [19.83]
IIV on VC	0.1634 (0.1336 — 0.1932)	9.295 [2.782]
IIV on VP	0.4439 (0.3187 — 0.5691)	14.39 [25.24]
IIV on Vmax	0.3149 (0.2119 — 0.4179)	16.69 [29.93]

CL_IGG = power law coefficient for IgG below CUT_IGG; CL_IGG1 = power law coefficient for IgG above CUT_IGG; FLC = (total) free light chains
IIV on CL CV%: 54.4; IIV on VC CV%: 42.1; IIV on VP CV%: 74.8; VD = VC + VP = 7.154 (IIV CV%: 91.4); IIV on Vmax CV%: 60.8
Note: IIV CV% computed for log-mean distribution as $CV\% = \sqrt{e^{\omega^2} - 1}$, where ω^2 is the IIV expressed as variance.

Random effects were normally distributed and unbiased. Model fit, evaluated with conditional weighted residuals (CWRES), individual plots, and ETA distribution plots, was generally unbiased over time and predicted concentration, although some exceptions were identified.

The VPCs graphs (**Figure 3**) for the recommended dosing regimen 5/25/200mg suggest that the model describe reasonably well the median observed data, however, a clear underprediction of low concentrations and on the contrary overprediction of high concentrations (5 and 95% percentiles) was observed most likely due to limited amount of data at those extremes.

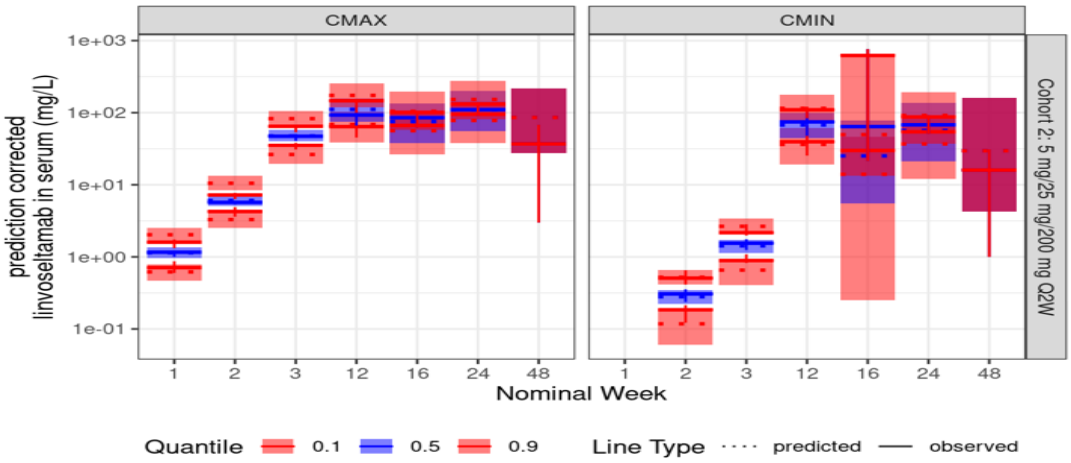
Figure 3. Visual predictive check for Cohort 2 over entire treatment



To improve interpretability, especially during treatment period beyond 48+ weeks dosing, new pcVPCs were created that separated Cmax and Ctrough samples into box plots by protocol time (e.g.

Figure 4. for patients 5/25/200 mg patients who did not swich to Q4W), with data past 48 weeks combined into the week 48 bin.

Figure 4. Prediction corrected VPC plots of linvoseltamab Cmax and Ctrough (by nominal week) in Phase 2 cohort 1 5/25/200 mg patients who did not swich to Q4W



CI, Confidence interval; C_{max}, Maximum concentration; C_{min} = Minimum (or trough) concentration; VPC, Visual predictive check.
Note: observed median and 95% CI at each quantile are shown by horizontal and vertical solid lines. Predicted median and 95% CI at each quantile are shown by horizontal dotted lines and shaded boxes, respectively.

2.6.2.1. Pharmacokinetics

Absorption

Linvoseltamab was administered via IV infusion over 1 to 4 hours; as such, bioavailability was not assessed.

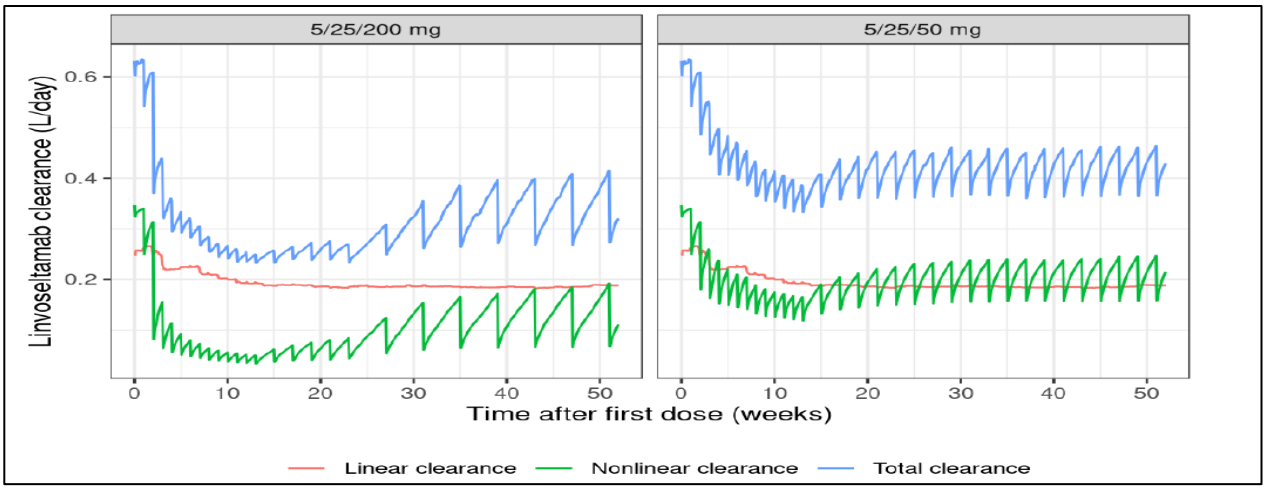
Distribution

Linvoseltamab is a bispecific antibody and primarily distributes in the vascular system. Based on the population PK analysis in patients with RRMM, the estimated geometric mean (CV% of geometric mean) of volume of distribution at steady state is 7.05 (33.6%) L.

Elimination

Linvoseltamab exhibits concentration- and time-dependent elimination. Based on the population PK analysis in patients with RRMM, the total clearance of linvoseltamab is composed of linear and non-linear (Michaelis-Menten) components (**Figure 5**).

Figure 5. Population PK Simulated Total, Linear, and Nonlinear Clearance Profiles of Linvoseltamab over Time, in Patients with RRMM



The linear clearance estimate declined modestly during first 15 weeks of treatment and reached a plateau that was consistent with non-saturable proteolytic catabolism and values typically reported for mAbs. The target-mediated (non-linear) clearance pathway was described by a concentration and time-dependent clearance term. The estimated total clearance at the end of QW dosing (week 14) and at steady state on Q4W dosing for the 5 mg/25 mg/200 mg dosing regimen was reduced by 49.6% and 30%, respectively, compared to baseline clearance (0.676 L/day) in patients with RRMM. The decline in target-mediated clearance is presumably due to a reduction in the tumour burden (malignant plasma cells) by linvoseltamab and improved disease status of the patients.

Model-based post hoc analyses were performed to simulate concentrations of linvoseltamab during the wash-out period after the administration of the last dose at the end of the QW and Q2W dosing intervals, and at steady-state. Times to reach various fractions of the Cmax and to LLOQ (0.078 mg/L) from the Cmax at these various times are presented in **Table 5**.

Table 5. Median [5th, 95th] estimated time to reach given concentration, on cessation of treatment for 5 mg/25 mg/200 mg dosing regimen of linvoseltamab, by concentration and time of last dose

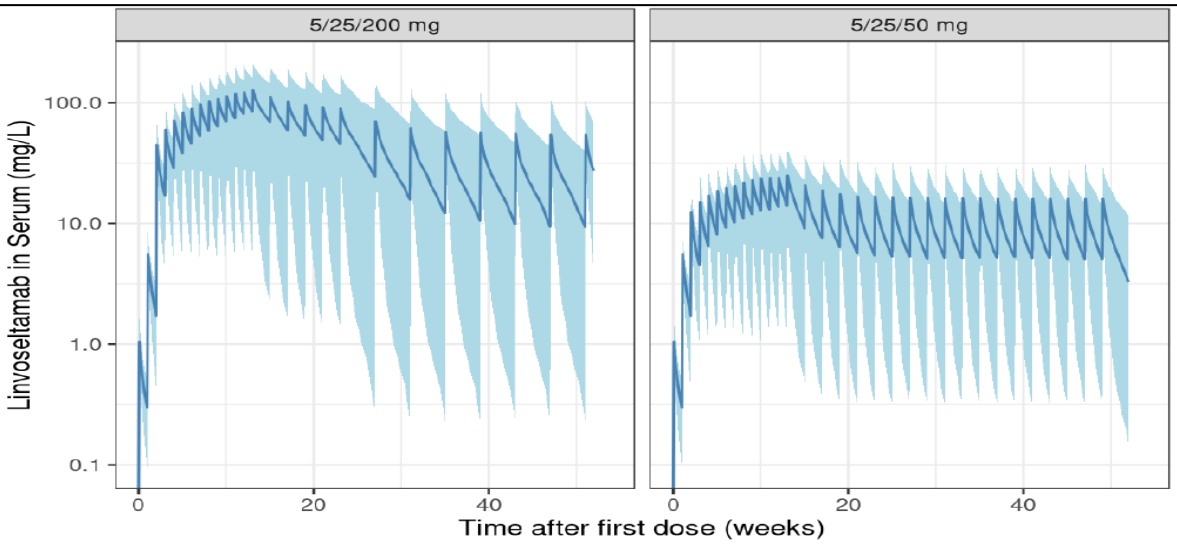
Time of Last Dose/Dose/ Interval	Time to reach 50% of C_{max} (weeks)	Time to reach 3% of C_{max} (weeks)	Time to reach 1% of C_{max} (weeks)	Time to reach LLOQ (0.078 mg/L) (weeks)
Week 14 / 200 mg/QW	2 [0.286, 4.29]	11.1 [2.57, 22]	13.6 [4, 27.3]	20.1 [5.86, 40.3]
Week 24/ 200 mg/Q2W	1.79 [0.286, 4.41]	10.6 [2.14, 22.3]	13.1 [3.44, 27.4]	18.9 [5.43, 40.3]
Week 48 / 200 mg/Q4W	1 [0.286, 3]	8.64 [2, 18.7]	11.1 [3.29, 24.8]	15.6 [5.15, 36.4]

Dose proportionality and time dependencies

Dose proportionality of linvoseltamab concentrations differed over the duration of treatment. During step-up dosing in the lower dose cohorts of phase 1, where the split dose regimens were implemented in the first two weeks (0.5 to 16 mg in week 1; 1.5 to 48 mg in week 2), concentrations were generally dose proportional. Dose proportionality in drug concentrations was also observed for 50 mg and 200 mg dose groups in phase 2 after the first full dose administration with dose normalised Ctrough value of approximately, 0.08 (Ctrough,50mg: 3.98 mg/L and Ctrough,200mg: 15.5 mg/L) for both dose groups. However, as weekly dosing continued, exposures of total linvoseltamab showed greater than dose-proportional increase at the end of QW dosing interval with dose-normalised Ctrough values of 0.22 and 0.31 (Ctrough,50mg: 11 mg/L; Ctrough,200mg: 61.8 mg/L) for the 50 and 200 mg dose groups, respectively.

Based on the population PK analysis, following the administration of the proposed regimen, patients will have received 12 doses of 200 mg QW and achieved 90% of steady-state concentration by week 12 (**Figure 6**). Over the course of this per protocol treatment regimen, Cmax and Ctrough increased, approximately, 2.4-fold and 4-fold, respectively, from week 3 to week 13.

Figure 6. Population PK simulated linvoseltamab concentration over time after simulated administration of the 5 mg/25 mg/50 mg and 5 mg/25 mg/200 mg dose regimens, respectively.



PK, pharmacokinetics.
Blue line = median predicted concentration; Blue band = 90% prediction interval.

Dosing with 200 mg Q4W started at week 24 and 97% of the steady state estimated by Ctrough was achieved by weeks, approximately, 44 to 48. The Ctrough and Caverage at steady state (200 mg Q4W) were, approximately, 10% and 24% relative to the respective values at week 13 (**Figure 7**).

Figure 7. Population PK simulated linvoseltamab exposure after Administration of the 5 mg/ 25 mg/200 mg dose regimens

	Nominal Time (Weeks)	Dose (mg)	Dosing Interval	C_{trough}(mg/L)[a] Median (5^{th}, 95^{th} percentiles)	C_{max}(mg/L)[a] Median (5^{th}, 95^{th} percentiles)	AUC_{τ}(mg*day/L)[a] Median (5^{th}, 95^{th} percentiles)
5 mg/25 mg step-up doses	1	5	QW	0.271 (61.3)	1.27 (37.4)	3.99 (32.2)
	2	25	QW	1.58 (62.8)	6.64 (37)	22 (33.8)
First full dose	3	50	QW	3.98 (68.2)	14.5 (36.4)	51.4 (37)
		200	QW	15.5 (64.8)	52.7 (37.2)	192 (34.2)
Last QW dose	13	50	QW	11 (115)	25.9 (48.2)	114 (69)
		200	QW	61.8 (123)	124 (50.4)	592 (74.6)
Full dose Q2W[b]	22	50	Q2W	4.27 (173)	19.4 (47.5)	122 (78.6)
		200	Q2W	30.2 (213)	97.9 (52.7)	727 (95.3)
Full dose Q2W[b]	48	50	Q2W	3.91 (159)	18.5 (45.4)	113 (72.2)
		200	Q4W	6.3 (362)	64.8 (45.1)	574 (84.6)
	72	50	Q2W	3.83 (157)	18.3 (44.9)	111 (71)
		200	Q4W	5.95 (338)	63.3 (43.4)	549 (78.8)
	96	50	Q2W	3.81 (156)	18.3 (44.9)	111 (70.8)
		200	Q4W	5.88 (333)	63.1 (43.1)	546 (77.7)

[a] Values are model-predicted Geometric Mean (CV%) for the last dose of specified period. Dosing occurred QW up to week 14, and Q2W from week 14 onwards.
[b] 200 mg Q4W dosing starts from week 24 for patients who achieve a response of ≥VGPR.
AUC_{τ}, area under the concentration-time curve under specified time period; C_{max}, maximum (peak) concentration; C_{trough}, trough concentration at predose before the next dose; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly.
Note: All patients in the trial are simulated at the indicated doses.

Special populations

The median age of Study 1826 Phase 1 patients was 64.0 years; 20.5% of Phase 1 patients were 75 years and older and no patients aged ≥ 85 years were enrolled. The mean age of patients in Study 1826 was similar in the Phase 2 50 mg (65.5 years) and Phase 2 200 mg patients (67.6 years). A limited number of patients ≥ 85 years (N=3) was enrolled (**Table 6**).

Table 6. Summary of elderly subjects in the pivotal studies of linvoseltamab

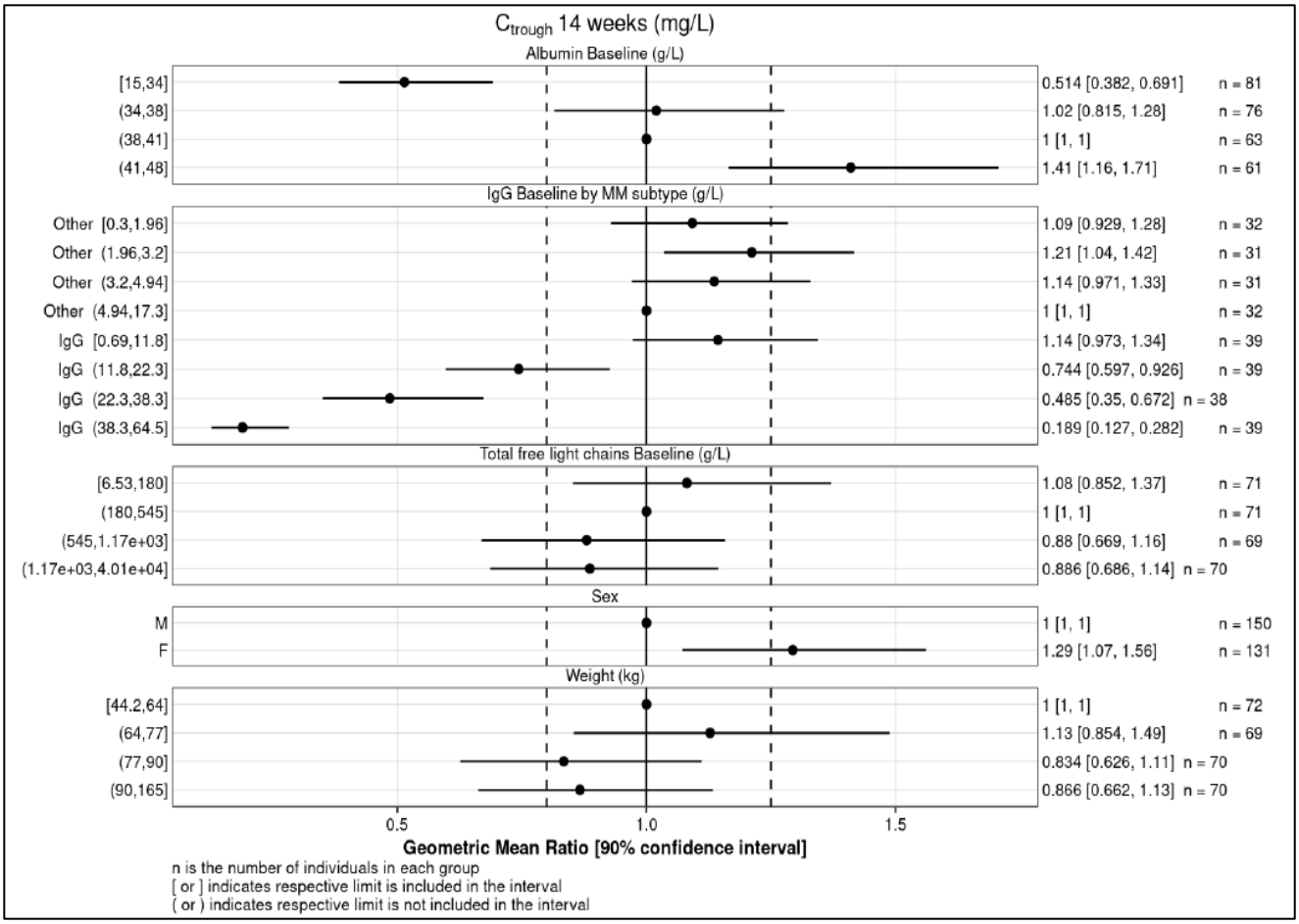
	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	98/282	58/282	3/282

Like most therapeutic mAbs, linvoseltamab is not expected to be eliminated by the kidney or metabolised by CYP450 in the liver or other tissues. As such, specific studies in renally or hepatically impaired patients were not conducted. Patients with mild (N=116; CrCL ≥60 to <90 mL/min), moderate (N=76; CrCL ≥30 to <60 mL/min), and severe (N=11; CrCL ≥15 to <30 mL/min) degrees of renal impairment or with mild hepatic function (N=27; total bilirubin >ULN to 1.5× ULN or AST >ULN) were enrolled in linvoseltamab studies and the influence of renal or hepatic impairment on linvoseltamab PK was assessed by population PK analysis but no difference in exposures were observed across the groups with various degrees of renal or hepatic impairment.

Covariate effects on linvoseltamab exposure following the 5 mg/25 mg/200 mg dosing regimen were assessed for AUC, Cmax, and Ctrough at the end of QW dosing interval, at the end of Q2W dosing interval and at steady state (week 48) for Q4W dosing frequency. Similar trends were obtained for the 3 exposure parameters and across all the time points evaluated (data not shown).

For the assessment of the effect of covariates on the PK of linvoseltamab and the post-hoc estimates of exposures, 30 covariates were tested. Of all the covariates tested, 5 covariates were identified as statistically significant for having an effect on linvoseltamab exposure. The post hoc exposures at 14 weeks stratified by covariates of interest are shown in **Figure 8**.

Figure 8. Population PK simulated effects of relevant intrinsic factors on post-hoc estimates of exposure at Week 14 - Ctrough



The patients with a IgG heavy chain involvement in their myeloma disease have much higher baseline IgG levels, which increases clearance and significantly lowers exposure. Low albumin also significantly lowers exposure. IgG and albumin were incorporated in the model as time-varying effects.

Total FLC concentrations were included in a similar fashion and had a lesser magnitude of impact.

Compared with the patients in the third quartile of albumin (38 to 41 g/L), patients with albumin in the lowest quartile (15 to 34 g/L) are simulated to achieve approximately 49% lower Ctrough. The Ctrough of patients with MM of IgG subtype who are in the top quartile of baseline IgG (38.3 to 64.5 g/L) was 18.6% of that for patients with non-IgG secreting tumours in the top quartile of baseline IgG (4.89 to 17.3 g/L).

Sex reduces central volume of distribution (Vc) by 14.8% which, given the relatively slow clearance relative to infusion time, this results in a Cmax 17.4% higher for females.

The baseline body weight in patients with RRMM from Study 1826 ranged from 44.2 to 171 kg; mean body weight was 110 kg. Based on the population PK analysis, the effect of body weight on predicted Ctrough was modest; as expected, predicted median linvoseltamab Ctrough values were lower in patients with higher body weight. Baseline weight was directly correlated with linear clearance and intercompartmental clearance.

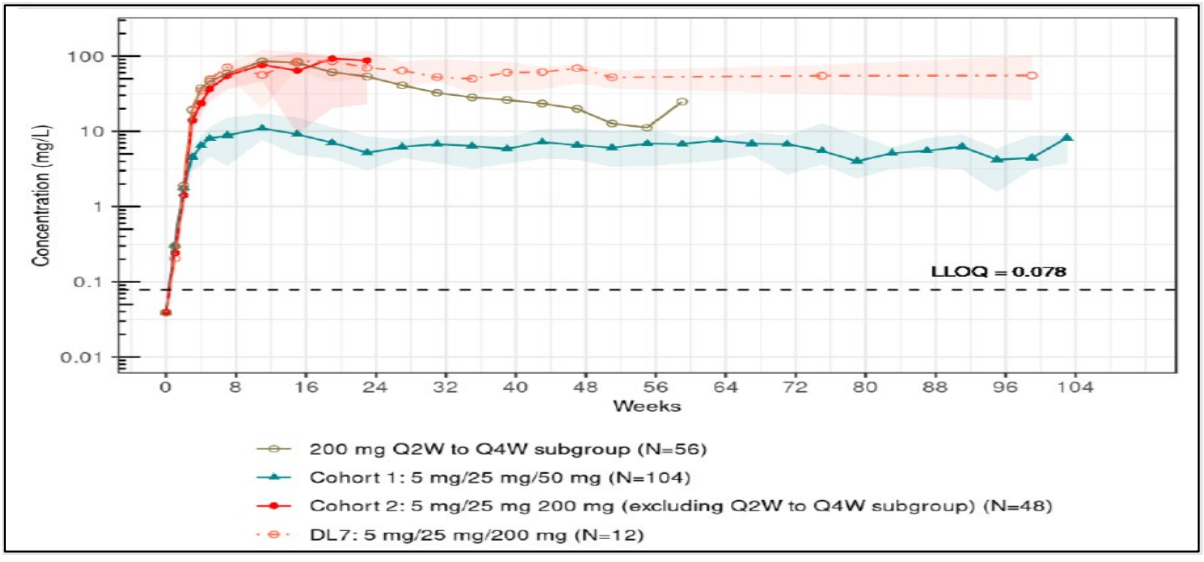
Pharmacokinetics in the target population

Linvoseltamab PK was investigated in study 1826, a Phase 1/2 FIH Study in patients with RRMM. The study consisted of two parts; phase 1 included 9 dose levels in order to evaluate a range of doses and phase 2, where 2 expansion cohorts allowed the safety/efficacy evaluation of 2 different dosing regimens.

The Phase 1 portion of the study followed a modified 3+3 (4+3) dose escalation design while enrolment in Phase 2 was conducted in 2 cohorts, with different full doses of linvoseltamab: cohort 1 with 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 at week 3 and cohort 2with 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 at week 3. After 12 full 50 mg or 200 mg QW doses, both cohorts continue the treatment with a Q2W regimen. 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. PK samples were mostly taken predose and at the end of the infusion (EOI). Following IV infusion, Cmax was observed at the EOI.

Median concentrations of total linvoseltamab in serum over time in the 200 mg Q2W to Q4W subgroup were lower than median concentrations for the all 200 mg dose group (**Figure 9**), however still higher than the median concentrations for the 50 mg dose group. At week 48, the group of patients who changed to 200 mg Q4W had a mean Ctrough of 24.5 mg/L, representing a 61% decline from mean Ctrough for the entire 200 mg cohort at week 24.

Figure 9. Median Ctrough of total linvoseltamab in serum by time and dose level in patients with RRMM who switched from 200 Mg Q2W to Q4W, compared to phase 2 Cohort 1 (50mg) and patients who maintained dosing with 200 Mg Q2W-Study R548-ONC-1826, Log-Scaled, PK Analysis Set



Pharmacokinetic interaction studies

Linvoseltamab is not anticipated to interact directly with CYP450 enzymes, other drug metabolising enzymes, or drug transporters, and therefore, no drug-drug interaction studies have been conducted with linvoseltamab. Transient elevation of cytokines may suppress CYP450 enzyme activities. However, based on recent literature data on a similar bispecific mAb, teclistamab, the risk of CYP450-mediated drug-drug interactions because of linvoseltamab related IL-6 elevation appears to be low and highest within the initial weeks of treatment.

2.6.2.2. Pharmacodynamics

Mechanism of action

Linvoseltamab is a human IgG4-based bispecific monoclonal antibody binding to CD3 and BCMA expressed on the surface of malignant multiple myeloma B-lineage cells, late-stage B cells and plasma cells. Such double binding results in T cell activation with consequent polyclonal cytotoxic T cell response, which causes the lysis of the targeted cells, including malignant multiple myeloma B-lineage cells.

Primary and Secondary pharmacology

Mechanism of action was substantiated through determination of several biomarkers in both phase 1 and 2 of study R5458-ONC-1826.

- change in concentration of IL-2, IFN-gamma and IL-6. Transient elevation in cytokines was registered following linvoseltamab administration, with returning to near baseline levels within 1 day after dosing. Within the 5 mg/25 mg step-up regimen, the highest cytokine concentration peaks occurred in the first 2 weeks of dosing. In terms of phase 2 full doses, slightly lower peaks for IL-6 were registered for the 200 mg dose with respect to the 50 mg, while no significant differences were found in terms of IFN-gamma and IL-2.
- T cell dynamics. In phase 1 cohorts, at week 1 the population of CD3 T cells showed transient decreases of about 60% - 80% of baseline on days 2 and 3 and then climbed to about 70% - 100% of baseline by day 4. A similar pattern was observed on first days of week 4 after administration of full doses. Similar trend was observed in phase 2 cohorts (50mg and 200mg full doses). In terms of CD69/CD8 cells, in phase 1 cohorts, the median percentages were 3- to 9-fold higher than baseline at week 1 day 2. After the peak at week 1 day 2, the population tended to decrease toward baseline at week 1 day 4. Following administration of full doses on week 4 day 1, the median percentages of CD69/CD8 cells again showed transient increases, even if with a smaller magnitude. In phase 2 cohorts, during full-dose period, the increase in frequency of CD69/CD8 was quite similar to levels register in the same period of phase 1.
- B cell dynamics. CD19 B cells overall decreased relative to baseline during treatment with linvoseltamab in both phase 1 and 2 cohorts. In all higher dose groups (i.e., full doses ≥ 6 mg), CD19 B cells concentration reached low levels within the first few months and subsequently remained at constant low levels (≤10% of baseline) for the duration of treatment. In phase 2 cohorts the decrease was comparable for full doses of 50 and 200 mg.

- Kappa and lambda free-light chain. In phase 1 cohorts, median concentrations of FLC at baseline ranged from 27.2 to 2200 mg/L. After the start of treatment with linvoseltamab, FLC concentrations decreased in cohorts with full doses ranging from 6 to 800 mg. At week 4 day 1, median concentrations for these cohorts ranged from 9.09 to 457 mg/L and at week 12 day 1 ranged from 1.77 to 6.01 mg/L. In phase 2, median concentrations of FLC in serum at baseline ranged from 316 to 658 mg/L, while at week 4 day 1 after start of linvoseltamab treatment, median concentrations in the two cohorts ranged from 48.5 to 257 mg/L and at week 12 day 1 ranged from 2.88 to 3.48 mg/L. From week 12 through the end of treatment, median concentrations of FLC in serum remained within the range of approximately 3 to 5 mg/L.
- sBCMA (exploratory). In phase 1 cohorts, concentrations of total sBCMA increased relative to baseline right after the start of treatment with linvoseltamab and generally reached maximum pre-dose concentrations around week 5 and then subsequently declined. At week 8 predose concentrations were overall lower than baseline. In phase 2, the concentration-time profiles of total sBCMA were similar in the two cohorts (50 mg and 200 mg). 5-fold higher than baseline concentration of sBCMA were found approximately at week 4 and then decreased. By approximately week 8, they were generally below baseline and continued to decline to levels similar to concentrations of sBCMA reported for healthy subjects.

Immunogenicity

Within study 1826, 55 participants from phase 1 and 140 from phase 2 (67 for 50 mg cohort 1 and 73 for 200 mg cohort 2) were included in the ADA analysis set. 1 participant (1.8%) from phase 1 DL7 (5/25/200 mg) had a treatment-emergent, transient, low titre ADA response at the week 12 visit. The next determination (at the week 24 visit) and all subsequent determinations were negative. 1 participant (0.7%) from phase 2 cohort 1 (50 mg) had a treatment-emergent, transient, low titre ADA response. This participant has similar linvoseltamab exposure compared to others in the same cohort.

Exposure – response (efficacy)

Exposure – Objective Response Rate (ORR)

Phase 1 and Phase 2 response data from 282 patients were modelled with 4 different sub-cuts of the data due to the two ways the response data was reported (Investigator and/or Independent Assessor) depending on the phase of the trial and treatment cohort:

• Phase 1 (Investigator, N = 73)

• Phase 2 (Independent Assessor, N = 209)

• Phase 2 and Phase 1 200 mg Cohort (Independent Assessor, N = 221)

• Phase 1 and Phase 2 (Investigator, N = 282)

Investigator reported response was provided in all Phase 1 and Phase 2 cohorts, and independent assessor reported response was only provided in Phase 2 and the 200 mg cohort in Phase 1. For efficacy analyses, response was grouped by sCR+CR+VGPR+PR or sCR+CR.

E-R analyses of efficacy endpoints were performed in an automated fashion, where relevant exposures (Cmax, Cmin, Cavg) in serum predicted from the final population PK model were evaluated on each of the endpoints to determine which of the exposure parameters was the best predictor for a particular endpoint (i.e., lowest AIC value).

The final models-predicted ORR (as sCR+CR+VGPR+PR) and odds ratio (OR) for 50 and 200 mg treatment of linvoseltamab using mean exposures of 50 mg and 200 mg cohorts from phase 1 and 2 and baseline covariates of patients are shown.

Table 7. Predicted response rates and OR from the final multivariate logistic model fit of ORR (sCR+CR+VGPR+PR) comparing nominal doses of 50 mg and 200 mg

Population	N	Nominal Dose	Exposure metric	Mean Exposure	Predicted Objective Response Rate (95% CI)	Odds Ratio (95% CI)
Ph1	73	50 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	5.77	0.397 (0.117, 0.766)	
Ph1	73	200 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	28.7	0.758 (0.361, 0.945)	4.75 (2.42, 11.7)
Ph2	209	50 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	6.28	0.393 (0.161, 0.686)	
Ph2	209	200 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	29.5	0.744 (0.46, 0.908)	4.49 (2.66, 8.08)
Ph2 + Ph1 200 mg Cohort	221	50 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	6.28	0.396 (0.156, 0.699)	
Ph2 + Ph1 200 mg Cohort	221	200 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	29.5	0.768 (0.48, 0.922)	5.06 (2.99, 9.16)
Ph1 + Ph2	282	50 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	6.28	0.408 (0.246, 0.593)	
Ph1 + Ph2	282	200 mg	Avg of weekly log C_{min} (mg/L) up to final dose week	29.5	0.717 (0.539, 0.846)	3.67 (2.59, 5.39)

Avg, Average; CI, Confidence interval; N, Number of patients; Ph1, Phase 1; Ph2, Phase 2
Note: Log exposures were transformed to natural space.

Exposure – Progression Free Survival (PFS), Overall Survival (OS), Duration of Response (DOR)

Time-to-event analysis of efficacy endpoints was assessed by Cox proportional-hazards modelling, since it was determined that the data was proportional in nature over the relevant time course, as seen by the KM and associated plots and statistics. The purpose of the modelling was to determine if any of the efficacy endpoints (i.e., PFS, OS and DOR) may be associated with drug exposure and to establish a quantitative relationship between either of the endpoints and their significant predictors. Phase 1 and Phase 2 response data from 282 patients were modelled with 3 different sub-cuts of the data due to the two ways the response data was reported (Investigator and/or Independent Assessor) as mentioned above for E-R Analysis of ORR:

- Phase 2 (Independent Assessor, N = 209)
- Phase 2 and Phase 1 200 mg Cohort (DL7) (Independent Assessor, N = 221)
- Phase 1 and Phase 2 (Investigator, N = 282)

Time-To-Event analysis of efficacy data were performed in an automated fashion in order to derive the final fit model, which contained the most significant covariates as assessed by both univariate and multivariate analyses for each endpoint, including PFS, OS, and DOR.

Exposure as CAVGAVG (i.e. the weekly average of the Cavg up until the last dose) or CAVGWK14 (i.e. Cavg at week14) could be considered as significant predictors of PFS or OS in the cases shown in **Table 8.**

Table 8. Summary of most significant exposure metrics and Hazard Ratios across efficacy endpoints and data sub-cuts comparing the exposure metric medians of the 200 mg to the 50 mg Cohorts

Endpoint	Population	N	Exposure Medians (mg/mL) 200 mg : 50 mg cohorts	Exposure Metric	Hazard Ratio (Univariate)	Hazard Ratio (Multivariate)
PFS	Phase 2	209	77.421 : 14.843	CAVGWK14	0.539 (0.395 — 0.735)	0.605 (0.443 — 0.827)
PFS	Phase 1 DL7 + Phase 2	221	77.421 : 14.843	CAVGWK14	0.51 (0.377 — 0.692)	0.563 (0.416 — 0.763)
PFS	Phases 1 + 2	282	77.421 : 14.843	CAVGWK14	0.543 (0.431 — 0.683)	0.553 (0.436 — 0.7)
OS	Phase 2	209	77.421 : 14.843	CAVGWK14	0.569 (0.395 — 0.822)	0.694 (0.486 — 0.991)
OS	Phase 1 DL7 + Phase 2	221	77.421 : 14.843	CAVGWK14	0.581 (0.414 — 0.815)	0.62 (0.441 — 0.87)
OS	Phases 1 + 2	282	43.127 : 8.098	CAVGAVG	0.698 (0.534 — 0.912)	0.73 (0.56 — 0.952)

DOR did not have an exposure metric associate with it. CAVGWK14 = C_{avg} at week14 (mg/L). CAVGAVG = The average of weekly C_{avg} up until the end of treatment (mg/L). N = number of patients at risk at time 0.

In all three data sub-sets, the Kaplan-Meier(KM) plots of CAVGWK14 (for 'phase2 only' and 'phase 2 + phase 1 DL7' data sub-sets) or CAVGAVG (for 'phase 2 + phase 1' data sub-set) for the PFS showed a relationship between increased probability of PFS with increase in drug exposure. The separation in PFS could be seen across all quartiles from early times, with a large number of events occurring in the first few weeks for Q1. The event rate decreases and the proportion of patients remaining progression-free at any given time increases, with increasing exposure.

In 'phase 2 only' and 'phase 2 + phase 1' data sub-sets, the KM plots of CAVGAVG for the OS showed a relationship between increased probability of OS with increase in drug exposure. The separation in OS could be seen across all quartiles from early times, with a large number of events occurring in the first few weeks for Q1, while only in the 'phase 2 only' data sub-set the separation between Q2 and Q4 begin to be clearly apparent after approximately week 20. The event rate decreases and the proportion of patients remaining alive at any given time increases with increasing exposure.

In 'phase 2 + phase 1 DL7' data sub-set models, exposure wasn't a predictor of OS; also, in all of three data sub-sets exposure wasn't a predictor of DOR.

Exposure – response (safety)

E-R analyses on various safety endpoints were performed including data from all patients in phase 1 and 2 (N=282). Analyses were performed using individual model predicted linvoseltamab exposure metrics (e.g. average weekly exposures [Cmax, Cavg] up to the event or final dose week, exposures [Cmax, Cmin] at weeks 14 and 16). For analysis of binary safety data, constant models (i.e. estimation of only an intercept) and logistic regression models were evaluated for each endpoint exposure-relationship. Models of longitudinal endpoints (e.g. repeated time to event analyses for infection) incorporate the time course of exposure into instantaneous hazard for events or probability of response.

Cytokine release syndrome (CRS) at week 1

The model showed that exposures (in terms of Cmax) higher than those at the initial step-up dose of 5 mg at week 1, part of the recommended step-up regimen at 200 mg dose regimen, predict increase in probability of incidence of CRS at week 1. Observed incidence of CRS at week 1 for the 50 mg and 200

mg cohorts was similar (42% vs 38%, respectively), which is expected as at week 1 both cohorts received the same step up-dose. Cmax at week 1 resulted as a significant predictor of CRS at week 1 in both uni- (OR 1.23; CI 95% (1.07,1.46); p=0.00843) and multivariate model (OR 1.21; CI 95% (1.05,1.45); p=0.0196).

Grade ≥3 infections

The model predicted an inverse relationship between exposure and the endpoint, which is also seen in the observed data. Log(Cmax) at week of event or time of max exposure resulted as a significant predictor of grade ≥3 infections in both uni- (OR 0.488; CI 95% (0.34,0.687); p=6.1e-05) and multivariate model (OR 0.481; CI 95% (0.331,0.685); p=7.48e-05). The KM plot stratified by quartile of CMAXWKE (Cmax at the week of the event or at censored) showed that the median times of not getting a grade ≥3 infection by increasing quartile (Q1 to Q4) were 15, 37, 42 and >176 weeks, respectively.

Grade ≥3 neutropenia

For neutropenia grade ≥3, most first incidences occurred during the first few weeks of the treatment. The KM plot for neutropenia grade ≥3 stratified by quartile of CMAXWKE (Cmax at the week of the event or at censored) shows that the median times to first neutropenia grade ≥3, by increasing

quartile (Q1-Q4), were 14, 17, 26 and >176 weeks. Comparing the 200 mg to the 50 mg cohorts, a relationship between the higher dose and a significant reduction in risk of getting neutropenia grade ≥3 in relation to time (earlier vs later) was determined.

The model predicted that for exposures higher than the median exposure of the 200 mg treatment of linvoseltamab, the probability of neutropenia grade ≥3 will continue to increase.

Average of weekly log(Cavg) up to final dose week resulted as a significant predictor of grade ≥3 neutropenia in both uni- (OR 1.93; CI 95% (1.34,2.83); p=0.000605) and multivariate model (OR 1.69; CI 95% (1.14,2.52); p=0.00954).

2.6.3. Discussion on clinical pharmacology

Linvoseltamab PK was investigated only in the target population, in study 1826, a Phase 1/2 FIH Study in patients with relapsed or refractory multiple myeloma. The study consisted of two parts; phase 1 included 9 dose levels in order to evaluate a range of doses (3 mg to 800 mg) and phase 2, where 2 expansion cohorts allowed the safety/efficacy evaluation of 2 different dosing regimens.

The final modelling dataset for the PopPK analysis included a total of 6995 PK observations from 281 patients with relapsed or refractory MM including 73 patients from the phase 1 part of the study and 208 patients from the phase 2 part of the study. The dataset included a wide range of doses, from 3 mg (DL1) up to 800 mg (DL9), administered intravenously. The low proportion of BLQ observations (46) and the low overall percentage (6%) of excluded observations, is not expected to result in significant bias on PK parameters estimation and thus is considered acceptable.

Concentrations of linvoseltamab in serum were well described by a two-compartment distribution model with parallel linear and nonlinear (Michaelis-Menten type) clearance processes. The final model contains covariate effects for baseline WGT on CL and Q, sex on VC, and the structural covariates of time-varying albumin and IgG on CL and time-varying FLC on Vmax. The magnitude of the proportional errors was moderate (26.37%). Inter-individual variability (IIV) terms were included on CL, Vc, Vp and Vmax and were moderate and contained within 20%.

The estimates of the final model show that all model parameters were estimated reasonably well with RSE ≤30% and random effects shrinkage was acceptable (< 30%). Random effects were normally

distributed and unbiased. Model fit was generally unbiased over time and predicted concentration accurately. An underprediction of low concentrations and conversely an overprediction at higher concentration could be seen in the plot of individual predictions versus observations for the 200 mg Cohort 2 treatment group. However, median values seem overall well captured and the 50th percentile can be reasonably used to predict wash–out time.

Based on the population PK analysis in patients with RRMM, the total clearance of linvoseltamab is by two parallel processes, a linear, non-saturable catabolic process, and a nonlinear, saturable target-mediated pathway. Model-based post hoc analyses simulated concentrations of linvoseltamab during the wash-out period after the administration of the last dose at the end of the QW and Q2W dosing intervals, and at steady-state.

Dose proportionality of linvoseltamab concentrations differed over the duration of treatment: dose proportional concentrations were observed during step-up dosing in the lower dose cohorts of phase 1, and for 50 mg and 200 mg dose groups in phase 2 after the first full dose administration. As weekly dosing continued, exposures of total linvoseltamab showed greater than dose-proportional increase at the end of QW dosing interval.

According to PopPK model, steady state at the proposed 200 mg QW dose is reached approximately by week 12, while, when linvoseltamab is administered as 200 mg Q2W dose, it is reached at Week 48 (34 elapsed weeks since the switch to Q2W). The 5mg/25mg/200mg regimen was simulated for responders (VGPR or better at week 24) who switched to Q4W dosing at week 24. The steady state simulated with PopPK model was compared to steady state calculated from observed data: the predicted concentrations for patients who remained on Q2W 200 mg throughout treatment are in line with observed data while a certain degree of underprediction in Cmin concentrations can be observed for those patients who switched to 200 mg Q4W, particularly after 48 weeks.

No dedicated studies have been conducted in special populations.

Results of population pharmacokinetic analyses indicate no clinically relevant differences in exposure to linvoseltamab between patients with normal renal function (N=78; CrCL ≥90 mL/min) and with mild (N=116; CrCL ≥60 to <90 mL/min), moderate (N=76; CrCL ≥30 to <60 mL/min), and severe (N=11; CrCL ≥15 to <30 mL/min) renal impairment.

Similarly, no clinically relevant differences in exposure to linvoseltamab between patients with normal (N=255) and with mild hepatic function (N=27; total bilirubin >ULN to 1.5× ULN or AST >ULN). The effects of moderate (total bilirubin >1.5 to 3× ULN, any AST) and severe (total bilirubin >3 to 10× ULN, any AST) hepatic impairment on the PK of linvoseltamab are unknown, as reflected in the product information.

The popPK did not indicate any clinically relevant differences in exposure (such as Ctrough, AUCτ) to linvoseltamab based on age (37 to 91 years; N=282), sex, and race [White (N=205), Asian (N=18), or Black (N=44)] and thus no posology adjustments are considered necessary for these subgroups.

No drug-drug interaction studies have been conducted with linvoseltamab. Linvoseltamab induced cytokine elevation however, which may suppress CYP450 enzymes. The highest risk of drug interaction is during the step-up dosing regimen and the first full 200 mg dose in patients who are receiving concomitant CYP450 substrates. Prescribers are advised to monitor for toxicity or concentrations of medicinal products that are CYP substrates where minimal changes in concentration may lead to serious adverse reactions (e.g., cyclosporine, phenytoin, sirolimus, and warfarin).

The primary pharmacology of linvoseltamab was adequately substantiated through the clinical investigation of several biomarkers (FLC; cytokines, T- and B cell dynamics).

A decrease in FLC was observed following drug administration with low concentrations maintained during the treatment. In both phase 1 and 2 parts of study 1826, a transient elevation of circulating cytokines (IL 2, IL 6, and IFN γ) was primarily observed during the step-up dose regimen and the first full 200 mg dose. The highest elevation of cytokines was generally observed 4 hours after each infusion and generally returned to baseline prior to the next dose. Limited cytokine release was observed following subsequent doses. The impact of linvoseltamab on B cell population is more evident than the one on T cells, since a sharp decline is observed at all dose levels from the start of therapy in both phase 1 and 2. Low levels of CD19 B cells are reached within the first months and subsequently remained at low levels (≤10% of baseline) for the duration of treatment. Overall, no relevant differences were found between 50 and 200 mg full doses with respect to variation of cytokines' levels, T- and B cells' frequency and FLC, thus no dose influence on PD response is predictable. However, results should be carefully interpreted due to the high inter-individual variability found in the PD response for all above mentioned biomarkers.

In terms of secondary pharmacology, no thorough QT/QTc study was performed. This is acceptable since a direct ion channel interaction for monoclonal antibodies is not expected and no impact on cardiac parameters were seen in the non-clinical analyses and the clinical study 1826.

The expected risk of immunogenicity is considered low as linvoseltamab causes a decrease of B-lineage cells, including plasma cells responsible for the production of immunoglobulins. This was confirmed by immunogenicity current results of study 1826, where treatment-emergent transient ADAs were only reported in 2 participants (1.0%) out of 195 included in the specific analysis set, with a max titre classified as low (<1.000) in both cases. No neutralisation assay nor correlation with adverse effects were performed. Despite the limited data, the low incidence and titre of ADAs found within study 1826, the impact of immunogenicity on efficacy and safety is expected to be low.

The E-R analysis on efficacy performed using observed data from study 1826 phases 1 and 2 shows that a higher Ctrough at Week 3 was associated with higher ORR. Indeed, a mean ORR of 0.529 (95% CI: 0.419 to 0.637) and 0.726 (95% CI: 0.631 to 0.809) were estimated for the 50 mg and 200 mg full dose groups, respectively. However, no trend was shown in the relationship between exposure and DOR.

Also, empirical model-based E-R analyses were performed to further characterise the relationship between exposure to linvoseltamab and efficacy endpoints (i.e. ORR and TTE as PFS, OS, DOR) and safety endpoints A relationship between exposure and PFS and OS was also suggested by data and confirmed by multivariate models, with an increased risk of disease progression and death, respectively, at lower quartiles of drug concentration.

No difference was found in terms of E-R on the incidence of CRS between 50mg and 200mg cohorts, which is expected since in the first weeks the exposure is similar to the dosage used within the step-up regimen.

In terms of the E-R analysis on grade ≥3 infections, the model predicted an inverse relationship between exposure (as Cmax) and such AE incidence over time. However, as many infections occurred early in the treatment period, they may be related more to the patients' status at initiation of treatment rather than an adverse drug effect and consequently these may not be correlated with the exposures to the drug.

2.6.4. Conclusions on clinical pharmacology

The applicant has adequately characterised the pharmacokinetic and pharmacodynamic properties of linvoseltamab which therefore can be recommended for (conditional) marketing authorisation.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Selection of Step-Up Dosing Regimen (5/25 mg)

The recommended dose regimen for linvoseltamab includes step-up doses of 5 mg and 25 mg, which are administered a week apart, followed by 200 mg once weekly for 12 doses and then every 2 weeks for 5 additional 200 mg doses.

The phase 1 part of the FIH study 1826 investigated the safety and tolerability of linvoseltamab utilising a modified 3+3 (4+3) dose escalation design. A total of 9 full dose levels (DLs) ranging from 3 mg and up to 800 mg were evaluated in the dose escalation part of the study.

A split dosing paradigm to manage anticipated CRS/IRR events for the initial step-up dose and the first full dose, was implemented from the first 6 cohorts in phase 1. However, with the observation of increased rates of grade 2 CRS at an initial dose of 8 mg, the starting dose was fixed at 5 mg. A second dose of 25 mg was implemented to avoid a large increment between the first and the full dose. This 5/25 step-up regimen was implemented in the phase 1 cohorts with full doses ranging from 96 mg (last 3 patients in DL6) to 800 mg starting at week 3.

Selection of Full Dose

Antitumour activity was observed even at the lowest DL evaluated in phase 1 (DL1: 1 mg/ 3 mg, **Table 9**).

Table 9. Objective Response Rate By Investigator Per IMWG Criteria (FAS)-Phase 1 Patients

	1* mg/ 3 mg (N=4)	2* mg/ 6 mg (N=10)	4* mg/ 12 mg (N=10)	8* mg/ 24 mg (N=10)	16* mg/ 48 mg (N=7)	32* mg/ 96 mg (N=8)	5* mg/ 25 mg/ 200 mg (N=12)	5* mg/ 25 mg/ 400 mg (N=8)	5* mg/ 25 mg/ 800 mg (N=4)
Best Overall Response Per IMWG Criteria, n (%)									
Stringent Complete Response (sCR) [a]	0	3 (30.0%)	1 (10.0%)	3 (30.0%)	1 (14.3%)	1 (12.5%)	7 (58.3%)	3 (37.5%)	2 (50.0%)
Complete Response (CR) [a]	1 (25.0%)	1 (10.0%)	0	0	0	0	0	0	0
Very Good Partial Response (VGPR) [a]	0	0	0	1 (10.0%)	1 (14.3%)	4 (50.0%)	2 (16.7%)	1 (12.5%)	0
Partial Response (PR) [a]	0	0	0	1 (10.0%)	0	0	1 (8.3%)	0	1 (25.0%)
Stable Disease (SD) [a,b]	2 (50.0%)	4 (40.0%)	5 (50.0%)	2 (20.0%)	2 (28.6%)	0	0	2 (25.0%)	1 (25.0%)
Progressive Disease (PD) [a]	1 (25.0%)	2 (20.0%)	4 (40.0%)	2 (20.0%)	1 (14.3%)	2 (25.0%)	2 (16.7%)	2 (25.0%)	0
Not Evaluable (NE) [c]	0	0	0	1 (10.0%)	2 (28.6%)	1 (12.5%)	0	0	0
Response Per IMWG Criteria									
Objective Response Rate (ORR: sCR+CR+VGPR+PR)	1 (25.0%)	4 (40.0%)	1 (10.0%)	5 (50.0%)	2 (28.6%)	5 (62.5%)	10 (83.3%)	4 (50.0%)	3 (75.0%)
95% CI for ORR [d]	(0.6%, 80.6%)	(12.2%, 73.8%)	(0.3%, 44.5%)	(18.7%, 81.3%)	(3.7%, 71.0%)	(24.5%, 91.5%)	(51.6%, 97.9%)	(15.7%, 84.3%)	(19.4%, 99.4%)
Rate of VGPR or Better (sCR+CR+VGPR)	1 (25.0%)	4 (40.0%)	1 (10.0%)	4 (40.0%)	2 (28.6%)	5 (62.5%)	9 (75.0%)	4 (50.0%)	2 (50.0%)
95% CI [d]	(0.6%, 80.6%)	(12.2%, 73.8%)	(0.3%, 44.5%)	(12.2%, 73.8%)	(3.7%, 71.0%)	(24.5%, 91.5%)	(42.8%, 94.5%)	(15.7%, 84.3%)	(6.8%, 93.2%)
Rate of CR or Better (sCR+CR)	1 (25.0%)	4 (40.0%)	1 (10.0%)	3 (30.0%)	1 (14.3%)	1 (12.5%)	7 (58.3%)	3 (37.5%)	2 (50.0%)
95% CI for CR Rate [d]	(0.6%, 80.6%)	(12.2%, 73.8%)	(0.3%, 44.5%)	(6.7%, 65.2%)	(0.4%, 57.9%)	(0.3%, 52.7%)	(27.7%, 84.8%)	(8.5%, 75.5%)	(6.8%, 93.2%)

[a] Confirmed responses as per IMWG criteria
[b] SD includes disease response assessment of SD as well as unconfirmed disease response of ≥PR for patients with a single, unconfirmed response of ≥PR at the time of the datacut.
[c] Not evaluable response includes the missing and unknown tumor response.
[d] Clopper-Pearson exact confidence interval.
CI, Confidence interval; CR, Complete response; FAS, Full analysis set; IMWG, International Myeloma Working Group; NE, Not evaluable; ORR, Objective response rate; PD, Progressive disease; PR, Partial response; PTT, Post-text table; sCR, Stringent complete response; SD, Stable disease; VGPR, Very good partial response.
*Initial dose
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

Efficacy estimates varied widely between DLs, possibly due to the relatively low sample size in each DL; doses were tolerated up to DL6 (96 mg). There was no MTD identified, and no dose dependent toxicities were observed with linvoseltamab up to 800 mg, the highest dose tested in Phase 1.

Based on data in the earlier phase 1 DLs, Phase 2 Cohort 1 began enrolling patients to receive a 50 mg full dose while doses higher than 50 mg continued to be evaluated in Phase 1.

Phase 2 Cohort 2 with 200 mg full dose was opened based on administrative data review 1 after it appeared that in phase 1 doses ≥96 mg had consistently higher efficacy than doses <96 mg, and safety profiles at higher DLs (up to 400 mg) were similar to lower full doses and were manageable. The 200mg dose regimen also consistently demonstrated better efficacy than the 50mg dose regimen in high-risk groups (e.g. high-risk cytogenetics, ISS Stages II/III, presence of EMP, penta-refractory status, age ≥75, and sBCMA ≥400 ng/L).

The durability of responses in patients treated with 200 mg were similar to patients treated with 50 mg: the probability of maintaining response (≥PR) at 6, 9, and 12 months in patients who received 200 mg was 91.5%, 88.5%, and 76.1%, respectively, which is comparable to responders who received 50 mg (89.3% 77.9%, and 75.6%, respectively).

Therefore, efficacy and safety data suggested that the 200 mg full dose might have a better benefit-risk profile than 50 mg. The exposure response analysis with ORR data from both dose escalation and dose expansion phases of Study 1826 also indicated that ORR increased with drug exposure with near maximal response (ORR of 70.9% in All 200 mg Patients) achieved at the median C_{trough} of 200 mg dosing regimen, which further supports the selection of the 200 mg dosing regimen for the treatment of RRMM.

Rationale for Decreasing Dosing Frequency for Patients Treated with 200 mg

As of Protocol Amendment 8 of Study 1826, the dosing regimen for patients treated at a dose of 200 mg who had received at least 24 weeks of treatment and achieved response of VGPR or better was modified from Q2W to Q4W. The rationale for decreasing dose intensity was based on the deep responses and prolonged DORs observed at all DLs, and by the observation that patients who experienced prolonged treatment delays due to AEs maintain sustained responses. Therefore, clinical benefit was not expected to be compromised by decreasing dose intensity in patients who have achieved a response of VGPR or better, while a decrease in dosing interval could improve patient convenience and reduce the risk of AEs.

2.6.5.2. Main study

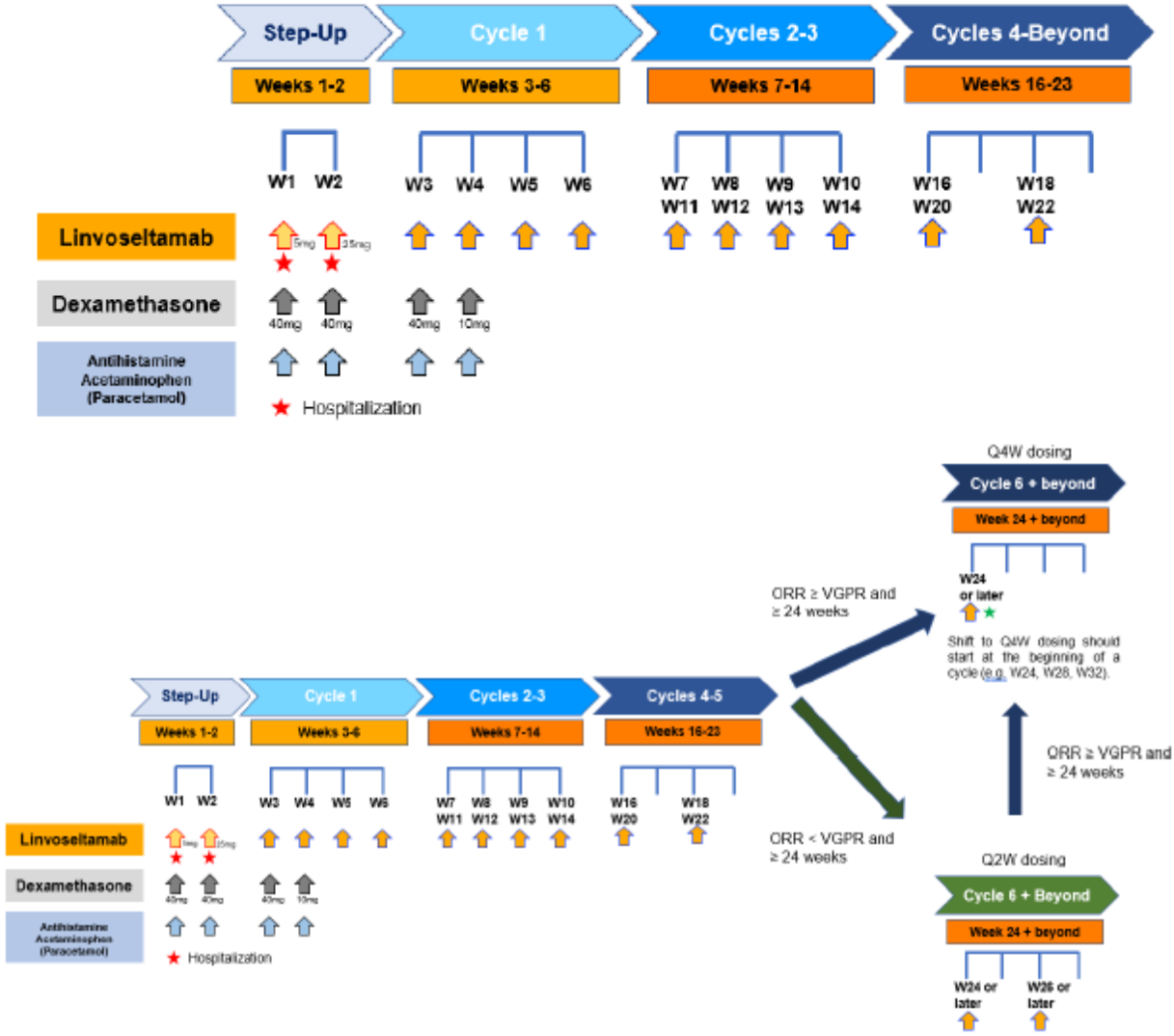
Study R5458-ONC-1826 (LINKER-MM1): Phase 1/2 FIH Study of REGN5458 (anti-BCMA × anti-CD3 Bispecific Antibody) in Patients with Relapsed or Refractory Multiple Myeloma.

This section of the report refers to the phase 2 part of the study (also referred to as Study 1826 throughout the report).

Methods

A diagrammatic representation of the phase 2 phase of the study design is presented in **Figure 10.** Study R5458-ONC-1826 Phase 2 cohorts schema, top panel: Cohort 1 (50 mg IV) and bottom panel: Cohort 2 (200 mg IV) for Cohort 1 (50 mg IV) top panel and for Cohort 2 (200 mg IV), bottom panel.

Figure 10. Study R5458-ONC-1826 Phase 2 cohorts schema, top panel: Cohort 1 (50 mg IV) and bottom panel: Cohort 2 (200 mg IV)



IV, intravenous; ORR, objective response rate; Q2W, every 2 weeks; Q4W, every 4 weeks; W, week; VGPR, very good partial response.

- **Study Participants**

Main inclusion criteria

- Age ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status ≤1 and life expectancy of at least 6 months
- Measurable disease defined as: serum M-protein ≥1 g/dL, urine M-protein ≥200 mg/24-hr, and/or FLC assay with involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio. Patients with IgA MM and no measurable M-protein could be enrolled if quantitative IgA levels were greater than or equal to 400 mg/dL and could be followed longitudinally. A patient with non-secretory MM could be considered for enrolment after discussion with the sponsor (only Phase 1)

- Up to 20 patients were to be enrolled with measurable extramedullary plasmacytomas (EMP) in Phase 2 cohort 1, and 20 patients with EMP in Phase 2 cohort 2. A soft tissue plasmacytoma target lesion was defined as measurable if >2 cm in long axis diameter on a CT-scan, MRI, or FDG PET/CT, longitudinally assessable and not previously irradiated
- **Phase 2**: Patients with MM whose disease met the following criteria:
    - Progression on or after at least 3 prior lines of therapy including a(n) PI, IMiD, and anti-CD38 antibody, OR
    - Patients must be triple- refractory, defined as being refractory to prior treatment with at least 1 PI, 1 IMiD, and an anti-CD38 antibody. Refractory disease was defined as progression during treatment or within 60 days after completion of therapy, or <25% response to therapy
- Adequate hematologic function as measured by: platelet count >50 x 10^9/L, ANC >1.0 x 10^9/L, haemoglobin >8.0 g/dL
- Adequate hepatic function, defined as: total bilirubin ≤1.5 x ULN, transaminase (ALT, AST) ≤2.5 x ULN, alkaline phosphatase ≤2.5 x ULN
- Serum creatinine clearance by Cockcroft-Gault or measured >30 mL/min

Main exclusion criteria

- Diagnosis of plasma cell leukaemia, primary systemic light-chain amyloidosis (excluding myeloma-associated amyloidosis), Waldenström macroglobulinemia, or POEMS syndrome)
- Patients with known MM brain lesions or meningeal involvement, or history of neurodegenerative condition, CNS movement disorder, or patients with a history of seizure within 12 months prior to study enrolment
- Cardiac ejection fraction <40% by echocardiogram or MUGA
- Continuous systemic corticosteroid treatment with more than 10 mg per day of prednisone or anti-inflammatory equivalent within 72 hours of start of study drug
- Prior treatment with BCMA-directed immunotherapies, including BCMA bispecific antibodies and BiTEs, and BCMA CAR T cells. BCMA antibody-drug conjugates were not excluded
- History of allogeneic stem cell transplantation at any time, or autologous stem cell transplantation within 12 weeks of the start of study treatment
- Evidence of significant concurrent disease or medical condition that could interfere with the conduct of the study or put the patient at significant risk, including but not limited to, significant cardiovascular disease (e.g., New York Heart Association class III or IV cardiac disease; myocardial infarction within the previous 6 months; unstable arrhythmias; unstable angina) and/or significant pulmonary disease (e.g., prior history or ongoing complicated interstitial lung disease; obstructive pulmonary disease and history of symptomatic bronchospasm)

- **Treatments**

Cohort 1: 5 mg initial dose at week 1, 25 mg intermediate dose at week 2, and 50 mg dose at week 3 and thereafter until disease progression or another discontinuation criterion was met. Linvoseltamab 50 mg was administered according to a weekly schedule for 12 doses, then Q2W. Patients who

progressed while on treatment and who continued to meet relevant study eligibility criteria were allowed to dose escalate to linvoseltamab 200 mg and continue study therapy.

Cohort 2: 5 mg initial dose at week 1, 25 mg intermediate dose at week 2, and 200 mg dose at week 3 and thereafter until disease progression or another discontinuation criterion was met. Linvoseltamab 200 mg was administered according to a weekly schedule for 12 doses, then Q2W. If a patient received linvoseltamab 200 mg for at least 24 weeks and also achieved a response of VGPR or better, then the frequency of study administration at 200mg was decreased from Q2W to Q4W intervals. Patients who did not achieve at least VGPR continued treatment according to the Q2W schedule.

The initial dose, intermediate dose, and first nominal dose of linvoseltamab were administered as a single infusion over 4 hours (±15 min). If the first nominal dose was adequately tolerated without CRS or IRR events of any grade, then subsequent infusions could be reduced to 1 hour. If the 1-hour infusion was tolerated, then subsequent infusions could be reduced to 30 minutes.

- **Objectives, endpoints and estimands**

The primary objective of the study is:

- To assess the anti-tumour activity of linvoseltamab separately in Phase 2 Cohorts 1 and 2, as measured by the Objective Response Rate (ORR) and as determined by an Independent Review Committee (IRC), in patients with RR MM who have progressed on or after 3 prior lines of therapy or who are triple-refractory (defined as refractory to a[n] PI, IMiD, and anti-CD38 monoclonal antibody).

Estimand for the primary objective

Table 10. Estimand for primary objective in Study R5458-ONC-1826

Population	**All patients defined by protocol eligibility criteria who had received at least 1 dose of study drug.**
Treatment condition	Assignment to linvoseltamab 5 mg/25 mg/200 mg monotherapy, regardless of discontinuation.
Endpoint (variable)	Objective Response Rate (ORR) as per the International Myeloma Working Group (IMWG) response criteria (Kumar S et. al. Lancet Oncol 2016), as assessed by IRC when all patients either complete at least 32 weeks of response assessment or discontinue efficacy evaluations early.
Population-level summary	The primary summary measure of efficacy is the Objective Response Rate (ORR) defined as the number of responders divided by the number of patients in the corresponding analysis set. A responder is a patient with a BOR of partial response (PR) or better, i.e., patients with a BOR of PR, Very Good PR (VGPR), complete response (CR) or stringent CR (sCR).
Intercurrent events and strategy to handle them	
Missing response data	Patients with non-evaluable responses were considered as non-responders for the primary analysis and were included in the denominator when calculating ORR.
Start of new treatment for MM	While on treatment strategy – overall response prior to start of new treatment for MM was used.
Discontinuation of treatment	Treatment policy strategy – all disease assessments after treatment discontinuation were used.

Population	All patients defined by protocol eligibility criteria who had received at least 1 dose of study drug.
for any reason other than PD	

The primary summary measure of efficacy was the ORR observed in Phase 2, defined as the number of responders divided by the number of patients in the corresponding analysis subset. A responder was a patient with a BOR of PR or better (including PR, VGPR, CR, or sCR). Confirmation of response required 2 consecutive readings of the applicable disease parameter consistent with IMWG criteria (Kumar, 2016) and as determined by an IRC.

Secondary and exploratory objectives

The secondary objectives of the study are:

– To assess the anti-tumour activity as measured by: ORR, as determined by the investigator, DOR and PFS as determined by an IRC and the investigator, rate of MRD negative status, OS

– To evaluate the effects of REGN5458 on health-related quality of life (HRQoL) and patient-reported functions and symptoms

Secondary endpoints included:

- ORR, DOR, and PFS after escalation, as measured using the IMWG criteria and as determined by the investigator
- Rate of MRD negative status after escalation using the IMWG criteria
- OS
- Evaluation of the effects of linvoseltamab after escalation on HRQoL and patient-reported symptoms and functioning (per EORTC QLQ-C30, QLQ-MY20, and per EQ-5D-3L)

DOR was defined for responders (patients with a BOR of sCR, CR, VGPR, or PR) as the time from the date of the first documented response until the first date of PD or death due to any cause, whichever occurred first. DOR by IRC and investigator evaluation was summarised by the KM method, if applicable.

PFS was defined as the time from the start of study treatment until the first date of PD, or death due to any cause, whichever occurred first. If a patient has not progressed or died by the analysis cutoff date, PFS will be censored at the time of the last adequate tumour assessment on or before the cutoff date. PFS by IRC and investigator evaluation was summarised by the KM method, if applicable.

OS was measured from the start of study treatment until death due to any cause. If a patient is not known to have died at the date of the analysis cutoff, OS will be censored at the last date that the patient is documented to be alive. OS was summarised by the KM method, if applicable.

Rate of MRD negativity was defined as the proportion of patients who had reached MRD negativity (i.e., reached the threshold of at least 1×10^{-5} cells) as evaluated at the time of suspected CR and sCR. Rate of MRD negativity was summarised descriptively, along with its exact 2-sided 95% CI

- **Sample size**

For each cohort of phase 2, a sample size of 104 patients was required to provide at least 80% power to reject the null hypothesis of an ORR ≤31%, based on an exact test, at a 1-sided significance level of 0.025 if the true ORR is 45%. In total, the planned sample size in phase 2 was approximately 208 patients.

- **Randomisation and Blinding (masking)**

This was an open label study.

- **Statistical methods**

The familywise type I error rate for phase 2 patients is controlled at a 1-sided alpha of 0.025, separately for each cohort. No interim analysis with hypothesis testing was performed.

Administrative data reviews were conducted at the following timepoints:

• Administrative data review 1: When 25 patients without extramedullary plasmacytoma(s) in cohort 1 (5/25/50 mg) had completed 24 weeks of follow-up or had discontinued efficacy evaluation early, or when 12 patients in Phase 1 DL 7 had completed 4 weeks of safety follow-up, whichever occurred later, all available cohort 1 and Phase 1 data were evaluated to determine if an additional Phase 2 cohort with nominal (full) dose of 200 mg would be initiated.

• Administrative data review 2: When 18 patients enrolled in cohort 2 (5/25/200 mg) had completed 12 weeks of follow-up or had discontinued efficacy evaluation early, all available trial data were evaluated to decide whether to fully enrol cohort 2.

• Administrative data review 3: This interim database lock took place on 31 Mar 2023, with a data cutoff date of 28 Feb 2023. It included all patients enrolled up to the data cutoff date.

• Administrative data review 4: This review was conducted when almost all patients had the opportunity for a minimum of 6 months follow-up from time of response. A patient was considered to have had the opportunity for 6 months of follow-up for DOR if onset of response per IMWG criteria occurred >6 months prior to the data cutoff date. These data were used to support regulatory pre-submission activities.

• Primary analysis: The primary analysis was conducted when almost all patients had the opportunity for a minimum of 9 months follow-up from time of response. A patient was considered to have had the opportunity for 9 months of follow-up for DOR if onset of response per IMWG criteria occurred >9 months prior to the data cutoff date.

No hypothesis testing was performed at any of the administrative data reviews mentioned above. Analysis for each administrative data review for each cohort was descriptive.

For regulatory regions where alpha spending for interim analysis is required, the final hypothesis test was conducted with a one-sided alpha of 0.022 (0.025 – 3 x 0.001) assuming a total of 3 administrative reviews. An additional administrative review was conducted for this study, raising the total to 4 administrative reviews. Therefore, 95.8% 2-sided CIs were utilised instead of the projected 95.6% 2-sided CIs as specified in the Statistical Analysis Plan. These 95.8% 2-sided CIs for summary measures of efficacy endpoints were constructed for each Phase 2 cohort for statistical inference.

Planned subgroup analyses

Descriptive analysis for subgroup efficacy in phase 2 portion were performed for the primary endpoint based on the following factors: Age, Sex, Race, Baseline extramedullary plasmacytoma status, Cytogenetic risk, Prior therapy exposed, Baseline ECOG performance status, Revised ISS Stage, ISS

Stage, Bone Marrow plasmacytosis, BCMA levels in bone marrow core biopsy by H score, Soluble BCMA at baseline, Refractory to last line of therapy, Refractory class, Baseline serum and urine M protein, Baseline involved light chain, Prior autologous stem cell transplant, Time from diagnosis.

Results

The initial data cut-off for efficacy and safety results for Study 1826 was 8 September 2023. During the evaluation the applicant submitted updated results with a cut-off date of 06 Jan 2024. Results presented in this section refer to the latest cut-off date unless otherwise specified.

- **Participant flow**

Patient disposition for the Phase 2 50mg and 200mg cohorts, the All 200 mg patient population and for the 200mg Phase 1 population is summarised in **Table 11** (8 September 2023 data cut-off).

- **Recruitment**

Study initiation date: 23 January 2019.

The study is ongoing.

- **Conduct of the study**

Changes in study conduct # are detailed in

Table 12.

Table 11. Patient disposition (Full analysis set), Phase 1 200 mg, Phase 2 (50 mg and 200 mg) and All 200 mg patients

	Phase 2		Phase 1 200 mg (N=12)	All 200 mg (N=117)
	50 mg (N=104)	200 mg (N=105)		
Disposition: Study Treatment				
Treated, n (%)	104 (100%)	105 (100%)	12 (100%)	117 (100%)
Ongoing Core Treatment,[a] n (%)	12 (11.5%)	49 (46.7%)	4 (33.3%)	53 (45.3%)
Off Core Treatment,[a] n (%)	92 (88.5%)	56 (53.3%)	8 (66.7%)	64 (54.7%)
Treatment Completed	0	0	0	0
Treatment Discontinued	92 (88.5%)	56 (53.3%)	8 (66.7%)	64 (54.7%)
ADVERSE EVENT	10 (9.6%)	13 (12.4%)	2 (16.7%)	15 (12.8%)
PREGNANCY	0	0	0	0
DEATH	3 (2.9%)	0	0	0
LOST TO FOLLOW-UP	1 (1.0%)	0	0	0
NON-COMPLIANCE WITH PROTOCOL BY THE PATIENT	0	1 (1.0%)	0	1 (0.9%)
PATIENT DECISION	4 (3.8%)	1 (1.0%)	0	1 (0.9%)
SPONSOR DECISION	0	0	0	0
PHYSICIAN DECISION	5 (4.8%)	6 (5.7%)	0	6 (5.1%)
DISEASE PROGRESSION	64 (61.5%)	31 (29.5%)	6 (50.0%)	37 (31.6%)
WITHDRAWAL OF CONSENT	2 (1.9%)	1 (1.0%)	0	1 (0.9%)
OTHER	3 (2.9%)	3 (2.9%)	0	3 (2.6%)
Discontinued Treatment Prior to Reaching Full Dose[c]	9 (8.7%)	6 (5.7%)	0	6 (5.1%)
Disposition: Study				
Ongoing study follow-up, n (%)	21 (20.2%)	52 (49.5%)	4 (33.3%)	56 (47.9%)

Table 12. Study 1826 protocol amendments

Amendment/ Date	Major Changes
Amendment 1 **20 Sep 2018**	The purpose of Amendment 1 was to respond to Health Authority feedback. Key changes were as follows: • The definition of DLT was clarified.
Amendment 2 **24 Oct 2018**	The purpose of Amendment 2 was to respond to Health Authority feedback. Key changes were as follows: • Safety monitoring was modified to include mandatory hospitalization of all patients for the initial dose and the first administration of the full dose as a split infusion (ie, week 1 and week 2 infusions).
Amendment 3 **17 Jan 2019**	The purpose of Amendment 3 was twofold: • The patient population has been revised to include patients with non-secretory MM. • An exclusion criterion has been updated to exclude only patients with severe allergic reactions or hypersensitivity reactions attributed to prior antibody treatments.
Amendment 4 **13 Aug 2019**	The purpose of Amendment 4 was: • To modify the criterion for the reduction of dose increments in successive dose cohorts to remove the requirement that a grade 2 or higher AEs must be related to study drug. • To update the guidelines for tapering or discontinuing premedication in response to HA feedback received for similar protocols. • To update the CRS guidelines from Lee, 2014 (Lee, 2014) to Lee, 2019 (Lee, 2019).
Amendment 5 **13 Aug 2020**	The purpose of Amendment 5 was to make the following updates: • The Phase 2 portion of the study has been amended to include approximately 84 patients with MM without extramedullary plasmacytomas and up to 20 patients with extramedullary plasmacytomas who are triple-refractory and penta-exposed in order to assess the efficacy of linvoseltamab. • The proposed RP2D and dose selected for the Phase 2 portion of the study consists of a 5 mg initial dose, followed by a 25 mg intermediate dose and 50 mg full dose, each administered as a single infusion. • The duration of study treatment was extended until the time of disease progression or other protocol-defined reason for treatment discontinuation. • Administrative updates were included to address the COVID-19 pandemic.
Amendment 6 **22 Jun 2021**	The purpose of Amendment 6 was to revise the Phase 2 portion of the study as follows: • Removed the formal interim analysis and incorporating administrative data reviews. • Defined the primary population and secondary populations and adding a hierarchical testing procedure for the primary endpoint • Expanded evaluation of the 200 mg full dose • Allowed patients in the Phase 2 cohort 1 (50 mg nominal dose) who progress after 4 to 12 weeks of treatment and while on treatment to dose escalate to 200 mg. • A blinded Independent Review Committee (IRC) was added to evaluate the primary efficacy endpoint (ORR) and secondary efficacy endpoints in Phase 2.

Amendment/ Date	Major Changes
	• A statement was added that acyclovir should be considered prophylactically to prevent herpes simplex virus stomatitis, per established standards for infection prophylaxis. • Premedication guidelines were updated to clarify that premedication with antihistamines and acetaminophen (paracetamol) as well as 40 mg dexamethasone is now required. Previously, premedication with antihistamines and acetaminophen was recommended, and premedication with dexamethasone was required at a 20-mg dose.
Amendment 7 **10 Dec 2021**	The purpose of Amendment 7 was to revise the Phase 2 portion of the study as follows: • The primary population for efficacy analysis in Phase 2 was revised to include an all-comers population of RRMM patients, irrespective of extramedullary disease status. Previously, patients without measurable extramedullary plasmacytomas were analyzed as the primary population. • The Phase 2 patient population was modified from triple-refractory, penta-exposed to either 3 prior lines of therapy or triple-refractory. • The time for primary analysis in Phase 2 was changed from 24 weeks for all patients to at least 32 weeks • The Phase 2 enrollment pausing rules were added for a group of safety events over the entire treatment period, including separate pausing rules for unacceptable rates of treatment-related grade ≥4 nonhematologic toxicities, treatment-related deaths (ie, grade 5 hematologic and nonhematologic toxicities), and grade ≥3 CRS and/or grade ≥3 ICANS • Added consideration of prophylaxis for Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) infections in accordance with local institutional guidelines. • Provided guidance on use of treatment with intravenous immunoglobulin (IVIG) in patients with severe hypogammaglobulinemia (<400 mg/dL) or in patients with recurrent episodes of infection with immunoglobulin levels between 400 mg/dL to 600 mg/dL
Amendment 8 **08 May 2022**	The purpose of Amendment 8 is as follows: • Updated dosing frequency of linvoseltamab in Phase 2 cohort 2 (200 mg full dose) from Q2W to Q4W for patients who have received at least 24 weeks of treatment and have also achieved response of VGPR or better • For Phase 2 patients, the required hospitalization duration has been changed for the initial dose (week 1) from 48 hours to 24 hours from the start of study drug administration. • For Phase 2 patients, administration of the initial and intermediate doses was permitted in a monitored setting, such as an infusion center with subsequent transfer to inpatient hospitalization. • Added that prophylaxis with antibacterial (eg, levofloxacin) and/or antifungal (eg, fluconazole) medication may be considered for high-risk patients (eg, persistent grade 4 neutropenia) and revised consideration of immunoglobulin replacement with intravenous immunoglobulin (IVIG) for patients with IgG concentrations <400 mg/dL

COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ICANS, immune effector cell-associated neurotoxicity; MM, multiple myeloma; Q2W, every 2 weeks; Q4W, every 4 weeks; RP2D, recommended Phase 2 dose; RRMM, relapsed or refractory multiple myeloma; VGPR, very good partial response.

Protocol deviations were defined as important if they met at least 1 of the following criteria: was a deviation from the inclusion/exclusion criteria based on the protocol deviation plan, could significantly affect the interpretability of the primary and/or key secondary objectives of the trial and/or could significantly affect a patient's rights and/or safety.

Phase 1

Important protocol deviations were reported in 12 (16.4%) Phase 1 Patients, none of which impacted the results in the study. The most frequently reported important deviations were inadequate informed consent administration and procedure not performed (5/73 [6.8%] patients each), and visit performed out of window (3/73 [4.1%] patients).

Phase 2 Patients and All 200 mg Patients

Important protocol deviations were reported in a total of 47 patients in the Phase 2 50 mg patient group, none of which impacted the results in the study. The most frequently reported important deviations were procedure not performed (16/104 [15.4%] patients), inadequate informed consent administration (8/104 [7.7%] patients), and visit performed out of window (6/104 [5.8%] patients).

Important protocol deviations were reported in a total of 41 patients in the Phase 2 200 mg group (see Table below), none of which impacted the results in the study. The most frequently reported important deviations were procedure not performed (17/105 [16.2%] patients) and received wrong treatment or incorrect dose (7/105 [6.7%] patients; these patients received the correct 200 mg dose but failed to progress to Q4W dosing after VGPR).

- **Baseline data**

Demographic and baseline characteristics of Phase 2 50 mg, Phase 2 200 mg, Phase 1 200 mg and All 200 mg Patients are summarised in **Table 13**.

Table 13. Demographic and baseline characteristics (FAS, study 1826)- Phase 1 200 mg, Phase 2 and All 200 mg patients

	Phase 2			
	50 mg (N=104)	200 mg (N=105)	Phase 1 200 mg (N=12)	All 200 mg Patients (N=117)
Age (years)				
n	104	105	12	117
Mean (SD)	65.5 (9.11)	67.6 (10.39)	65.1 (8.25)	67.3 (10.19)
Median	65.0	71.0	63.5	70.0
Q1 : Q3	59.0 : 72.0	62.0 : 75.0	60.5 : 72.5	62.0 : 75.0
Min : Max	45 : 90	37 : 91	52 : 77	37 : 91
Age Group (years), n (%)				
< 65	48 (46.2%)	37 (35.2%)	7 (58.3%)	44 (37.6%)
≥ 65	56 (53.8%)	68 (64.8%)	5 (41.7%)	73 (62.4%)
≥ 65 - < 75	39 (37.5%)	39 (37.1%)	3 (25.0%)	42 (35.9%)
< 75	87 (83.7%)	76 (72.4%)	10 (83.3%)	86 (73.5%)
≥ 75	17 (16.3%)	29 (27.6%)	2 (16.7%)	31 (26.5%)
≥ 75 - < 85	15 (14.4%)	28 (26.7%)	2 (16.7%)	30 (25.6%)
≥ 85	2 (1.9%)	1 (1.0%)	0	1 (0.9%)

Sex, n (%)				
Male	56 (53.8%)	61 (58.1%)	3 (25.0%)	64 (54.7%)
Female	48 (46.2%)	44 (41.9%)	9 (75.0%)	53 (45.3%)
Race, n (%)				
White	75 (72.1%)	74 (70.5%)	9 (75.0%)	83 (70.9%)
Asian	6 (5.8%)	10 (9.5%)	0	10 (8.5%)
Non-Asian	98 (94.2%)	95 (90.5%)	12 (100%)	107 (91.5%)
Black or African American	14 (13.5%)	17 (16.2%)	3 (25.0%)	20 (17.1%)
Non-Black or African American	90 (86.5%)	88 (83.8%)	9 (75.0%)	97 (82.9%)
Other	5 (4.8%)	1 (1.0%)	0	1 (0.9%)
Unknown	0	0	0	0
Not Reported	4 (3.8%)	3 (2.9%)	0	3 (2.6%)
Ethnicity, n (%)				
Not Hispanic or Latino	91 (87.5%)	96 (91.4%)	11 (91.7%)	107 (91.5%)
Hispanic or Latino	12 (11.5%)	3 (2.9%)	1 (8.3%)	4 (3.4%)
Not reported	1 (1.0%)	6 (5.7%)	0	6 (5.1%)
Country, n(%)				
Belgium	7 (6.7%)	6 (5.7%)	0	6 (5.1%)
Germany	2 (1.9%)	2 (1.9%)	0	2 (1.7%)
Spain	0	3 (2.9%)	0	3 (2.6%)
Korea (Republic of)	0	9 (8.6%)	0	9 (7.7%)
United States of America	95 (91.3%)	85 (81.0%)	12 (100%)	97 (82.9%)
BMI (kg/m^2)				
n	99	100	11	111
Mean (SD)	27.66 (5.105)	28.09 (6.066)	24.55 (4.284)	27.74 (5.992)
Median	26.76	28.06	22.05	27.91
Q1 : Q3	23.98 : 31.21	23.71 : 31.68	21.45 : 28.18	23.43 : 31.39
Min : Max	17.1 : 43.8	16.3 : 50.9	20.6 : 33.7	16.3 : 50.9
ECOG Performance Status, n (%)				
0	36 (34.6%)	29 (27.6%)	4 (33.3%)	33 (28.2%)
1	67 (64.4%)	76 (72.4%)	8 (66.7%)	84 (71.8%)
2	1 (1.0%)	0	0	0

BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group; FAS, Full analysis set; Max, Maximum; Min, Minimum; Q, Quartile; SD, Standard deviation.
*Initial dose

Baseline disease characteristics are summarised in

Table 14.

Table 14. Baseline disease characteristics (FAS, study 1826)- Phase 1 200 mg, Phase 2 and All 200 mg patients

	Phase 2			
	50 mg (N=104)	200 mg (N=105)	All 200 mg Patients (N=117)	All Study Patients (N=282)
ISS Stage at Study Entry, n (%) [a]				
I	43 (41.3%)	45 (42.9%)	49 (41.9%)	119 (42.2%)
II	35 (33.7%)	37 (35.2%)	41 (35.0%)	95 (33.7%)
III	24 (23.1%)	17 (16.2%)	21 (17.9%)	60 (21.3%)
Missing	2 (1.9%)	6 (5.7%)	6 (5.1%)	8 (2.8%)
Revised ISS Stage at Study Entry per CRF, n (%)				
I	25 (24.0%)	25 (23.8%)	28 (23.9%)	64 (22.7%)
II	61 (58.7%)	59 (56.2%)	65 (55.6%)	166 (58.9%)
III	14 (13.5%)	14 (13.3%)	17 (14.5%)	41 (14.5%)
Missing	4 (3.8%)	7 (6.7%)	7 (6.0%)	11 (3.9%)
Cytogenetic Risk				
High	28 (26.9%)	40 (38.1%)	46 (39.3%)	90 (31.9%)
t(4;14) Translocation	12 (11.5%)	9 (8.6%)	11 (9.4%)	28 (9.9%)
t(14;16) Translocation	0	5 (4.8%)	6 (5.1%)	7 (2.5%)
Deletion of 17p	22 (21.2%)	31 (29.5%)	35 (29.9%)	68 (24.1%)
Standard	74 (71.2%)	65 (61.9%)	71 (60.7%)	190 (67.4%)
Missing	2 (1.9%)	0	0	2 (0.7%)
Baseline Extra-Medullary Plasmacytoma per IRC				
With	17 (16.3%)	18 (17.1%)	19 (16.2%)	36 (12.8%)
Without	87 (83.7%)	87 (82.9%)	98 (83.8%)	246 (87.2%)
Missing	0	0	0	0

[a] ISS Stage at Study Entry is derived.
CRF, Case Report Form; FAS, Full analysis set; ISS, International Staging System; PTT, Post-text table.
Note: Revised ISS staging, or R-ISS, was included in this analysis per protocol. This metric is a different staging system that includes additional factors such as cytogenetic risk group.
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

Among the 12 patients who were dosed with 200 mg in phase 1, the majority of patients (66.7%) had IgG MM at study entry; 33.3% were at ISS stage II and 33.3% were at ISS stage III. High cytogenetic risk was reported for 50.0% patients. One patient (8.3%) had EMP at baseline (per IRC). A BMPC of ≥30% to <60% was reported in 8.3% of patients and a BMPC of ≥60% was reported in 33.3% of patients. Median sBCMA was 551.5 (range: 57.6 to 2590.0) ng/ml.

All Phase 2 patients had received prior systemic MM therapy as required per protocol.

Prior therapy data in the Phase 2 cohorts, All 200 mg patients and All study patients are summarised in

Table *15*.

Table 15. Number of *p*rior systemic multiple myeloma *t*herapies (FAS, Study 1826)- Phase 1 200 mg, Phase 2 And All 200 mg *p*atients

	Phase 2		All 200 mg Patients (N=117)	All Study Patients (N=282)
	50 mg (N=104)	200 mg (N=105)		
Number of prior lines, n (%)				
1	0	0	0	0
2	0	3 (2.9%)	4 (3.4%)	6 (2.1%)
3	8 (7.7%)	22 (21.0%)	24 (20.5%)	38 (13.5%)
4	17 (16.3%)	23 (21.9%)	24 (20.5%)	52 (18.4%)
5	19 (18.3%)	20 (19.0%)	23 (19.7%)	52 (18.4%)
6	17 (16.3%)	14 (13.3%)	17 (14.5%)	42 (14.9%)
7	5 (4.8%)	16 (15.2%)	16 (13.7%)	27 (9.6%)
8	7 (6.7%)	3 (2.9%)	3 (2.6%)	14 (5.0%)
9	10 (9.6%)	1 (1.0%)	1 (0.9%)	14 (5.0%)
10	6 (5.8%)	1 (1.0%)	2 (1.7%)	11 (3.9%)
11	10 (9.6%)	0	0	13 (4.6%)
12	3 (2.9%)	0	0	4 (1.4%)
13	0	2 (1.9%)	2 (1.7%)	2 (0.7%)
14	2 (1.9%)	0	0	4 (1.4%)
15	0	0	0	0
16	0	0	1 (0.9%)	3 (1.1%)
Number of prior lines				
n	104	105	117	282
Mean (SD)	6.8 (2.79)	5.0 (1.99)	5.1 (2.23)	6.0 (2.80)
Median	6.0	5.0	5.0	5.0
Q1 : Q3	5.0 : 9.0	4.0 : 6.0	4.0 : 6.0	4.0 : 7.0
Min : Max	3 : 14	2 : 13	2 : 16	2 : 16
Prior lines of therapy [a]				
Triple-exposed	104 (100%)	105 (100%)	117 (100%)	282 (100%)
Quadra-exposed	104 (100%)	101 (96.2%)	112 (95.7%)	276 (97.9%)
Penta-exposed	95 (91.3%)	81 (77.1%)	90 (76.9%)	234 (83.0%)
Refractory to prior lines of therapies [b]				
Triple-refractory	97 (93.3%)	85 (81.0%)	96 (82.1%)	249 (88.3%)
Quadra-refractory	86 (82.7%)	69 (65.7%)	77 (65.8%)	208 (73.8%)
Penta-refractory	56 (53.8%)	28 (26.7%)	33 (28.2%)	114 (40.4%)

[a] Triple-exposed: previous received therapies including 1 from proteasome inhibitor, 1 from immunomodulatory drug and 1 from anti-CD38 monoclonal antibody; Quadra-exposed: Triple -exposed plus an additional previous received drug either from proteasome inhibitor or from immunomodulatory drug; Penta-exposed: previous received therapies including 2 from proteasome inhibitor, 2 from immunomodulatory drug and 1 from anti-CD38 monoclonal antibody.

[b] Triple-refractory: refractory to previous therapies including at least 1 from proteasome inhibitor, 1from immunomodulatory drug and 1 from anti-CD38 monoclonal antibody; Quadra-refractory: Triple -class refractory plus at least one additional refractory drug either from proteasome inhibitor or from immunomodulatory drug; Penta-refractory: refractory to previous therapies including at least 2 from proteasome inhibitor, 2 from immunomodulatory drug and 1 from anti-CD38 monoclonal antibody.

FAS, Full analysis set; Max, Maximum; Min, Minimum; PTT, Post-text table; Q, Quartile; SD, Standard deviation.
*Initial dose
Medications were coded using WHODrug-Global- B3-202303
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

In Phase 1, the median number of prior lines of therapy received was 6, with patients having received between 2 and 16 prior lines of therapy. Almost all patients (94.5%) were refractory to the last line of therapy, including all (100%) Phase 1 200 mg patients.

- **Numbers analysed**

The following population of analysis were used for efficacy analysis:

The Full Analysis Set (FAS): the FAS included all patients who had received at least 1 dose of study drug. Efficacy endpoints were analysed using the FAS.

Patient-Reported Outcome (PRO) Analysis Set: the PRO analysis was based on the FAS. However, the longitudinal analysis of change from baseline included only patients in FAS with a baseline and at least one post-baseline assessment.

Biomarker Analysis Set: the biomarker analysis set included all treated patients who had an available baseline biomarker result. For biomarkers that were analysed over time this population included all patients who had an available baseline and at least one post-dose sample collected.

Total sBCMA Analysis Set: the total sBCMA analysis set included all treated patients who received at least 1 dose of study drug and who had at least 1 non-missing result following the first dose of study drug.

Subpopulations of Interest

• Phase 1: All dose levels in the dose-escalation portion of Phase 1

• Phase 2 50 mg Dose Set: Patients enrolled in cohort 1 (5-25-50 mg dosing regimen), excluding data collected after intra-patient dose escalation (IPDE) to 200mg

• Phase 2 200 mg Dose Set: Patients enrolled in cohort 2 (5-25-200 mg dosing regimen). The primary analyses of the primary and secondary efficacy variables were based on the Phase 2 200mg Dose Set.

• Combined 200 mg Dose Set: Combined patients enrolled in 5-25-200 mg dosing regimen from phase 1 DL7 and phase 2 cohort 2. Data from subjects enrolled and treated with this regimen across both phases was combined. Data from subjects who received the 200mg full dose following intra-patient dose escalation in phase 2 Cohort 1 were excluded. For the All 200 mg Patients set, differences in per protocol treatment across study phases were:

1. Splitting the first 200 mg dose into 2 separate 100 mg doses administered over successive days only in the phase 1 patients,

2. A switch from QW to Q2W dosing at week 16 in phase 1 vs the same at week 14 in phase 2

3. A switch from Q2W dosing to Q4W dosing at week 24 in patients with response of VGPR or better only in phase 2 patients (phase 1 patients did not make this change and remained on Q2W dosing).

4. All patients (phase 1 and phase 2) were required to have a diagnosis of response-evaluable MM that was refractory to or had progressed on or after at least 3 lines of prior treatment that included a PI, an IMiD, and an anti-CD38 antibody, OR was double- (phase 1) OR triple-refractory (phase 2).

- **Outcomes and estimation**

At the time of the updated DCO (06 Jan 2024) the median duration of follow-up for Phase 2 200 mg patients was 14.06 months. The median duration of follow up in the All 200 mg set was 14.26 months.

Objective Response Rate (ORR)

ORR by IRC assessment

Response data by IRC for the 50mg, 200mg and All 200mg cohorts are summarised in

Table 16.

Table 16. Objective response rate per IMWG Criteria (FAS)- Phase 1 200 mg, Phase 2 (50 and 200 mg), and all 200 mg patients per IRC assessment.

	Outcome (DCO 08 Sep 2023)				Outcome (DCO 06 Jan 2024)			
	Phase 2		Phase 1	All 200 mg	Phase 2		Phase 1	All 200 mg
	50 mg (N=104)	200 mg (N=105)	200 mg (N=12)	Patients (N=117)	50 mg (N=104)	200 mg (N=105)	200 mg (N=12)	Patients (N=117)
Duration of Study Follow-up (months)								
Median	7.38	11.07	--	11.10	7.38	14.06	--	14.26
Min:Max	(0.4:38.0)	(0.2:18.9)	--	(0.2:34.5)	(0.4:42.0)	(0.2:22.6)	--	(0.2:38.4)
Best Overall Response Per IMWG Criteria, n (%)								
Stringent Complete Response (sCR) [a]	19 (18.3%)	42 (40.0%)	6 (50.0%)	48 (41.0%)	19 (18.3%)	45 (42.9%)	7 (58.3%)	52 (44.4%)
Complete Response (CR) [a]	3 (2.9%)	5 (4.8%)	1 (8.3%)	6 (5.1%)	3 (2.9%)	6 (5.7%)	0	6 (5.1%)
Very Good Partial Response (VGPR) [a]	19 (18.3%)	18 (17.1%)	1 (8.3%)	19 (16.2%)	19 (18.3%)	15 (14.3%)	1 (8.3%)	16 (13.7%)
Partial Response (PR) [a]	9 (8.7%)	8 (7.6%)	2 (16.7%)	10 (8.5%)	9 (8.7%)	7 (6.7%)	2 (16.7%)	9 (7.7%)
Minimum Response (MR)	1 (1.0%)	1 (1.0%)	0	1 (0.9%)	1 (1.0%)	1 (1.0%)	0	1 (0.9%)
Stable Disease (SD) [b]	18 (17.3%)	12 (11.4%)	0	12 (10.3%)	18 (17.3%)	12 (11.4%)	0	12 (10.3%)
Progressive Disease (PD) [a]	23 (22.1%)	13 (12.4%)	2 (16.7%)	15 (12.8%)	23 (22.1%)	13 (12.4%)	2 (16.7%)	15 (12.8%)
Not Evaluable (NE) [c]	12 (11.5%)	6 (5.7%)	0	6 (5.1%)	12 (11.5%)	6 (5.7%)	0	6 (5.1%)
Unconfirmed response (≥PR) [d]	3 (2.9%)	1 (1.0%)	0	1 (0.9%)	3 (2.9%)	1 (1.0%)	0	1 (0.9%)
Response Per IMWG Criteria								
Objective Response Rate (ORR: sCR+CR+VGPR+PR)	50 (48.1%)	73 (69.5%)	10 (83.3%)	83 (70.9%)	50 (48.1%)	73 (69.5%)	10 (83.3%)	83 (70.9%)
95% CI for ORR[e]	(38.2%, 58.1%)	(59.8%, 78.1%)	(51.6%, 97.9%)	(61.8%, 79.0%)	(38.2%, 58.1%)	(59.8%, 78.1%)	(51.6%, 97.9%)	(61.8%, 79.0%)
95.8% CI for ORR[e]	(37.8%, 58.4%)	(59.4%, 78.4%)	n/a	(61.5%, 79.2%)	(37.8%, 58.4%)	(59.4%, 78.4%)	n/a	(61.5%, 79.2%)

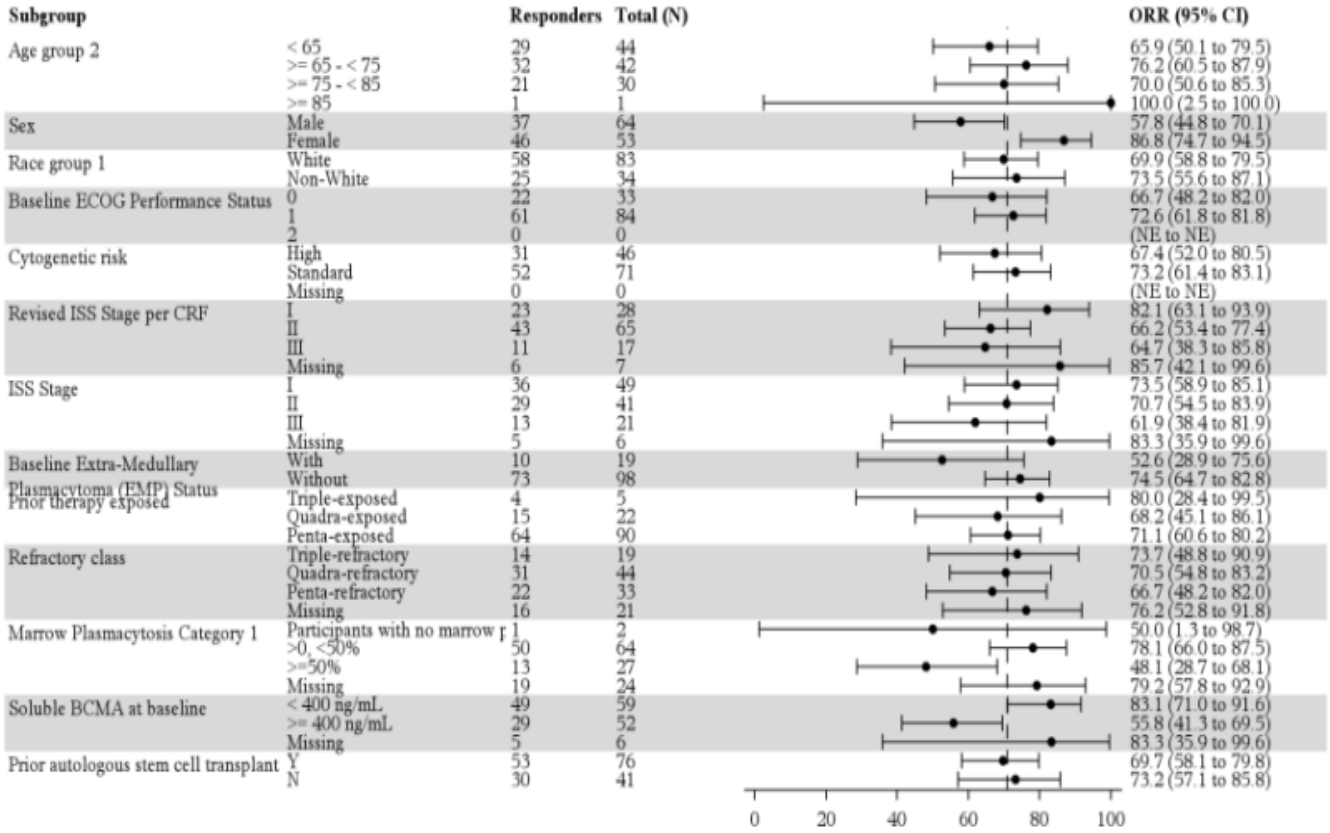
	Outcome (DCO 08 Sep 2023)				Outcome (DCO 06 Jan 2024)			
	Phase 2		Phase 1	All 200 mg	Phase 2		Phase 1	All 200 mg
	50 mg (N=104)	200 mg (N=105)	200 mg (N=12)	Patients (N=117)	50 mg (N=104)	200 mg (N=105)	200 mg (N=12)	Patients (N=117)
Rate of VGPR or Better (sCR+CR+VGPR)	41 (39.4%)	65 (61.9%)	8 (66.7%)	73 (62.4%)	41 (39.4%)	66 (62.9%)	8 (66.7%)	74 (63.2%)
95% CI[e]	(30.0%, 49.5%)	(51.9%, 71.2%)	(34.9%, 90.1%)	(53.0%, 71.2%)	(30.0%, 49.5%)	(52.9%, 72.1%)	(34.9%, 90.1%)	(53.8%, 72.0%)
95.8% CI[e]	(29.7%, 49.8%)	(51.6%, 71.5%)	n/a	(52.6%, 71.5%)	(29.7%, 49.8%)	(52.5%, 72.4%)	n/a	(53.5%, 72.3%)
Rate of CR or Better (sCR+CR)	22 (21.2%)	47 (44.8%)	7 (58.3%)	54 (46.2%)	22 (21.2%)	51 (48.6%)	7 (58.3%)	58 (49.6%)
95% CI[e]	(13.8%, 30.3%)	(35.0%, 54.8%)	(27.7%, 84.8%)	(36.9%, 55.6%)	(13.8%, 30.3%)	(38.7%, 58.5%)	(27.7%, 84.8%)	(40.2%, 59.0%)
95.8% CI[e]	(13.5%, 30.6%)	(34.7%, 55.1%)	n/a	(36.6%, 55.9%)	(13.5%, 30.6%)	(38.4%, 58.9%)	n/a	(39.9%, 59.3%)

[a]Confirmed responses as per IMWG criteria.
[b]Stable disease (SD) includes disease response assessment of SD as well as unconfirmed disease response of ≥PR for patients with a single, unconfirmed response of ≥PR at the time of the data cut.
[c]Not evaluable response includes missing and unknown tumor response.
[d]Unconfirmed disease response of ≥PR contains patients with a single, unconfirmed response of ≥PR at the time of the data cut.
[e]Clopper-Pearson exact confidence interval.
CI, Confidence interval; CR, Complete response; DCO, Data cutoff; FAS, Full analysis set; IMWG, International Myeloma Working Group; IRC, Independent review committee; MR, Minimum response; n/a, Not applicable; NE, Not evaluable; ORR, Objective response rate; PD, Progressive disease; PR, Partial response; sCR, Stringent complete response; SD, Stable disease; VGPR, Very good partial response.
Initial MAA data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023; Updated data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

Pre-defined subgroup analyses

Pre-defined subgroup analyses for the primary endpoint ORR by IRC assessment for the All 200mg patients are summarised in **Figure 11**.

Figure 11. Forest Plot of Objective Response Rate by IRC per IMWG Criteria by Key Demographics and Baseline Characteristics Considered of Clinical Relevance (FAS) – All 200 mg Patients



BCMA, B-cell maturation antigen; CI, Confidence interval; CRF, Case report form; ECOG, Eastern Cooperative Oncology Group; FAS, Full analysis set; IMWG, International Myeloma Working Group; IRC, Independent review committee; ISS, International Staging System; N, No; NE, Not evaluable; ORR, Objective response rate; Y, Yes.
Note: The dotted lines represent the ORR for that cohort.
Overall Response Rate (ORR: sCR+CR+VGPR+PR). Clopper-Pearson 95% exact CI provided.
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

Duration of Response

Phase 1

Among all phase 1 dose escalation patients (N=73) the KM estimated median DoR by Investigator (per IMWG criteria) at the 08 Sep 2023 DCO was >12 months, yet medians were not reached at several DLs (full doses) of linvoseltamab.

The estimated median DoR for phase 1 patients treated at the 200 mg full DL was 27.0 (5.3, NE) months with 60.0% (95% CI: 25.3, 82.7) of responders (≥PR) at this dose estimated to maintain their response for at least 24 months.

Phase 2

DoR by IRC

As of the updated data cutoff date, the median estimated DoR by IRC in Phase 2 50 mg patients was 31.5 months (95% CI: 20.0, NE) and the median estimated DoR by IRC in Phase 2 200 mg patients was not reached (95% CI: 16.6 months, NE).

For All 200 mg patients the estimated median DoR by IRC (per IMWG criteria) as of the updated data cutoff date was 29.4 months (95% CI: 19.2, NE).

DoR by IRC is summarised in

Table 17 and **Figure 12**.

Table 17. Kaplan-Meier estimation of duration of response per IMWG criteria (FAS) – Phase 2 (50 mg and 200 mg) and All 200 mg Patients with an Objective Response of PR or Better Per IRC Assessment

	Outcome (DCO 08 Sep 2023)			Outcome (DCO 06 Jan 2024)		
	Phase 2		All 200 mg Patients (N=83)	Phase 2		All 200 mg Patients (N=83)
	50 mg (N=50)	200 mg (N=73)		50 mg (N=50)	200 mg (N=73)	
KM Estimation of DOR (sCR , CR, VGPR or PR) (months)						
Number of events, n (%) [a]	20 (40.0%)	16 (21.9%)	19 (22.9%)	19 (38.0%)	20 (27.4%)	24 (28.9%)
Number of censored patients, n (%) [a]	30 (60.0%)	57 (78.1%)	64 (77.1%)	31 (62.0%)	53 (72.6%)	59 (71.1%)
Median (95% CI), (months)	31.2 (18.6, NE)	NR (14.0, NE)	NR (14.2, NE)	31.5 (20.0, NE)	NR (16.6, NE)	29.4 (19.2, NE)
KM Estimation of DOR (sCR, CR, VGPR or PR), n (%) [a]						
6 months	89.3 (76.2, 95.4)	91.5 (82.1, 96.1)	90.1 (81.1, 94.9)	89.3 (76.2, 95.4)	91.6 (82.3, 96.1)	90.1 (81.3, 94.9)
8 months	84.7 (70.6, 92.4)	90.1 (80.3, 95.1)	88.8 (79.5, 94.0)	84.7 (70.6, 92.4)	90.2 (80.5, 95.2)	88.9 (79.7, 94.1)
9 months	77.9 (62.7, 87.4)	88.5 (78.4, 94.1)	87.4 (77.9, 93.0)	77.9 (62.7, 87.4)	88.7 (78.6, 94.2)	87.6 (78.2, 93.1)
12 months	75.6 (60.2, 85.7)	76.1 (61.1, 85.9)	77.5 (64.7, 86.1)	75.6 (60.2, 85.7)	81.0 (69.5, 88.5)	80.9 (70.3, 88.0)
18 months	69.9 (53.6, 81.4)	NE (NE, NE)	65.0 (48.7, 77.3)	70.0 (53.8, 81.5)	64.9 (48.5, 77.3)	66.5 (52.6, 77.2)
24 months	59.0 (41.1, 73.2)	NE (NE, NE)	65.0 (48.7, 77.3)	60.7 (43.5, 74.2)	NE (NE, NE)	61.0 (43.9, 74.3)

[a]Events include progressive disease or deaths. Percentages are based on number of patients with sCR or CR.

CI, Confidence interval; CR, Complete response; DCO, Data cutoff; DOR, duration of response; FAS, Full analysis set; IMWG, International Myeloma Working Group; IRC, Independent review committee; KM, Kaplan-Meier; NE, Not evaluable; NR, Not reached; PD, Progressive disease; PR, Partial response; PTT, Post-text table; sCR, Stringent complete response; VGPR, Very good partial response.

Note: Duration of response is defined as the time from the date of the first documented confirmed response (sCR, CR, VGPR or PR) per IMWG until the date of the first documented confirmed progression (PD) or death due to any cause, whichever occurs first.

One 50 mg patient had a PD at the 08 Sep 2023 DCO which became an unconfirmed PD based on new emerging data in the 06 Jan 2024 DCO. This accounts for the decrease in the number of events from the initial MAA to the updated data cutoff.

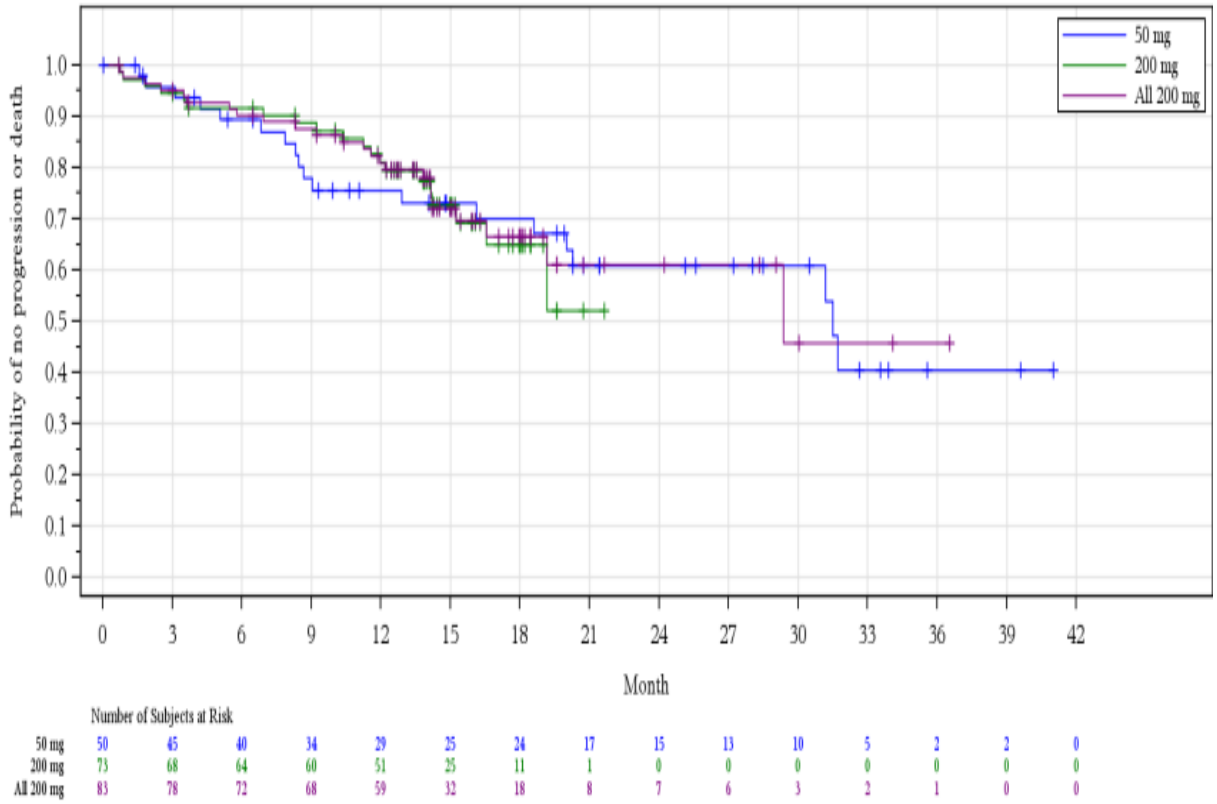
Initial MAA data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023; Updated data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

Of the 61/105 (58.1%) Phase 2 200 mg Patients who had ≥24 weeks of study drug exposure, 59 patients achieved an investigator-assessed response of ≥VGPR and 58 patients switched to Q4W therapy, with a median observed total study follow-up of 16.08 (range: 7.5 to 22.6) months.

The probability of maintaining response (≥VGPR) at 6, 9, and 12 months in Phase 2 200 mg Patients who transitioned to Q4W dosing was 98.3%, 94.8%, and 89.3%, from first documented confirmed response (sCR, CR, VGPR, or PR). For patients who transitioned to Q4W dosing, the KM estimated median DOR by IRC (n=58) was not reached (95% CI: 19.2 months, NE); 12/58 [20.7%] patients progressed after transitioning to Q4W dosing at a median time of 5.24 months, and there was no apparent relationship to the transition to Q4W dosing.

After transitioning to Q4W dosing, the majority of responders (≥VGPR per investigator assessment) maintained durable responses that were ongoing at the time of the updated DCO (45/58 patients). Additionally, responses deepened over time after transitioning to Q4W dosing. Out of 31 patients who transitioned to Q4W dosing prior to achieving a response ≥CR, 20 (64.5%) patients subsequently achieved ≥CR.

Figure 12. Kaplan-Meier Curve of Duration of Response Per IMWG Criteria (FAS) – Phase 2 (50 mg and 200 mg) and All 200 mg Patients with an Objective Response of PR or Better Per IRC Assessment



FAS, Full analysis set; IMWG, International Myeloma Working Group; IRC, Independent review committee; PR, Partial response.
Data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

Sensitivity analyses

A "Per Protocol" sensitivity analysis, which excludes patients with important protocol deviations, is summarised in **Table 18** and

Table 19.

Table 18. Sensitivity analysis of overall response rate and rate of CR or better per IRC

	Phase 2 200 mg (N=77)	All 200 mg Patients (N=88)
Response Per IMWG Criteria		
Objective response rate (ORR: sCR+CR+VGPR+PR)	50 (64.9%)	59 (67.0%)
95% CI for ORR [a]	(53.2%, 75.5%)	(56.2%, 76.7%)
Rate of CR or better (sCR+CR)	37 (48.1%)	43 (48.9%)
95% CI [a]	(36.5%, 59.7%)	(38.1%, 59.8%)

[a]Clopper-Pearson exact confidence interval.
CI, Confidence interval; CR, Complete response; IMWG, International Myeloma Working Group; IRC, Independent review committee; ORR, Objective response rate; PR, Partial response; sCR, Stringent complete response; VGPR, Very good partial response.
Data cut-off as of 06 Jan 2024; Data extract as of 19 Feb 2024

Table 19. Sensitivity analysis of duration of response per IRC

	Phase 2 200 mg (N=50)	All 200 mg Patients (N=59)
KM Estimation of Duration of Response (sCR, CR, VGPR, or PR)		
n	50	59
Number of events, n (%) [a]	15 (30.0%)	19 (32.2%)
Number of censored patients, n (%) [a]	35 (70.0%)	40 (67.8%)
Median (95% CI), (months)	19.2 (15.2, NE)	29.4 (16.6, NE)

[a]Events include confirmed progressive disease or deaths. Percentages are based on number of patients with sCR, CR, VGPR, or PR.

ORR by Investigator

The ORR by investigator assessment for Phase 2 200 mg Patients was 67.6% (95% CI: 57.8, 76.4), including 42.9% ≥CR, and for Phase 2 50 mg Patients was 46.2% (95% CI: 36.3, 56.2), including 22.2% ≥CR. The ORR for All 200 mg Patients was 69.2% (95% CI: 60.0, 77.4), including 44.4% ≥CR.

DoR by Investigator

As of the updated data cutoff date, the KM estimated median DoR by Investigator assessment was 19.8 months (95% CI: (15.2, NE) for Phase 2 200 mg patients. The DoR by Investigator assessment for All 200 mg patients was 20.9 (95% CI: 16.6, NE) months.

Time to response (TTR) by IRC

Responses to linvoseltamab occurred by the first efficacy assessment (week 4) and deepened over time. The observed median TTR by IRC for Phase 2 200 mg and All 200 mg patients was 0.95months, with over 94% of responses occurring within 4 months. The median time to ≥CR at the 200 mg dose was 8.38 months (range: 1.6, 14.1). Similarly, the median time to ≥CR for All 200 mg patients was 8.49 months (range: 1.6, 14.1).

The TTR by Investigator assessment for Phase 1 200mg patients, Phase 2 50mg and 200 mg patients, and All 200mg dose patients were consistent with the IRC assessment.

Progression-free survival (PFS)

Phase 1

At the 08 Sep 2023 DCO date, a trend of increasing KM estimated median PFS as dose increased was observed for Phase 1 patients. In the Phase 1 patients treated at 200 mg, the KM estimated median PFS was 25.9 (95% CI: 0.8, NE) months.

Phase 2

As of the updated DCO, the KM-estimated median PFS by IRC for Phase 2 200 mg Patients was 19.8 months (95% CI: 16.2 months, NE). For the All 200 mg Patients the KM-estimated median PFS by IRC was still not reached at the updated DCO (range: 17.3 months to NE). (**Table 20**).

Table 20. Kaplan-Meier estimation of PFS Per IMWG criteria (FAS) – Phase 2 (50 mg and 200 mg) and All 200 mg Patients Per IRC Assessment

	Outcome (DCO 08 Sep 2023)			Outcome (DCO 06 Jan 2024)		
	Phase 2		All 200 mg Patients (N=117)	Phase 2		All 200 mg Patients (N=117)
	50 mg (N=104)	200 mg (N=105)		50 mg (N=104)	200 mg (N=105)	
Number of events, n (%)	57 (54.8%)	32 (30.5%)	36 (30.8%)	56 (53.8%)	35 (33.3%)	39 (33.3%)
Progressive disease, n (%)	48 (46.2%)	28 (26.7%)	31 (26.5%)	47 (45.2%)	31 (29.5%)	34 (29.1%)
Death, n (%)	9 (8.7%)	4 (3.8%)	5 (4.3%)	9 (8.7%)	4 (3.8%)	5 (4.3%)
Number of censored patients, n (%)	47 (45.2%)	73 (69.5%)	81 (69.2%)	48 (46.2%)	70 (66.7%)	78 (66.7%)
KM median PFS (95% CI), (months)	9.3 (2.0, 20.7)	NR (13.6, NE)	NR (14.7, NE)	9.3 (2.0, 20.7)	19.8 (16.2, NE)	NR (17.3, NE)
Kaplan-Meier Estimated Probability of PFS, % (95% CI)						
6 months	53.8 (43.0, 63.5)	76.8 (66.8, 84.1)	77.6 (68.4, 84.4)	53.8 (43.0, 63.5)	76.8 (66.9, 84.1)	77.6 (68.4, 84.4)
9 months	51.1 (40.2, 61.0)	74.3 (64.1, 82.0)	73.3 (63.7, 80.8)	51.1 (40.2, 61.0)	74.4 (64.2, 82.1)	73.4 (63.8, 80.8)
12 months	45.6 (34.7, 55.8)	68.9 (57.5, 77.9)	68.8 (58.3, 77.1)	45.6 (34.7, 55.8)	70.6 (60.0, 78.9)	70.0 (60.1, 78.0)
18 months	42.6 (31.7, 53.0)	53.4 (37.7, 66.9)	57.2 (44.0, 68.4)	42.6 (31.7, 53.0)	57.3 (44.2, 68.5)	59.2 (47.6, 69.1)
24 months	36.1 (25.0, 47.3)	NE (NE, NE)	57.2 (44.0, 68.4)	36.9 (26.0, 47.8)	NE (NE, NE)	55.0 (41.3, 66.7)

CI, Confidence interval; DCO, Data cutoff; FAS, Full analysis set; IMWG, International Myeloma Working Group; IRC, Independent Review Committee; NE, Not evaluable; PFS, Progression-free survival.

Initial MAA data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023; Updated data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

PFS by Investigator

Results of the PFS analysis were similar by IRC and by Investigator assessment. As of the updated data cutoff date, the KM estimated median PFS by Investigator assessment for Phase 2 200 mg patients was 19.8 months (95%CI 15.2, NE). For All 200 mg patients, the KM estimated median PFS by Investigator assessment was 19.8 months (95%CI 15.2, NE).

Overall survival (OS)

Phase 1

At the 08 Sep 2023 DCO date, the KM estimated median OS of Phase 1 patients was not reached for DLs ≥24 mg including for patients treated with 200 mg linvoseltamab (median OS not reached, 95% CI: 7.3, NE). For patients treated with 200 mg, the estimated probability of surviving through 12 months was 75.0% (95% CI: 40.8, 91.2) and through 24 months was 58.3% (95% CI: 27.0, 80.1).

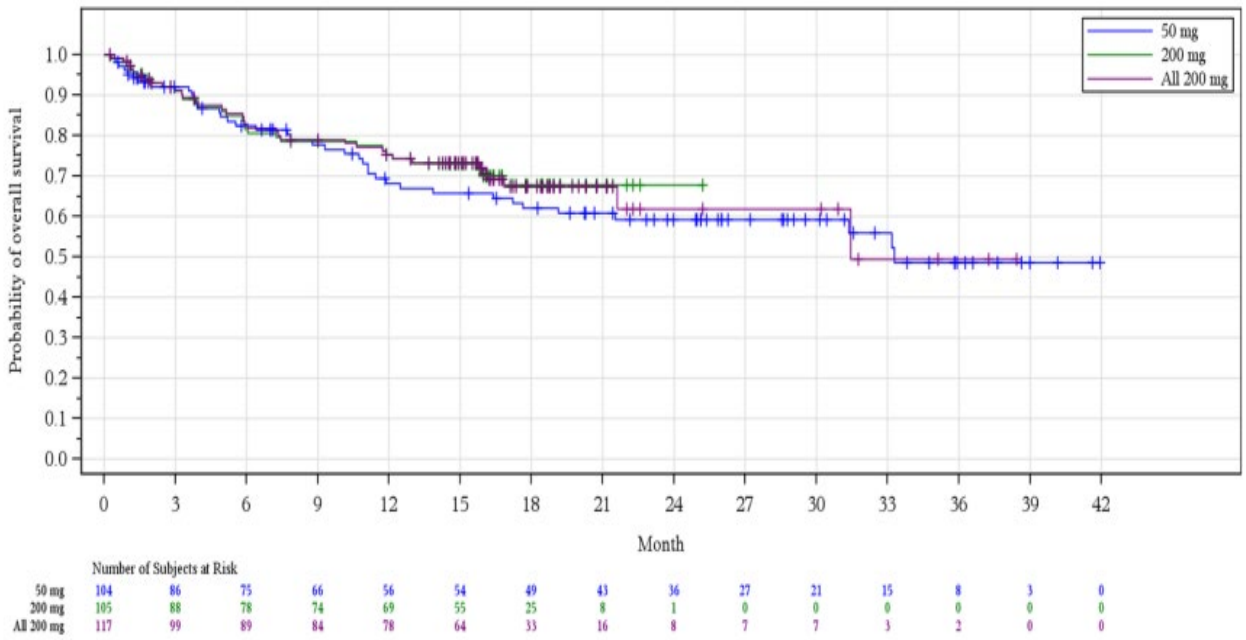
Phase 2

The updated KM estimated median survival was 33.3 (95% CI: 19.1, NE) months for Phase 2 50 mg patients and was not reached for Phase 2 200 mg patients. The median OS for All 200 mg patients was 31.3 months (95%CI 21.6, NE).

Over 70% of Phase 2 200 mg Patients and All 200 mg Patients were alive at the updated DCO (06 Jan 2024). The KM-estimated probability of survival at 12 months was 75.3% (95% CI: 65.4, 82.7) for Phase 2 200 mg Patients and 75.3% (95% CI: 66.0, 82.3) for All 200 mg Patients.

As of updated DCO (06 Jan 2024), the data in Phase 2 200 mg Patients were immature for landmark analysis beyond 15 months (**Figure 13**).

Figure 13. Kaplan-Meier Curve of Overall Survival (FAS) – Phase 2 (50 mg and 200 mg) and All 200 mg Patients



FAS, Full analysis set.
Data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

MRD Negativity

Of the patients who achieved ≥CR in Phase 1 and the Phase 2 cohorts, many had missing samples required for MRD testing in the clonoSEQ or Euroflow assays. The calibration failures resulted in the inability to determine MRD in a subset of patients in CR using the clonoSEQ assay. MRD results are summarised in **Table 21**.

Table 21. Minimum residual disease status 10^{-5} Test Sensitivity (FAS) – Phase 1 200 mg, Phase 2 (50 mg and 200 mg), and All 200 mg patients with an Objective Response of CR or better per IRC assessment

	Outcome (DCO 08 Sep 2023)				Outcome (DCO 06 Jan 2024)			
	Phase 2		Phase 1	All 200 mg	Phase 2		Phase 1	All 200 mg
	50 mg (N=22)	200 mg (N=47)	200 mg (N=7)	Patients (N=54)	50 mg (N=22)	200 mg (N=51)	200 mg (N=7)	Patients (N=58)
MRD Status by clonoSEQ, n(%)								
Negative	12 (54.5%)	13 (27.7%)	3 (42.9%)	16 (29.6%)	12 (54.5%)	16 (31.4%)	3 (42.9%)	19 (32.8%)
95% CI for Negative [a]	(32.2%, 75.6%)	(15.6%, 42.6%)	(9.9%, 81.6%)	(18.0%, 43.6%)	(32.2%, 75.6%)	(19.1%, 45.9%)	(9.9%, 81.6%)	(21.0%, 46.3%)
Positive	2 (9.1%)	2 (4.3%)	0	2 (3.7%)	2 (9.1%)	2 (3.9%)	0	2 (3.4%)
Indeterminate	0	0	0	0	0	0	0	0
Calibration Failure	2 (9.1%)	10 (21.3%)	0	10 (18.5%)	2 (9.1%)	7 (13.7%)	0	7 (12.1%)
Missing	6 (27.3%)	22 (46.8%)	4 (57.1%)	26 (48.1%)	6 (27.3%)	26 (51.0%)	4 (57.1%)	30 (51.7%)
MRD Status by Euroflow, n(%)								
Negative	7 (31.8%)	9 (19.1%)	4 (57.1%)	13 (24.1%)	7 (31.8%)	10 (19.6%)	4 (57.1%)	14 (24.1%)
95% CI for Negative [a]	(13.9%, 54.9%)	(9.1%, 33.3%)	(18.4%, 90.1%)	(13.5%, 37.6%)	(13.9%, 54.9%)	(9.8%, 33.1%)	(18.4%, 90.1%)	(13.9%, 37.2%)
Positive	13 (59.1%)	28 (59.6%)	2 (28.6%)	30 (55.6%)	13 (59.1%)	30 (58.8%)	2 (28.6%)	32 (55.2%)
Missing	2 (9.1%)	10 (21.3%)	1 (14.3%)	11 (20.4%)	2 (9.1%)	11 (21.6%)	1 (14.3%)	12 (20.7%)
MRD Status by clonoSEQ or Euroflow, n(%)								
Negative	15 (68.2%)	16 (34.0%)	5 (71.4%)	21 (38.9%)	15 (68.2%)	19 (37.3%)	5 (71.4%)	24 (41.4%)
95% CI for Negative [a]	(45.1%, 86.1%)	(20.9%, 49.3%)	(29.0%, 96.3%)	(25.9%, 53.1%)	(45.1%, 86.1%)	(24.1%, 51.9%)	(29.0%, 96.3%)	(28.6%, 55.1%)
Positive	6 (27.3%)	22 (46.8%)	1 (14.3%)	23 (42.6%)	6 (27.3%)	22 (43.1%)	1 (14.3%)	23 (39.7%)
Indeterminate	0	0	0	0	0	0	0	0
Calibration Failure	0	2 (4.3%)	0	2 (3.7%)	0	1 (2.0%)	0	1 (1.7%)
Missing	1 (4.5%)	7 (14.9%)	1 (14.3%)	8 (14.8%)	1 (4.5%)	9 (17.6%)	1 (14.3%)	10 (17.2%)

[a]Clopper-Pearson exact CI.
CI, confidence interval; CR, Complete response; FAS, Full analysis set; MRD, Minimum residual disease.
Note: Indeterminate results are due to either insufficient cells or sequences profiled to achieve a particular threshold
Note: Missing data is due to missing specimens, poor specimen quality (insufficient, clotted specimens, samples submitted outside stability of test).
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023 Data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

Patient-reported Outcomes (PROs)

The Least Square (LS) mean changes from baseline for the investigated PROs in the Phase 2 200 mg group are summarised in **Table 22**.

Table 22. Overall LS Mean Change in EORTC QLQ-C30 (GHS/QoL, PF, Fatigue, Pain) and EORTC QLQ-MY20 (DS and TSE) – Phase 2 200

	Baseline Score	Overall LS Mean Change[b,c]	
	Mean (SD)[a]	LS Mean	95% CI
Phase 2 200 mg[d]			
EORTC QLQ-C30			
GHS/QoL	62.33 (20.117)	4.9	(2.5, 7.4)
PF	71.75 (22.154)	2.9	(0.5, 5.3)
Fatigue	37.40 (26.045)	-5.7	(-8.4, -2.9)
Pain	39.77 (30.365)	-10.2	(-13.9, -6.5)
EORTC QLQ-MY20			
DS	30.17 (22.063)	-5.8	(-8.7, -2.9)
TSE	17.92 (14.180)	-3.2	(-5.0, -1.4)

[a] Baseline mean scores correspond to the total with at least 1 baseline score for each respective scale.
[b] Positive LS mean changes represent improvements from baseline in GHS/QoL and PF scales and negative LS mean changes represent improvements in fatigue, pain, DS and TSE scales.
[c] Estimates of LS mean change from baseline correspond to patients with a baseline and at least one post-baseline score.
[d] 76 weeks of data for GHS/QoL, PF, pain and fatigue scales; 68 weeks of data for DS and TSE scales
CI, Confidence interval; DS, Disease symptoms; EORTC QLQ-C30; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma module 20; GHS, Global health status; LS, Least square; PF, Physical functioning; QoL, Quality of life; SD, Standard deviation; TSE, Treatment side effects.
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

Across all weeks, LS mean change from baseline for the GHS/QoL for Phase 2 200 mg patients suggest nominal statistically significant improvements overall through week 60. Similar overall findings were generally observed for All 200 mg patients (data not shown). LS mean change for GHS/QoL scores did not reach the threshold for clinically meaningful deterioration at any timepoint for Phase 2 200 mg and All 200 mg patients.

Overall LS mean change from baseline in fatigue and pain scales for Phase 2 200 mg patients suggest nominal statistically significant improvements in fatigue and pain through week 60. The LS mean changes from baseline first reached the threshold for clinically meaningful improvement for fatigue by week 52 and for pain by week 20; LS means did not exceed the threshold for clinically meaningful deterioration for fatigue and pain scores at any timepoint. Generally similar findings were observed among All 200 mg patients.

The median TTDD was not reached for EORTC QLQ-C30 GHS/QoL, PF, and fatigue scales nor for EORTC QLQ-MY20 DS and TSE scales.

- **Ancillary analyses**

Not applicable.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23. Summary of Efficacy for trial R5458-ONC-1826

Title: Phase 1/2 FIH Study of REGN5458 (anti-BCMA × anti-CD3 Bispecific Antibody) in Patients with Relapsed or Refractory Multiple Myeloma (LINKER-MM1)	
Study identifier	R5458-ONC-1826 EU CT number: 2018-003188-78
Design	Phase 1/2, open-label, First-In-Human (FIH) study of the safety, tolerability, anti-tumor activity, and PK of linvoseltamab (anti-BCMA x anti-CD3 bispecific antibody) in patients with RRMM. The study consisted of a phase 1 dose escalation portion and phase 2 dose expansion portion. The phase 1 portion of the study was designed to explore the safety and tolerability of escalating dose levels of linvoseltamab and to determine one or more recommended phase 2 dose regimens of linvoseltamab as monotherapy. The phase 2 portion consisted of 2 cohorts designed to evaluate the safety and efficacy of 2 full doses of linvoseltamab: 50 mg (Cohort 1) and 200 mg (Cohort 2).

Title: Phase 1/2 FIH Study of REGN5458 (anti-BCMA × anti-CD3 Bispecific Antibody) in Patients with Relapsed or Refractory Multiple Myeloma (LINKER-MM1)			
Study identifier	R5458-ONC-1826 EU CT number: 2018-003188-78		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Trial start date: 23 January 2019. Enrolment completed. Follow-up: variable duration not applicable not applicable
Hypothesis	The hypothesis is that treatment with linvoseltamab will demonstrate ORR >31% at the targeted recommended Phase 2 dose level in subjects with relapsed or refractory multiple myeloma.		
Treatments groups	Phase 2 200 mg cohort (Phase 2 200mg)		N=105; linvoseltamab iv 5/25/200mg
	Pooled Phase 1/Phase 2 200mg (All 200mg)		N=117; linvoseltamab iv 5/25/200mg
Endpoints and definitions	Primary endpoint Objective response rate	ORR by IRC	ORR (i.e. ≥PR) as determined by blinded IRC, as measured using the IMWG criteria (Kumar, 2016)
	Secondary endpoint Duration of response	DoR by IRC	DoR according to IMWG criteria (Kumar, 2016) and as determined by an IRC
	Secondary endpoint Complete remission rate	CRR by IRC	ORR (CR + sCR) as determined by blinded IRC, as measured using the IMWG criteria (Kumar, 2016)
	Secondary endpoint Progression-free survival	PFS by IRC	PFS according to IMWG criteria (Kumar, 2016) and as determined by an IRC
	Secondary endpoint Overall survival	OS	Survival times
	Secondary Endpoint MRD negativity rate	MRD	Rate of MRD negative status (threshold 10^{-5}) by clonoSEQ or Euroflow
Database lock	06 January 2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy was the primary objective for the phase 2 expansion cohorts, as measured by objective response as assessed by IRC. Overall, a combined total of 117 patients were treated with the 5/25/200 mg regimen ("All 200 mg Patients") in Study 1826, including Phase 2 200 mg Patients (N=105) and the patients treated at DL7 in phase 1 with 200 mg full dose (N=12). The analyses of the primary endpoint (i.e., ORR) are determined by an IRC and performed when all patients complete at least 32 weeks of response assessment or discontinue efficacy evaluation early.		

Title: Phase 1/2 FIH Study of REGN5458 (anti-BCMA × anti-CD3 Bispecific Antibody) in Patients with Relapsed or Refractory Multiple Myeloma (LINKER-MM1)			
Study identifier	R5458-ONC-1826 EU CT number: 2018-003188-78		
Descriptive statistics and estimate variability	Treatment group	Phase 2 200 mg	All 200 mg
	Number of subject	N=105	N=117
	ORR by IRC (%)	73 (69.5%)	83 (70.9%)
	(95%CI) [95.8%CI]	(59.8, 78.1) [59.4, 78.4]	(61.8, 79.0) [61.5, 79.2]
	Median DOR by IRC in months	NR	29.4
	(95%CI)	(16.6, NE)	(19.2, NE)
	CRR by IRC (%)	51 (48.6%)	58 (49.6%)
	(95%CI)	(38.7, 58.5)	(40.2, 59.0)
	Median PFS by IRC in months	19.8	NR
	(95%CI)	(16.2, NE)	(17.3, NE)
	OS in months	NR	31.4
	(95%CI)	(NE, NE)	(21.6, NE)
	MRD %	37.3%	41.4%
	(95%CI)	(24.1, 51.9)	(28.6, 55.1)
Notes	None		

2.6.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Non Controlled Trials	42/117	30/117	1/117

Linvoseltamab is not subject to elimination through the renal or hepatic pathways, and no specific studies for renal or hepatic impairment were conducted.

ORR and DoR data in subgroups defined by renal impairment in the Phase 2 200 mg cohort and in the All 200 mg cohort of study 1826 are summarised in **Tables 24** and **25** (DCO Jan 2024). Renal impairment is based on eGFR calculated by the CKD-EPI equation (Normal: ≥90, Mild: 60 to 89, Moderate: 30 to 59, Severe: 15 to 29, Failure: <15).

Table 24. Overall response rate per IMWG criteria by IRC assessment by renal impairment status at baseline

	Phase 2 200 mg	All 200 mg Patients
Response Per IMWG Criteria		
Renal Impairment: Normal	(N=25)	(N=28)
Objective response rate (ORR: sCR+CR+VGPR+PR)	17 (68.0%)	20 (71.4%)
95% CI for ORR [a]	(46.5%, 85.1%)	(51.3%, 86.8%)
Rate of CR or better (sCR+CR)	11 (44.0%)	13 (46.4%)
95% CI [a]	(24.4%, 65.1%)	(27.5%, 66.1%)
Renal Impairment: Mild	(N=51)	(N=57)
Objective Response Rate (ORR: sCR+CR+VGPR+PR)	38 (74.5%)	43 (75.4%)
95% CI for ORR [a]	(60.4%, 85.7%)	(62.2%, 85.9%)
Rate of CR or Better (sCR+CR)	26 (51.0%)	30 (52.6%)
95% CI [a]	(36.6%, 65.2%)	(39.0%, 66.0%)
Renal Impairment: Moderate	(N=26)	(N=28)
Objective response rate (ORR: sCR+CR+VGPR+PR)	17 (65.4%)	18 (64.3%)
95% CI for ORR [a]	(44.3%, 82.8%)	(44.1%, 81.4%)
Rate of CR or better (sCR+CR)	13 (50.0%)	13 (46.4%)
95% CI [a]	(29.9%, 70.1%)	(27.5%, 66.1%)
Renal Impairment: Severe	(N=2)	(N=3)
Objective response rate (ORR: sCR+CR+VGPR+PR)	1 (50.0%)	2 (66.7%)
95% CI for ORR [a]	(1.3%, 98.7%)	(9.4%, 99.2%)
Rate of CR or better (sCR+CR)	1 (50.0%)	2 (66.7%)
95% CI [a]	(1.3%, 98.7%)	(9.4%, 99.2%)

[a]Clopper-Pearson exact confidence interval.
CI, Confidence interval; CR, Complete response; IMWG, International Myeloma Working Group; ORR, Objective response rate; PR, Partial response; sCR, Stringent complete response; VGPR, Very good partial response.
Data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

Table 25. Duration of response per IRC by renal impairment status at baseline

	Phase 2 200 mg	All 200 mg Patients
KM Estimation of Duration of Response (sCR, CR, VGPR, or PR)		
Renal Impairment: Normal		
n	17	20
Number of events, n (%) [a]	5 (29.4%)	6 (30.0%)
Number of censored patients, n (%) [a]	12 (70.6%)	14 (70.0%)
Median (95% CI), (months)	NR (12.0, NE)	NR (12.0, NE)
Renal Impairment: Mild		
n	38	43
Number of events, n (%) [a]	10 (26.3%)	12 (27.9%)
Number of censored patients, n (%) [a]	28 (73.7%)	31 (72.1%)
Median (95% CI), (months)	19.2 (16.6, NE)	29.4 (16.6, NE)
Renal Impairment: Moderate		
n	17	18
Number of events, n (%) [a]	5 (29.4%)	6 (33.3%)
Number of censored patients, n (%) [a]	12 (70.6%)	12 (66.7%)
Median (95% CI), (months)	NR (13.8, NE)	NR (13.8, NE)
Renal Impairment: Severe		
n	1	2
Number of events, n (%) [a]	0	0
Number of censored patients, n (%) [a]	1 (100%)	2 (100%)
Median (95% CI), (months)	NR (NE, NE)	NR (NE, NE)

[a] Events include confirmed progressive disease or deaths. Percentages are based on number of patients with sCR, CR, VGPR or PR.
CI, Confidence interval; CR, Complete response; IRC, Independent review committee; KM, Kaplan-Meier; NE, Not evaluable; NR, Not reached; PR, Partial response; sCR, Stringent complete response; VGPR, Very good partial response.
Duration of response is defined as the time from the date of the first documented confirmed response (sCR, CR, VGPR or PR) per IMWG until the date of the first documented confirmed progression (PD) or death due to any cause, whichever occurs first.
Data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

An overview of the efficacy of linvoseltamab compared to approved EU treatments for patients with RRMM who have received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 mAb is provided in **Table 26** below. However, indirect unadjusted comparisons of the clinical activity of linvoseltamab to other therapies approved in the EU are limited by important differences in the respective patient populations.

Table 26. Comparison of efficacy between linvoseltamab and therapies approved in EU in RRMM

Therapy (Number of subjects studied at approved / proposed dose)	Mode of Action	ORR	CR or better	Median DOR (months)	Current Approval Status	Indicated population in the EU
Linvoseltamab, n=117	BCMA x CD3 bispecific antibody	70.9% (61.8%-79.0%)	46.2% (36.9%-55.6%)	NR (14.2-NE)	N/A	Proposed: received at least 3 prior therapies, requires prior immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb
Teclistamab (Tecvayli), n=165	BCMA X CD3 bispecific antibody	63% (55.2%, 70.4%)	39.4%	18.4 (14.9-NE)	CMA	Received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
Elranatamab (Elrexfio), n=123	BCMA X CD3 bispecific antibody	61.0%	35.8%	NE (NE, NE)	CMA	Received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
Talquetamab (Talvey), 0.8mg/kg biweekly n=145	GPRC5D X CD3 bispecific antibody	71.7% (63.7%-78.9%)	38.7%	NE (13.0-NE)	CMA	Received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody

Therapy (Number of subjects studied at approved / proposed dose)	Mode of Action	ORR	CR or better	Median DOR (months)	Current Approval Status	Indicated population in the EU
Talquetamab (Talvey), 0.4mg/kg weekly n=143		74.1% (66.1%-81.1%)	33.6%	9.5 (6.7, 13.3)		and have demonstrated disease progression on the last therapy
Belantamab mafodotin (Blenrep), n=97	BCMA-antibody drug conjugate	31% (21%, 43%)	3%	11.0	CMA	Received at least 4 prior therapies and whose disease is refractory to at least one PI, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy
Idecabtagene vicleucel (Abecma), n=128	BCMA CAR-T Cell	73.4% (65.8%, 81.1%) (67.1% based on ITT)	32.8% (24.7,% 40.9%) (30% based on ITT)	10.6	MA*	Received at least 3 prior therapies, including an immunomodulatory agent, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
Cilta-cel (Carvykti), n=113	BCMA CAR-T Cell	97.9% (92.7%, 99.7%) (84.1% based on ITT)	82.5% (70.8% based on ITT)	NR (28.3, NE)	MA*	Received at least 3 prior therapies, including an immunomodulatory agent, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy
Selinexor/dexamethasone (Nexpovio), n=83	Selective inhibitors of nuclear export	25% (16.4%, 36%)	1%	3.8	MA*	Received at least 4 prior therapies and whose disease is refractory to at least one PI, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy
Melphalan flufenamide (Pepaxti), n=52	Alkylating agent	28.8% (17.1%, 43.1%)	0%	7.6	MA	Received at least 3 prior lines of therapies, whose disease is refractory to at least one PI, one immunomodulatory agent, and one anti-CD38 mAb, and who have demonstrated disease progression on or after the last therapy

CHMP, Committee for Medicinal Products for Human Use; CMA, Conditional marketing authorisation; CR, Complete response; DOR, Duration of response; EU, European Union; ITT, Intention-to-treat; MA; Marketing authorisation; mAb, Monoclonal antibody; NE, Not evaluable; NR, Not reached; PI, proteosome inhibitor; ORR, Objective response rate.

*Initially approved as CMA and converted to MA
Source: Abecma Summary of Product Characteristics, 2021; Blenrep Summary of Product Characteristics, 2022; Carvykti Summary of Product Characteristics, 2023; Elranatamab Summary of Product Characteristics, 2023; Nexpovio (Chari, 2019); Pepaxti Summary of Product Characteristics, 2022; Talvey Summary of Product Characteristics, 2023; Tecvayli Summary of Product Characteristics, 2022.

Note: Blenrep was subsequently withdrawn from the EU market and is not discussed further in this report.

When comparing linvoseltamab with non T cell engaging products (selinexor/dexamethasone and melphalan flufenamide) and BCMA targeting antibody-drug conjugate (belantamab mafodotin), linvoseltamab shows a clear efficacy benefit with higher ORR, CR rates and increased projected DOR.

Indirect unadjusted comparison of linvoseltamab's efficacy against approved BCMA targeting CAR-Ts, as measured by ORR/CR and projected DOR are within range of CAR-T efficacy (based upon the ITT population).

Compared with the BCMAxCD3 bispecifics, teclistamab, (Tecvayli [Summary of Product Characteristics], 2022) and elranatamab (Elrexfio [Summary of Product Characteristics], 2023), linvoseltamab shows a numerically higher response rate and a similar response rate to the GPRC5DxCD3 bispecific, talquetamab.

Additionally, linvoseltamab showed consistent high efficacy across difficult to treat subgroups (presence of baseline EMP, ISS and R-ISS stage III, penta-refractory, high cytogenetic risk), which was not observed with the other bispecific agents.

Not all RRMM patients are candidates for CAR T cell therapies, as they have many barriers affecting access (i.e., accessibility is limited to specialised administration centres).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Pivotal study 1826 was designed to explore the tolerability and anti-MM activity of different doses/administration schedules for linvoseltamab and was structured in two distinct parts:

- Phase 1 adopted a modified 3+3 (4+3) dose-escalation design to investigate the dose-limiting toxicity (DLT) of linvoseltamab at 9 different dose-levels (DLs). Due to reduced sample size in each DL and high disease heterogeneity, limited efficacy information could be gathered from Phase 1.
- Phase 2 was designed to investigate the safety and activity of linvoseltamab in advanced settings of RR MM, and two different recommended Phase 2 doses (RP2Ds 50 mg and 200 mg) were selected for further testing in dedicated cohorts.

Dose and administration regimen

The linvoseltamab administration regimen proposed for this marketing authorisation application (MAA) includes an initial step-up phase (5 mg iv at week 1, 25 mg iv at week 2), followed by 200 mg iv weekly for 12 doses and then Q2W for 5 additional doses. Then, patients who have achieved a response of VGPR or better can switch to a less frequent Q4W schedule, while patients who have not, must continue their treatment according to a Q2W schedule.

Dose recommendations for linvoseltamab were based on the totality of PK, efficacy and safety data from study 1826. The available clinical evidence supports the rationale for the selected 5/25 mg step-up regimen.

Although antitumour activity was observed even at the lowest dose levels evaluated in Phase 1 (DL1: 1 mg/3 mg), the applicant opted for a twofold increase in the full dose (200 mg versus 96 mg) as the intended dosing regimen. Both the 5/25/50 mg and 5/25/200 mg regimens were further developed in Phase II, and response rates and depth of response data were consistently in favour of the 200 mg dose, although some signals pointing towards increased toxicity were observed (see the Safety section below).

Starting with protocol Amendment 8, subjects who received linvoseltamab at the proposed 5/25/200 mg dose regimen and achieved at least VGPR could switch to a less frequent regimen (i.e. Q4W) after 24 weeks of treatment. The rationale for decreasing dose intensity in responders was based on the observation that durable responses could still be observed at lower DLs in phase I, and that dose delays due to AEs did not appear to impact on long-term disease control. Preliminary data showed that responses continued to deepen over time after deintensification, and at the time of the data cutoff date no sign of reduced efficacy could be observed in subjects who switched to Q4W. This is reassuring, and the possibility to reduce the administration frequency in responders is considered of potential value for the patients (see e.g. Kvam AK et al, Haematologica 2015). More comprehensive data on the efficacy of the Q4W to "maintain" response in the long-term will be provided by the final analysis of study 1826 that the applicant has committed to provide as specific obligation in the context of the requested CMA.

Mandatory concomitant therapy included dexamethasone iv as premedication. It is noted that the proposed dose for dexamethasone premedication (40 mg) is within the range known to have anti-MM activity, and it could be reduced to 10 mg only in those subjects who tolerated linvoseltamab with no relevant CRS and/or IRR events. It cannot be excluded that exposure to high-dose dexamethasone might result in increased toxicity, especially in older patients (see e.g. Rosenberg AS et al, Leukemia & Lymphoma 2023).

Study population

The study inclusion/exclusion criteria were overall consistent with the claimed indication and were selected to define a reasonably fit adult population.

Patients with severe anaemia (i.e. <8 g/dl) and/or severe renal failure (i.e. GFR <30 mL/min) were excluded from study 1826, yet anaemia and renal failure are known complications of MM that can develop/worsen during the course of the disease. Although the rationale to limit trial participation to "fitter" patients is understood considering the limited information on linvoseltamab toxicity profile at the time of study initiation (study 1826 was a first-in-human trial), the generalisability of the results to patients with severe manifestations of MM is necessarily limited.

Subjects with CNS/meningeal involvement by MM or other severe neurologic conditions were excluded from trial participation. Patients with low cardiac ejection fraction or patients with rarer forms of plasma cell neoplasms, such as plasma cell leukaemia, primary systemic light-chain amyloidosis, Waldenstrom macroglobulinemia, or POEMS syndrome were also excluded and this information is reflected in section 5.1 of the SmPC.

Only patients with measurable disease, as per the IMWG consensus criteria (see e.g. Kumar S et al, Lancet Oncol 2016; Garderet L et al, Biol Blood Marrow Transplant 2017), could be enrolled. The applicant initially limited the enrolment of subjects with extramedullary plasmacytoma (EMP) to a maximum of 20 subjects in each Phase 2 cohort. Several studies have suggested that EMD, either at diagnosis or at relapse, is a poor prognostic factor (see e.g. Pour L et al, Haematologica 2014). Considering that approximately 6% to 20% of MM patients develop EMP during the course of the disease, the enrolment threshold chosen by the applicant was considered overall acceptable.

Study objectives and endpoints

The primary efficacy objective in the Phase II part of study 1826 was to evaluate the anti-MM activity of linvoseltamab in terms of objective response rate (ORR, i.e. subjects with a best overall response of PR, VGPR, CR or sCR), as assessed by an independent review committee (IRC). Responses were adjudicated based on the 2016 IMWG response criteria, as per current guidelines and clinical practice, and confirmation of response was required in at least two consecutive readings (see e.g. Dimopoulos MA et al, Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Ann Oncol 2021).

ORR is considered an acceptable endpoint to measure anti MM-activity in uncontrolled exploratory trials since spontaneous tumour regression is unlikely in advanced settings of relapse and can provide a sufficient basis of evidence to support early access in advanced settings of RR MM. MM is a chronic disease and clinical benefit evaluations ideally also require the demonstration of significant improvements in relevant time-to-event endpoints (e.g. OS, PFS, see e.g. EMA/CHMP/205/95 Rev.6). The interpretation of time-to-event endpoints in single arm trials is not straightforward, mainly because unmeasurable/unknown variables that could impact on survival times can only be controlled through randomisation. Comprehensive data in terms of relevant improvements in time-to-event endpoints are, however, expected in the post-approval setting to confirm clinical benefit.

Overall, the estimand strategy used for ORR in pivotal study 1826 is considered acceptable: response was considered prior to start a new treatment for MM (on treatment strategy), while a treatment policy strategy was used for discontinuation of treatment for any reason. In particular, subjects with non-evaluable responses were adjudicated as non-responders which is considered conservative and agreed.

Secondary endpoints in study 1826 (i.e. ORR as determined by the Investigator, DoR and PFS by IRC, OS, MRD negativity rate) were selected to further characterise the efficacy of linvoseltamab in the target indication and are considered overall standard and acceptable. In particular, measures of depth of response (e.g. CRR, MRD negativity rate) and response duration (DoR) are considered key secondary endpoints to further support clinical benefit in late lines of MM relapse

Statistical analysis

The main analysis set for efficacy was the FAS (full analysis set), which included all subjects who received at least 1 dose of study drug. In principle, this is not considered in line with the ITT assumption, since enrolled patients who fail to receive linvoseltamab are excluded from efficacy evaluations. However, since all subjects enrolled in the Phase 2 cohorts of study 1826 were eventually treated, the FAS reflected the ITT population.

The applicant provided efficacy analyses pooling subjects who received linvoseltamab at the 5/25/200 mg dose regimen across both Phase 1 (DL7) and Phase 2. Pooled data can be acceptable as primary source of evidence for efficacy if lack of structural differences resulting in outcomes heterogeneity and high homogeneity in terms of e.g. patient and disease characteristics, prior therapies etc. are demonstrated across cohorts. In this regard, although differences regarding the administration schedule could be observed across Phase 1 and Phase 2, their impact on efficacy is expected to be limited. The applicant pooling strategy is considered acceptable.

The planned sensitivity and subgroup analyses are considered, overall, adequate to further characterise the efficacy of linvoseltamab. With respect to PROs, no formal statistical testing was planned, and no claim based on HR-QoL data was raised by the applicant. Considering the limits of PROs interpretation outside of a RCT, this is agreed.

Several amendments were issued for study 1826, which is not unexpected when its exploratory nature is taken into consideration. Although Amendment 7 resulted in relevant changes in some patient characteristics (e.g. subjects enrolled before study Amendment 7 were significantly more likely to be penta-refractory) the majority of patients in the All 200 mg analysis set (N=87) were enrolled under Amendments 7 and 8, which limited intra-cohort heterogeneity.

At least one important protocol deviation was reported in 41/105 patients who received linvoseltamab in the Phase 2 200 mg cohort: reassuringly, a "post-hoc" "per-protocol" sensitivity analysis, which excluded all subjects with important protocol deviations, showed consistent results with the primary analysis.

Efficacy data and additional analyses

Patient disposition

At the time of the data cutoff date of the primary analysis (DCO 08 Sept 2023), a total of 349 patients were screened for study participation and 282/349 (~80%) were enrolled and treated in pivotal study 1826. The main reason for screening failure was not meeting the inclusion/exclusion criteria (76%), and "Death" accounted for 3% of all the enrolment failure. The low rates of patients who failed to be treated because of death or other disease-related conditions is reassuring, since the selective exclusion

of subjects with more severe or rapidly progressing disease would have negatively impacted on results generalisability.

All enrolled patients received at least one dose of linvoseltamab. At the DCO, approximately half of the patients treated in the Phase 2 200 mg cohort were still receiving linvoseltamab in the "core treatment" Phase, highlighting the limited follow-up in the study. The main reasons for treatment discontinuation were disease progression (29.5%) and AE (12.4%), as expected in such a heavily pre-treated population.

The main efficacy analysis sets were the Phase 2 200 mg FAS (N=105) and the pooled All 200 mg FAS (N=117). Results from the Phase 2 50 mg FAS (N=104) were considered supportive.

Baseline characteristics

Median age in the Phase 2 200 mg and All 200 mg cohorts was ~70 years, which is in line with the known epidemiology of MM (see e.g. Padala SA et al, Med Sci Basel. 2021). Consistent with the study inclusion criteria, all subjects had a ECOG PS score ≤1, suggesting that patients in study 1826 should be considered representative of an overall "fit" population.

Most patients were Caucasian and subjects of African descent represented ~17% of the studied population. Study 1826 was mainly conducted in US centres, with EU subjects comprising ~10% of the study population.

Most subjects in the Phase 2 200 mg cohort and All 200 mg cohort had IgG (54.3% and 55.6%, respectively), IgA (21% and 21.4%) or light-chain MM (21.9% and 20.5%), which is generally in line with literature data (see e.g. Kyle RA et al, Mayo Clin Proc. 2003). Approximately 16% and 18% of subjects in the Phase 2 200 mg and All 200 mg cohorts had ISS stage III disease, respectively, and 13.3% and 14.5% had R-ISS stage III, respectively. High risk cytogenetics could be observed in approximately 40% of subjects in both 200 mg efficacy cohorts, and the most prevalent alterations were del(17p) (~30%) and t(4;14) (~9%). The relatively high incidence of del(17p) can be justified considering the significant acquired chemoresistance requested by the study inclusion criteria (see e.g. Cui J et al, Haematologica. 2024). Further evidence of the advanced stage of disease is provided by the significant proportion (~30%) of subjects in the Phase 2 and All 200 mg groups who had at least one baseline plasmacytoma by IRC assessment (with extramedullary disease detectable in ~17%).

All patients included in the Phase 2 200 mg and All 200 mg data set had received prior therapies for MM, in line with the claimed indication. The median number of prior lines of therapy was 5 in both sets (range 2-13 and 2-16, respectively). The proposed indication is restricted to subjects with at least 3 prior lines of therapy, which is consistent with the study population (~97% of subjects had ≥3 prior lines of therapy). Although, following Amendment 7, triple-refractory subjects could be enrolled irrespectively of number of prior lines of therapy, the impact of the very low number of subjects with 2 prior lines of therapy in the Phase 2 200 mg cohort(n=3) on results generalisability to the targeted population was negligible.

All subjects in the Phase 2 200 mg and All 200 mg sets were triple exposed to at least one PI, one IMiD and one anti-CD38 mAb, and the majority (77%) were penta-exposed. As expected in such an advanced setting of relapse, refractoriness was widespread, with ~80% of subjects in the Phase 2 200 mg and All 200 mg sets being triple-refractory (~27% penta-refractory), and ~84% of subjects in the 200mg efficacy analysis sets were refractory to their last line of therapy. During the assessment, the CHMP requested an amendment of the indication to adult patients with relapsed and refractory multiple myeloma, rather than relapsed or refractory as initially claimed by the application, who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy to better reflect the studied population and this was accepted by the applicant.

Baseline demographic and disease characteristics of patients in the supportive Phase 2 50 mg cohort were generally consistent with those in the 200 mg cohort, with the exception of a lower median age (65 years), a higher proportion of subjects with ISS stage III (23%), and a lower proportion of del(17p) (21%). Subjects in the 50 mg cohort were also more heavily pre-treated: the median number of prior lines of therapy was 6, and a greater proportion of subjects were penta-exposed (91%), triple-refractory (93%) or penta-refractory (53.8%). This substantial imbalance across Phase 2 cohorts with respect to previous treatment lines and refractoriness raises uncertainties on the reliability of the efficacy evaluations that guided dose selection, especially considering the small number of patients studied.

Compared to the Phase 2 200 mg cohort, subjects who received linvoseltamab 200 mg in Phase 1 were generally younger (<65 years 35.2% and 58.3%, respectively; ≥75 years 27.6% vs. 16.7%, respectively), and more likely to be female (41.9% vs. 75%, respectively). With respect to disease characteristics, only a minority of subjects in the Phase 1 200 mg group had light-chain MM (8.3%) compared to 21.9% in the Phase 2 and 200 mg cohort, and only 2 out of the 12 patients who received linvoseltamab 200 mg in Phase 1 had extramedullary disease (by IRC assessment) compared to 32.4% in the Phase 2 200 mg cohort.

Pooled efficacy data across Phase 1 and Phase 2 are reported in Section 5.1 of the SmPC: since the relevance of the observed differences on the efficacy of linvoseltamab is uncertain, this is considered acceptable to maximise the clinical information, especially when the limited sample size is taken into consideration.

Outcomes and estimation

At the latest data cut-off date (DCO Jan 2024), the median follow-up (mFU) in the pivotal Phase 2 200 mg cohort was approximately 14 months (maximum duration of follow-up 22.6 months), and a similar mFU (~14.3 months) could be observed in the pooled All 200 mg analysis set (although the maximum follow-up duration was longer, i.e. 38.4 months, reflecting the longer follow-up in Phase 1).

The length of study FU is not considered adequate to fully characterise the long-term clinical benefit with linvoseltamab as MM is often characterised by an indolent behaviour. To fully characterise the long-term efficacy and safety of linvoseltamab, the MAH has committed to submit the final clinical study report (CSR) for study 1826, with the regulatory submission planned in January 2027.

Study 1826 met its primary objective: the Objective response rate (ORR) by IRC in the Phase 2 200 mg cohort in the most updated analysis was 69.5% (95%CI 59.8, 78.1), which significantly exceeded the pre-specified threshold for efficacy (31%). Despite the advanced setting of relapse, a high rate of deep responses could be observed, with the VGPR or better rate and the CR or better rate (CRR) by IRC being 62.9% (95%CI 52.9, 72.1) and 48.6% (95%CI 38.7, 58.5), respectively.

ORR in the pooled All 200 mg analysis set were consistent with those reported in the Phase 2 200 mg cohort: the ORR by IRC was 70.9% (95%CI 61.8, 79.0), the VGPR or better rate 63.2% (95%CI 53.8, 72.0) and the CRR 49.6% (95%CI 40.2, 59.0). Response rates in the Phase 1 200 mg patients (ORR 83.3%, VGPR or better rate 66.7%, CRR 58.3%) were higher than those observed in Phase 2, highlighting the heterogeneity of MM and the limits in weighing clinical benefit in the absence of controls.

Results from the pre-specified sensitivity analyses were consistent with the primary analysis: the ORRs by Investigator assessment in the Phase 2 and All 200 mg sets were 67.6% (95%CI 57.8, 76.4) and 69.2% (95%CI 60.0, 77.4), respectively, and the ORRs by IRC only based on MM laboratory data were 70.5% (95%CI 60.8, 79.0) and 71.8% (95%CI 62.7, 79.7) in the Phase 2 200 mg and All 200 mg sets, respectively.

Subgroup analyses for ORR in the All 200 mg set at the latest DCO date showed that response rates were generally consistent across the majority of the pre-specified subgroups, and clinically relevant ORRs could be observed irrespectively of age (ORR 66% and 71% in subjects aged <65 and ≥75 years, respectively), ethnicity, baseline ECOG PS score and cytogenetic risk (ORR 67% and 73% in high and standard risk patients, respectively). Higher response rates could be observed in females compared to males (ORR 87% vs. 58%), yet such findings have been reported before with immunotherapy (see e.g. Wang S et al, Molecules. 2019).

Consistent ORRs could also be observed in triple- (ORR 80%) or penta-exposed patients (71%), as well as in patients who were triple- (ORR 74%) or penta-refractory (ORR 68%). A similar ORR (71%) could also be observed in subjects refractory and non-refractory to their last line of therapy: small numbers in the non-refractory subgroup (n=17) did not allow, however, for specific B/R evaluations in this population, for whom therapeutic alternatives might still be available. Ten subjects in the Phase 2 200 mg cohort had received prior therapy with the anti-BCMA conjugated mAb belantamab mafodotin: the ORR (70%) and CRR (40%) in this small subset were encouraging, yet too limited to draw any definitive conclusions on the B/R of linvoseltamab in subjects exposed to anti-BCMA conjugated mAbs.

A trend towards lower ORRs could be observed in subjects with high-disease burden features, such as high ISS or R-ISS score (62% and 65%, respectively), presence of EMP (ORR 53%), high bone marrow plasma cell count (ORR 44% in subjects with a bone marrow plasma cell count ≥60%), high baseline sBCMA levels (ORR 56%) and high serum/urine M-protein or involved light chain levels, although limited sample size hampered definitive conclusions.

Responses were usually rapidly induced, with a median time to response (TTR) by IRC in the Phase 2 200 mg cohort of 0.95 months (range 0.5, 6.3) and deepened over time (median TTCR 8.38 months; range 1.6, 14.1). Sixty-one out of 105 patients in the Phase 2 200 mg cohort achieved VGPR or better after at least 24 weeks of treatment, and 58/61 were switched to a Q4W regimen. Although limited follow-up did not allow to fully characterise the adequacy of the Q4W regimen to maintain response in the long run, it is noted that at the most recent DCO 20 patients out of 31 who switched to Q4W before reaching CR improved their response after switching, which is reassuring.

Responses appeared to be durable, and the median DoR by IRC in the Phase 2 200 mg cohort was not reached at the time of the updated DCO (95%CI 16.6, NE), as expected considering the limited follow-up (only 27.4% of the study population experienced an event). KM estimates suggested that ~81% of responder could still be relapse/progression free after 12 months from treatment start, yet heavy censoring reduced the estimate reliability. Although the longer estimated median DoR in the Phase 1 200 mg DL group (27 months, 95%CI 5.3, NE) could suggest the possibility for some patients to achieve long-lasting remission, limited sample size (n=10), disease heterogeneity and differences in the linvoseltamab administration schedule reduced the reliability of Phase 1 data. The median DoR by IRC in the All 200 mg efficacy set was 29.4 months (95%CI 19.2, NE), and the 12-month KM DOR estimation was 80.9% (95%CI 70.3, 88.0).

The median DoR by Investigator assessment (19.8, 95%CI 15.2, NE and 20.9 months, 95%CI 16.6, NE in the Phase 2 200 mg cohort and All 200 mg efficacy set, respectively) was shorter than that assessed by the IRC, as also observed in the Phase 2 50 mg cohort. Such differences are not unexpected, however, since in such advanced setting of relapse Investigators might be reluctant to wait for overt PD before switching treatment to minimise the risk of developing MM-related complications. More mature data will be provided in the final analysis of study 1826 which the applicant has committed to submit as specific obligation in the context of the pursued CMA.

Supportive data from the Phase 2 50 mg cohort also showed a lower yet not-negligible anti-MM activity: the ORR by IRC was 48.1% (95%CI 38.2, 58.1), the VGPR or better rate 39.4% (95%CI 30.0, 49.5) and the CRR 21.2% (95%CI 13.8, 30.3). The median TTR (1.33 months) was slightly longer than

that observed in the 200 mg cohort, yet DoR data suggested the possibility for long-term response maintenance (median DoR by IRC 31.5 months, 95%CI 20.0, NE). The possibility for responders to achieve long-term disease control also with the lower 50 mg can be looked at as supportive of the ability of the proposed Q4W "maintenance" regimen to also maintain response in the long run.

Overall survival (OS) data were still largely immature at the latest DCO: only 27.6% of subjects had an event in the Phase 2 200 mg cohort, and the median OS was not estimable (NR, 95%CI NE, NE); more mature estimates from the Phase 2 50 mg cohort (event rate 37.5%) showed a mOS of 33.3 months (95%CI 19.1, NE). Due to the short follow-up, OS data should be evaluated with caution, especially when the everchanging landscape of RR MM therapy is considered: high heterogeneity in subsequent treatments is, in fact, expected and its impact on OS is difficult to assess, especially in the absence of proper controls.

Minimal residual disease (MRD) data from the Phase 2 200 mg cohort showed that 19 out of 51 (37.3%) patients who achieved ≥CR reached a MRD negative status by either NGS or flow cytometry, further showing the potential of linvoseltamab to obtain deep responses in advanced settings of MM. Uncertainties remain, however, on the generalisability of MRD evaluations in study 1826 because of the observed high rate of missing data (9/51) and clonoSEQ calibration failures (7/51).

Patient-reported outcomes (PROs) data collected at baseline and through week 44 showed a high completion rate (≥80%), and completion rates were generally above 50% across the majority of subsequent timepoints. Baseline scores were consistent with the "fit" population defined by the inclusion/exclusion criteria, The LS mean changes from baseline for global health status/QoL did not cross the threshold for clinically meaningful improvement, yet reassuringly no clinically relevant deterioration was either observed. The LS mean changes from baseline for fatigue and pain reached the threshold for clinically meaningful improvement by week 52 and week 20, respectively, suggesting the possibility for clinical benefit in responders who achieved long-lasting disease control. However, interpretation of uncontrolled PRO data from an exploratory open-label study needs caution, and their regulatory value is limited.

Additional efficacy data needed in the context of a conditional MA

Linvoseltamab is intended to be administered continuously until disease progression/unbearable toxicity, yet the limited follow-up in study 1826 did not allow to thoroughly characterise long-term clinical benefit. To further characterise duration of response with linvoseltamab and the efficacy of the proposed Q4W "maintenance" administration regimen, the applicant has committed to submit the final clinical study report of study 1826 as a specific obligation in the context of the requested CMA.

The applicant is planning to provide comprehensive confirmatory data from a Phase III, open-label, randomised, controlled study (study R5458-ONC-2245) comparing linvoseltamab monotherapy at the same dose regimen proposed for this MAA vs elotuzumab plus pomalidomide and low-dose dexamethasone (EPd).

The primary analysis for PFS in study 2245 will be limited to patients with R/R MM who are triple-exposed to lenalidomide, a PI and an anti-CD38 mAb (although the requirements in terms of number of prior lines of therapy [≥2] are less demanding), for whom EPd is considered a suitable option. The planned regulatory submission date is June 2027.

2.6.7. Conclusions on the clinical efficacy

The clinical efficacy data submitted in this MAA support the benefit of linvoseltamab in the final agreed indication. The CHMP considers the following measures necessary to address the not sufficiently comprehensive efficacy data in the context of a conditional MA:

• The final study report of the pivotal study R5458-ONC-1826 (LINKER-MM1) should be provided.

• The final study report from study R5458-ONC-2245 (LINKER-MM3) investigating the efficacy and safety of linvoseltamab monotherapy vs. elotuzumab plus pomalidomide and low-dose dexamethasone in adults with relapsed/refractory multiple myeloma should be provided.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Within Study 1826, summaries of safety data are presented for all patients who were administered the 200 mg full dose across Phase 1 (n=12) and Phase 2 (n=105) for a total of 117 patients, referred to in this report as the "All 200 mg Patients" subset of the Safety Analysis Set (SAF).

Phase 1 and Phase 2 patients treated with a 200 mg dose, were combined because differences in per protocol treatment of these patients did not seem to have any known or anticipated meaningful effects on safety variables. These differences were:

1. Splitting the first 200 mg dose into 2 separate 100 mg doses administered over successive days only in the Phase 1 patients,
2. A switch from QW to Q2W dosing at Week 16 in Phase 1 versus Week 14 in Phase 2, and
3. A switch from Q2W dosing to Q4W dosing at Week 24 in patients with response of VGPR or better only in Phase 2 patients (Phase 1 patients remained on Q2W dosing throughout).

Supportive evidence is provided by the individual Phase 2 cohorts, Cohort 1 50 mg full dose (n=104) (hereafter referred as "Phase 2 50 mg Patients"), Cohort 2 200 mg full dose (n=105) (hereafter referred as "Phase 2 200 mg patients"), and all Study Patients treated in Study 1826, including both Phase 1 and Phase 2 (n=282) (hereafter referred to as "All study patients").

As of the data cutoff date, 08 Sep 2023, core treatment was ongoing for 53/117 (45.3%) patients. A total of 64/117 (54.7%) of All 200 mg Patients had discontinued treatment. The most common reason for discontinuation of treatment was disease progression for 37/117 (31.6%) patients. A total of 61/117 (52.1%) of the All 200 mg Patients discontinued the study. The most frequently reported reason for discontinuation of study for All 200 mg Patients was progressive disease (27/117 [23.1%]).

There were 56/117 (47.9%) patients ongoing on the study as of the data cutoff date.

The median duration of follow up in All 200 mg Patients was 11.10 months (range: 0.2 to 34.5 months). The median duration of follow up for Phase 2 50 mg Patients was lower at 7.4 months (range 0.4 to 38 months).

The mean (SD) duration of exposure of All 200 mg Patients was 40.9 (32.8) weeks and the median duration of exposure was 47.4 (range: 1 to 151) weeks. The majority of All 200 patients, 69/117 [59.0%], had ≥6 months of exposure to linvoseltamab and 42/117 (35.9%) had ≥12 months of exposure to linvoseltamab. The mean (SD) exposure of Phase 2 50 mg Patients was 38.8 (43.69) weeks; the median duration of exposure was 13.9 weeks.

Overall, 86/117 (73.5%) of All 200 mg Patients had at least one dose delay and/or infusion interruption and/or dose modification. 82/117 (70.1%) patients experienced at least 1 dose delay, 9/117 (7.7%) patients experienced at least 1 infusion slowed or interrupted, and 21/117 (17.9%) patients experienced at least 1 dose modification. There was a lower incidence of at least one dose

delay in Phase 2 50 mg Patients (47.1%), whereas the incidences of infusion slowed or interrupted (6.7%) and dose modification (20.2%) were similar between Phase 2 50 mg Patients and All 200 mg Patients.

Phase 2 200 mg Patients Switching from Q2W to Q4W

Of the 61 Phase 2 200 mg Patients who had completed at least 24 weeks on-study, 59 (96.7%) achieved a BOR of VGPR or better and were eligible for transition from Q2W to Q4W. Of these, 56 (91.8%) patients transitioned from Q2W to Q4W and received treatment for a mean (SD) of 22.89 (11.795) weeks after the transition. The median duration of exposure after the transition was 22.00 weeks (range: 2.0 to 52.0 weeks). After transitioning to Q4W dosing, the majority of Phase 2 200 mg Patients who transitioned from Q2W to Q4W (47/61 [77.0%]) had ≥3 months of exposure to linvoseltamab, 18/61 (29.5%) had ≥6 months of exposure, and 4/61 (6.6%) had ≥9 months of exposure to linvoseltamab. Of the patients who transitioned to Q4W dosing, 41 did so at week 24 and 15 did so after week 24.

2.6.8.2. Adverse events

An overview of the Treatment-Emergent Adverse Events (TEAEs) reported in study 1826 are summarised in

Table 27.

Table 27. Overview of Treatment-Emergent Adverse Events - Phase 2 and All 200 mg Patients (SAF) (Study 1826)

	Phase 2		
	50 mg (N=104)	**200 mg (N=105)**	**All 200 mg* (N=117)**
Number of TEAEs	2059	1680	2123
Number of NCI grade 3/4/5 TEAEs	400	346	415
Number of Serious TEAEs	215	186	217
Number of patients with any TEAE, n (%)	102 (98.1%)	105 (100%)	117 (100%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	84 (80.8%)	88 (83.8%)	99 (84.6%)
Number of patients with any serious TEAE, n (%)	77 (74.0%)	77 (73.3%)	86 (73.5%)
Number of Patients who discontinued study treatment due to TEAEs, n (%)	13 (12.5%)	17 (16.2%)	19 (16.2%)
Number of patients with any TEAE leading to a dose interruption/delay, n (%)	54 (51.9%)	76 (73.4%)	86 (73.5%)
Number of patients with any TEAE leading to a dose reduction, n (%)	19 (18.3%)	12 (11.4%)	16 (13.7%)
Number of patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	15 (14.4%)	10 (9.5%)	14 (12.0%)
Number of patients with any TEAE resulting in death, n (%)	9 (8.7%)	14 (13.3%)	14 (12.0%)

- **Common Treatment Emergent Adverse Events**

The most common TEAEs were similar between the All 200 mg Patients and the Phase 2 50 mg patients (**Table 28**).

Table 28. Summary of Most Common TEAEs by Preferred Term (≥20% in Either of the Phase 2 Cohorts) – Phase 2 and All 200 mg Patients (SAF) (Study 1826)

Preferred Term, n (%)	Phase 2		All 200 mg* (N=117)
	50 mg (N=104)	200 mg (N=105)	
Total number of TEAEs	2059	1680	2123
Number of patients with any TEAE, n (%)	102 (98.1%)	105 (100%)	117 (100%)
Cytokine release syndrome	57 (54.8%)	49 (46.7%)	54 (46.2%)
Anaemia	43 (41.3%)	39 (37.1%)	45 (38.5%)
Cough	36 (34.6%)	36 (34.3%)	42 (35.9%)
Diarrhoea	31 (29.8%)	36 (34.3%)	41 (35.0%)
Fatigue	31 (29.8%)	31 (29.5%)	39 (33.3%)
Neutrophil count decreased	21 (20.2%)	33 (31.4%)	38 (32.5%)
Arthralgia	34 (32.7%)	31 (29.5%)	35 (29.9%)
Hypokalaemia	17 (16.3%)	23 (21.9%)	29 (24.8%)
Nausea	27 (26.0%)	22 (21.0%)	27 (23.1%)
Headache	31 (29.8%)	22 (21.0%)	25 (21.4%)
Backpain	24 (23.1%)	18 (17.1%)	23 (19.7%)
Dyspnoea	21 (20.2%)	18 (17.1%)	23 (19.7%)
COVID-19	22 (21.2%)	19 (18.1%)	20 (17.1%)
Constipation	21 (20.2%)	18 (17.1%)	20 (17.1%)

MedDRA, Medical Dictionary for regulatory authorities, SAF, Safety analysis set, TEAE=Treatment Emergent Adverse Events
*All 200 mg (N=117) = Phase 1 200 mg patients (n=12) + Phase 2 200 mg patients (n=105)
Note: All adverse events were coded using MedDRA Version 26.0.
Note: A patient who reported multiple TEAEs with the same preferred term is counted only once for that term.
Note: The table is sorted by decreasing frequency in the All 200 mg Dose group.
Note: CRS was graded by adapted criteria from Lee (2019).
Data cut-off as of 08 Sep 2023; Data extract as of 16 Oct 2023

- **Treatment-Emergent Adverse Events by Severity**

In the All 200 mg Patients, 85/117 (72.6%) experienced Grade 3 or 4 TEAEs and 14/117 (12.0%) experienced Grade 5 TEAEs. The most common Grade 3 or 4 TEAEs (≥5%) by PT were events reflecting decreases in hematologic parameters, as well as Pneumonia, Acute kidney injury, and COVID-19. In Phase 2 50 mg Patients, the overall incidence of Grade 3 or 4 TEAEs was similar to All 200 mg Patients (**Table 29**).

Table 29. Summary of grade 3 or higher treatment-emergent adverse events by preferred term and NCI grade (≥5% in either Phase 2 Cohort) - Phase 2 and All 200 mg patients (SAF) (Study 1826)

	Phase 2				All 200 mg* (N=117)	
	50 mg (N=104)		200 mg (N=105)			
Preferred Term, n (%)	Grades 3/4	Grade 5	Grades 3/4	Grade 5	Grades 3/4	Grade 5
Total number of TEAEs	391	9	332	14	401	14
Number of patients with any TEAE, n (%)	75 (72.1%)	9 (8.7%)	74 (70.5%)	14(13.3%)	85 (72.6%)	14 (12.0%)
Neutrophil count decreased	20 (19.2%)	0	32 (30.5%)	0	37 (31.6%)	0
Anaemia	39 (37.5%)	0	31 (29.5%)	0	36 (30.8%)	0
Pneumonia	10 (9.6%)	0	13 (12.4%)	0	17 (14.5%)	0
Neutropenia	10 (9.6%)	0	12 (11.4%)	0	14 (12.0%)	0
Platelet count decreased	12 (11.5%)	0	10 (9.5%)	0	12 (10.3%)	0
Lymphocyte count decreased	10 (9.6%)	0	8 (7.6%)	0	10 (8.5%)	0
Febrile neutropenia	7 (6.7%)	0	7 (6.7%)	0	9 (7.7%)	0
Acute kidney injury	11 (10.6%)	0	7 (6.7%)	0	7 (6.0%)	0
COVID-19	4 (3.8%)	3 (2.9%)	6 (5.7%)	0	6 (5.1%)	0
Thrombocytopenia	6 (5.8%)	0	5 (4.8%)	0	5 (4.3%)	0
White blood cell count decreased	9 (8.7%)	0	1 (1.0%)	0	2 (1.7%)	0
Lymphopenia	8 (7.7%)	0	1 (1.0%)	0	3 (2.6%)	0

CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; SAF, Safety analysis set; TEAE, Treatment-emergent adverse event.
*All 200 mg (N=117) = Phase 1 200 mg patients (n=12) + Phase 2 200 mg patients (n=105)
Note: All adverse events were coded using MedDRA Version 26.0. NCI grades were coded using CTCAE Version 5.0.
Note: A patient is counted only once for multiple occurrences within a preferred term.
Note: The table is sorted by decreasing incidence rate of grade 3/4 events in the All 200 mg Dose group.
Note: If a patient had an event with more than one occurrence with multiple grades, the worst grade occurrence is reported
Data cut-off as of 08 Sep 2023; Data extract as of 16 Oct 2023

- **Treatment-Related Treatment Emergent Adverse Events**

In All 200 mg Patients, 101/117 (86.3%) had a treatment-related TEAE with 70/117 (59.8%) experiencing Grade ≥3 treatment related TEAE and 65/117 (55.6%) experiencing serious treatment related TEAEs (**Table 30**).

Table 30. Overview of treatment-emergent adverse events (SAF) - Phase 2 (50 mg and 200 mg) and All 200 mg Patients (SAF) (Study 1826)

	Phase 2		
	50 mg (N=104)	200 mg (N=105)	All 200 mg** (N=117)
Number of treatment-related TEAEs	642	561	701
Number of NCI grade 3/4/5 treatment-related TEAEs	162	163	197
Number of Serious treatment-related TEAEs	109	103	124
Number of patients with any treatment-related TEAE, n (%)	88 (84.6%)	91 (86.7%)	101 (86.3%)
Number of patients with any NCI grade 3/4/5 treatment-related TEAE, n (%)	49 (47.1%)	61 (58.1%)	70 (59.8%)
Number of patients with any serious treatment-related TEAE, n (%)	53 (51.0%)	58 (55.2%)	65 (55.6%)
Number of Patients who discontinued study treatment due to treatment-related TEAEs, n (%)	4 (3.8%)	6 (5.7%)	8 (6.8%)
Number of patients with any treatment-related TEAE leading to a dose interruption/delay, n (%)	33 (31.7%)	51 (48.6%)	59 (50.4%)
Number of patients with any treatment-related TEAE leading to a dose reduction, n (%)	10 (9.6%)	10 (9.5%)	12 (10.3%)
Number of patients with any treatment-related TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	7 (6.7%)	8 (7.6%)	9 (7.7%)
Number of patients with any treatment-related TEAE resulting in death, n (%)	1 (1.0%)	3 (2.9%)	3 (2.6%)

NCI, National Cancer Institute; SAF, Safety analysis set; TEAE, Treatment-emergent adverse event.
**All 200 mg (N=117) = Phase 1 200 mg Patients (n=12) + Phase 2 200 mg Patients (n=105)
Note: A patient is counted only once for multiple occurrences within a category.
Note: NCI grades were coded using CTCAE Version 4.03.

The most common treatment-related TEAEs (≥10% patients by PT) were Cytokine release syndrome and hematologic abnormalities (**Table 31**).

Table 31. Summary of Treatment-Related Treatment-Emergent Adverse Events by Preferred Term (≥10% in Either Phase 2 Cohort) (SAF) – Phase 2 (50 mg and 200 mg) and All 200 mg Patients (Study 1826)

	Phase 2		
Preferred Term, n (%)	**50 mg (N=104)**	**200 mg (N=105)**	**All 200 mg* (N=117)**
Number of patients with any TEAE, n (%)	88 (84.6%)	91 (86.7%)	101 (86.3%)
Cytokine release syndrome	57 (54.8%)	49 (46.7%)	54 (46.2%)
Neutrophil count decreased	16 (15.4%)	26 (24.8%)	30 (25.6%)
Fatigue	16 (15.4%)	16 (15.2%)	21 (17.9%)
Anaemia	11 (10.6%)	14 (13.3%)	17 (14.5%)
Diarrhoea	6 (5.8%)	14 (13.3%)	15 (12.8%)
Cough	7 (6.7%)	13 (12.4%)	14 (12.0%)
Platelet count decreased	6 (5.8%)	11 (10.5%)	12 (10.3%)
Headache	15 (14.4%)	10 (9.5%)	10 (8.5%)

SAF, Safety analysis set; TEAE, Treatment-emergent adverse event.
*All 200 mg (N=117) = Phase 1 200 mg Patients (n=12) + Phase 2 200 mg Patients (n=105)
Note: All adverse events were coded using MedDRA Version 26.0.
Note: A patient who reported multiple TEAEs with the same preferred term is counted only once for that term.
Note: The table is sorted by decreasing frequency in the All 200 mg Dose group.
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

2.6.8.3. Serious adverse event/deaths/other significant events

- **Serious Adverse Events**

In the All 200 mg Patients, 86/117 (73.5%) patients experienced an SAE. The most common SAEs by PT are summarised in **Table 32**.

In Phase 2 50 mg Patients, the percentage of patients experiencing an SAE (77/104 [74.0%]) was similar to All 200 mg Patients. The most common SAEs by PT and the most common treatment-related SAEs by PT were also similar to All 200 mg Patients.

Table 32. Summary of Treatment-Emergent Serious Adverse Events by Preferred Term (≥2% of Patient in Either Phase 2 Cohort) – Phase 2 (50 mg and 200 mg) and All 200 mg Patients (SAF) (Study 1826)

	50 mg (N=104)			200 mg (N=105)			All 200 mg * (N=117)		
	All Grades	Grades 3/4	Grade 5	All Grades	Grades 3/4	Grade 5	All Grades	Grades 3/4	Grade 5
Total number of TEAEs	215	124	9	186	107	14	217	122	14
Number of patients with any TEAE, n (%)	77 (74.0%)	45 (43.3%)	9 (8.7%)	77 (73.3%)	43 (41.0%)	14 (13.3%)	86 (73.5%)	50 (42.7%)	14 (12.0%)
Cytokine release syndrome	39 (37.5%)	2 (1.9%)	0	28 (26.7%)	1 (1.0%)	0	32 (27.4%)	1 (0.9%)	0
Pneumonia	9 (8.7%)	9 (8.7%)	0	11 (10.5%)	11 (10.5%)	0	15 (12.8%)	15 (12.8%)	0
COVID-19	6 (5.8%)	3 (2.9%)	3 (2.9%)	8 (7.6%)	6 (5.7%)	0	8 (6.8%)	6 (5.1%)	0
Acute kidney injury	7 (6.7%)	7 (6.7%)	0	6 (5.7%)	6 (5.7%)	0	6 (5.1%)	6 (5.1%)	0
COVID-19 pneumonia	3 (2.9%)	3 (2.9%)	0	5 (4.8%)	2 (1.9%)	3 (2.9%)	5 (4.3%)	2 (1.7%)	3 (2.6%)
Febrile neutropenia	6 (5.8%)	6 (5.8%)	0	4 (3.8%)	4 (3.8%)	0	5 (4.3%)	5 (4.3%)	0
Infusion related reaction	1 (1.0%)	1 (1.0%)	0	5 (4.8%)	2 (1.9%)	0	5 (4.3%)	2 (1.7%)	0
Pneumocystis jirovecii pneumonia	0	0	0	4 (3.8%)	3 (2.9%)	1 (1.0%)	5 (4.3%)	3 (2.6%)	1 (0.9%)
Immune effector cell-associated neurotoxicity syndrome	1 (1.0%)	1 (1.0%)	0	4 (3.8%)	3 (2.9%)	0	4 (3.4%)	3 (2.6%)	0
Confusional state	3 (2.9%)	1 (1.0%)	0	2 (1.9%)	0	0	3 (2.6%)	0	0
Respiratory failure	3 (2.9%)	3 (2.9%)	0	2 (1.9%)	1 (1.0%)	1 (1.0%)	3 (2.6%)	2 (1.7%)	1 (0.9%)
Pyrexia	5 (4.8%)	1 (1.0%)	0	2 (1.9%)	0	0	2 (1.7%)	0	0
Back pain	4 (3.8%)	4 (3.8%)	0	0	0	0	1 (0.9%)	1 (0.9%)	0
Cellulitis	3 (2.9%)	3 (2.9%)	0	1 (1.0%)	1 (1.0%)	0	1 (0.9%)	1 (0.9%)	0

SAF, Safety analysis set; TEAE, Treatment-emergent adverse event.
*All 200 mg (N=117) = Phase 1 200 mg Patients (n=12) + Phase 2 200 mg Patients (n=105)
Note: A patient is counted only once for multiple occurrences within a category.
Note: The table is sorted by decreasing frequency in the All 200 mg Dose group.
Note: All adverse events were coded using MedDRA Version 26.0. NCI grades were coded using CTCAE Version 5.0
Note: CRS was graded by adapted criteria from Lee (2019).
Note: If a patient had an event with more than one occurrence with multiple grades, the worst grade occurrence is reported.
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

- **Death**

In All 200 mg Patients, 8/117 (6.8%) died between the first dose of core treatment up to 30 days after the last dose day of core treatment, or the day prior to the start of new treatment, whichever came first (Table 11). The most common cause of death was "AE" and occurred in 6/117 (5.1%) patients.

In Phase 2 50 mg Patients, total deaths up to 30 days from end of treatment occurred in a higher proportion of patients (12/104 [11.5%] vs 8/117 [6.8%]) than in All 200 mg Patients, and deaths due to an AE were slightly higher (7/104 [6.7%] vs 6/117 [5.1%]).

TEAEs Leading to Death

In All 200 mg Patients, there were 14/117 (12.0%) patients with a TEAE leading to death, In Phase 2 50 mg Patients, a lower proportion of patients experienced a TEAE leading to death (9/104 [8.7%]) compared with All 200 mg. (**Table 33**).

Table 33. Summary of TEAEs Resulting in Death by Primary System Organ Class and Preferred Term (SAF) – Phase 2 (50 mg and 200 mg) and All 200 mg Patients (Study 1826)

	Phase 2		
System Organ Class, n (%) Preferred Term, n (%)	**50 mg (N=104)**	**200 mg (N=105)**	**All 200 mg* (N=117)**
Number of patients with any TEAE, n (%)	9 (8.7%)	14 (13.3%)	14 (12.0%)
Infections and infestations	5 (4.8%)	11 (10.5%)	11 (9.4%)
COVID-19 pneumonia	0	3 (2.9%)	3 (2.6%)
Septic shock	1 (1.0%)	2 (1.9%)	2 (1.7%)
Escherichia sepsis	0	1 (1.0%)	1 (0.9%)
Haemophilus sepsis	0	1 (1.0%)	1 (0.9%)
Pneumocystis jirovecii pneumonia	0	1 (1.0%)	1 (0.9%)
Pneumonia influenzal	0	1 (1.0%)	1 (0.9%)
Progressive multifocal leukoencephalopathy	1 (1.0%)	1 (1.0%)	1 (0.9%)
Pseudomonal sepsis	0	1 (1.0%)	1 (0.9%)
COVID-19	3 (2.9%)	0	0
Citrobacter sepsis	0	0	0
Sepsis Pasteurella	0	0	0
Nervous system disorders	1 (1.0%)	1 (1.0%)	1 (0.9%)
Encephalopathy	0	1 (1.0%)	1 (0.9%)
Haemorrhage intracranial	1 (1.0%)	0	0
Renal and urinary disorders	0	1 (1.0%)	1 (0.9%)
Chronic kidney disease	0	1 (1.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	1 (1.0%)	1 (1.0%)	1 (0.9%)
Respiratory failure	0	1 (1.0%)	1 (0.9%)
Pulmonary embolism	1 (1.0%)	0	0
General disorders and administration site conditions	2 (1.9%)	0	0
Death	1 (1.0%)	0	0
Sudden death	1 (1.0%)	0	0

The TEAEs leading to death were assessed as related to linvoseltamab in 3/117 (2.6%) patients and were Pneumocystis jirovecii pneumonia (PJP), Progressive multifocal leukoencephalopathy, and Pseudomonal sepsis.

Adverse events of special interest (AESIs)

AESIs for linvoseltamab include Cytokine release syndrome (CRS), neurotoxicity (including ICANS), infections, and TLS.

- **Cytokine Release Syndrome**

In All 200 mg Patients, the overall incidence of CRS was 46.2% (n= 54/117), similar to Phase 2 50 mg Patients (n= 57/104; 54.8%) (**Table 34**).

Table 34. Summary of CRS by Severity – Phase 2 and All 200 mg Patients (SAF) (Study 1826)

System Organ Class, n (%) Preferred Term, n (%)	50 mg (N=104)	200 mg (N=105)	All 200 mg** (N=117)
Cytokine release syndrome	57 (54.8%)	49 (46.7%)	54 (46.2%)
Grade 1	41 (39.4%)	36 (34.3%)	41 (35.0%)
Grade 2	14 (13.5%)	12 (11.4%)	12 (10.3%)
Grade 3	2 (1.9%)	1 (1.0%)	1 (0.9%)

CRS, Cytokine release syndrome; SAF, Safety analysis set
**All 200 mg (N=117) = Phase 1 200 mg Patients (n=12) + Phase 2 200 mg Patients (n=105)
Note: All adverse events were coded using MedDRA Version 26.0. NCI grades were coded using CTCAE Version 5.0.
Note: A patient is counted only once per the worst grade for multiple occurrences within a system organ class/preferred term.
Data cutoff as of 08Sep2023; Data extract as of 16Oct2023

These events occurred mostly during the step-up period (**Table 35**) and were generally of a transient nature.

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), and Tachycardia (8/117 [6.8%] patients) and Hypotension (6/117 [5.1%] patients). In the All 200 mg Patients, the median (range) time to onset of any grade CRS from end of infusion was 11.04 (-1.1 to 183.6) hours. The median duration of CRS event was 14.81 hours. The time to onset for the Grade ≥2 CRS events was 5.76 (-1.1 to 104.8) hours. The median duration of Grade ≥2 CRS events was 23.65 hours. The time to onset for the Grade ≥2 CRS events was 5.76 (-1.1 to 104.8) hours. The median duration of Grade ≥2 CRS events was 23.65 hours. All Grade ≥2 CRS events except one began within approximately 24 hours of the end of the infusion.

There were no CRS events leading to discontinuation. Of the 54 patients who experienced CRS, 23/54 (42.6%) had recurrent CRS (23/117 [19.7%] in All 200 mg patients). All recurrent CRS events were Grade 1 (21/23 [91.3%] patients) or Grade 2 (2/23 [8.7%] patients) and there were no recurrent CRS events of Grade ≥3.

Overall, 29/117 (24.8%) patients received treatment for the management of CRS after the infusion of linvoseltamab. The most common treatments were tocilizumab (22/117 [18.8%] patients) and corticosteroids (13/117 [11.1%] patients). 1/17 (5.9%) patient who received tocilizumab to treat a first episode of CRS experienced recurrence.

Table 35. CRS by Sequential Dose (SAF) - Phase 2 (50 mg and 200 mg) and All 200 mg Patients (Study 1826)

	Initial Dose	Intermediate Dose	First Full Dose*	Second Full Dose	Third Full Dose and beyond	Any Period
5* mg/25 mg/50 mg Phase 2	N=104	N=101	N=95	N=89	N=80	N=104
Number of patients with at least one CRS, n (%)	44 (42.3%)	25 (24.8%)	8 (8.4%)	2 (2.2%)	3 (3.8%)	57 (54.8%)
Grade 1	36 (34.6%)	18 (17.8%)	7 (7.4%)	2 (2.2%)	2 (2.5%)	41 (39.4%)
Grade 2	7 (6.7%)	6 (5.9%)	1 (1.1%)	0	1 (1.3%)	14 (13.5%)
Grade 3	1 (1.0%)	1 (1.0%)	0	0	0	2 (1.9%)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
5* mg/25 mg/200 mg Phase 2	N=105	N=101	N=99	N=98	N=88	N=105
Number of patients with at least one CRS, n (%)	40 (38.1%)	16 (15.8%)	10 (10.1%)	4 (4.1%)	2 (2.3%)	49 (46.7%)
Grade 1	31 (29.5%)	14 (13.9%)	8 (8.1%)	4 (4.1%)	1 (1.1%)	36 (34.3%)
Grade 2	8 (7.6%)	2 (2.0%)	2 (2.0%)	0	1 (1.1%)	12 (11.4%)
Grade 3	1 (1.0%)	0	0	0	0	1 (1.0%)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
5* mg/25 mg/200 mg All**	N=117	N=113	N=111	N=110	N=99	N=117
Number of patients with at least one CRS, n (%)	45 (38.5%)	19 (16.8%)	11 (9.9%)	4 (3.6%)	2 (2.0%)	54 (46.2%)
Grade 1	36 (30.8%)	17 (15.0%)	9 (8.1%)	4 (3.6%)	1 (1.0%)	41 (35.0%)
Grade 2	8 (6.8%)	2 (1.8%)	2 (1.8%)	0	1 (1.0%)	12 (10.3%)
Grade 3	1 (0.9%)	0	0	0	0	1 (0.9%)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0

CRS, Cytokine release syndrome; SAF, Safety analysis set.
* One patient received a split dose (100mg, 100mg) for the first planned dose of 200 mg
**All 200 mg (N=117) = Phase 1 200 mg Patients (n=12) + Phase 2 200 mg Patients (n=105)
Note: Initial Dose = first 5 mg assigned dose; two patients received a 2.5 mg dose in between 5 mg doses
Intermediate Dose = first 25 mg assigned dose
Note: A patient who reported multiple events within the same dosing period is counted only once, with the maximum grade reported.
Note: If a patient had an event with more than one occurrence with multiple grades, the worst grade occurrence is reported
Data cutoff as of 08Sep2023; Data extract as of 16Oct2023

- **Infusion-Related Reactions (IRR)**

An acute Infusion-Related Reaction (IRR) was defined as any AE that occurred less than 6 hours from the start of the infusion, or within 2 hours after completion of the infusion (whichever is later) and was associated with typical signs and symptoms including flushing, tachycardia, hypotension, dyspnoea, bronchospasm, back pain, fever, urticaria, oedema, nausea, and rashes. IRR were reported as AEs and graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0).

In All 200 mg Patients, 11/117 (9.4%) patients experienced an event of IRR and 2/117 (1.7%) patients experienced a Grade 3 IRR event. The IRR occurrence was highest following the initial dose (6/117 [5.1%]), with fewer patients experiencing IRR following the intermediate dose (3/117 [2.7%]) and first full dose and beyond (4/111 [3.6%]). In All 200 mg Patients, the signs and symptoms reported by >1 patient were Pyrexia (7/117 [6.0%]), Chills (4/117 [3.4%]), Hypertension, and Hypotension (2/117 [1.7%] each).

In Phase 2 50 mg Patients, the frequency and severity of IRR was similar to All 200 mg Patients (n= 8/104, 7.7%).

- **Neurotoxicity (including immune effector cell associated neurotoxicity syndrome/ICANS)**

Adjudicated ICANS

In 9/117 (7.7%) patients experienced at least one event adjudicated as ICANS, for a total of 10 events. 7 of 10 events adjudicated as ICANS were coded to the PTs of Immune effector cell-associated neurotoxicity syndrome. The other PTs adjudicated as ICANS were Depressed level of consciousness, Encephalopathy, and Toxic encephalopathy (1/117 [0.9%] each). The median time to onset was 1.0 days (range: 1 to 4 days) and the median duration of adjudicated ICANS was 2.0 days (range: 1 to 11 days). The incidence of ICANS was highest after the initial dose and decreased with sequential doses (**Table 36**).

Table 36. Adjudicated ICANS by Sequential Dose (SAF) - Phase 2 (50 mg and 200 mg) and All 200 mg Patients (Study 1826)

	Initial Dose	Intermediate Dose	First Full Dose	Second Full Dose	Third Full Dose and beyond	Any Period
5* mg/25 mg/50 mg Phase 2	N=104	N=101	N=95	N=89	N=80	N=104
Number of patients with at least one adjudicated ICANS, n (%)	3 (2.9%)	2 (2.0%)	0	0	0	5 (4.8%)
Grade 1	1 (1.0%)	0	0	0	0	1 (1.0%)
Grade 2	2 (1.9%)	1 (1.0%)	0	0	0	3 (2.9%)
Grade 3	0	0	0	0	0	0
Grade 4	0	1 (1.0%)	0	0	0	1 (1.0%)
Grade 5	0	0	0	0	0	0
5* mg/25 mg/200 mg Phase 2	N=105	N=101	N=99	N=98	N=88	N=105
Number of patients with at least one adjudicated ICANS, n (%)	6 (5.7%)	0	0	0	1 (1.1%)	7 (6.7%)
Grade 1	2 (1.9%)	0	0	0	0	2 (1.9%)
Grade 2	2 (1.9%)	0	0	0	0	2 (1.9%)
Grade 3	2 (1.9%)	0		0	1 (1.1%)	3 (2.9%)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
5* mg/25 mg/200 mg All	N=117	N=113	N=111	N=110	N=99	N=117
Number of patients with at least one adjudicated ICANS, n (%)	6 (5.1%)	2 (1.8%)	0	0	1 (1.0%)	9 (7.7%)
Grade 1	2 (1.7%)	1 (0.9%)	0	0	0	3 (2.6%)
Grade 2	2 (1.7%)	1 (0.9%)	0	0	0	3 (2.6%)
Grade 3	2 (1.7%)	0	0	0	1 (1.0%)	3 (2.6%)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0

ICANS, Immune effector cell-associated neurotoxicity syndrome; SAF, Safety analysis set.
Note: A patient who reported multiple events within the same dosing period is counted only once, with the maximum grade reported.
Data cutoff as of 08Sep2023; Data extract as of 16Oct2023

When evaluating ICANS leading to dose delays/interruptions, dose reduction and discontinued treatment, 2/117 (1.7%) patients had dose delays/interruptions due to ICANS, 1/117 (0.9%) patient had dose reduction due to ICANS and 1/117 (0.9%) patient discontinued treatment. In the All 200 mg Patients, 8/117 (6.8%), experienced ICANS concurrently with CRS, on the same day as CRS or soon after the onset of CRS; the remaining patient experienced ICANS concurrently (same dosing week) with IRR. One out of nine patients (11.1%) experienced recurrent ICANS.

Potential encephalopathy

In All 200 mg Patients, 20/117 (17.1%) patients experienced events of potential encephalopathy (**Table 37**). The most commonly reported terms (≥3 patients) were Confusional state (4/117 [3.4%]), Encephalopathy (3/117 [2.6%]), and Depressed level of consciousness (3/117 [2.6%]). The majority of events were Grade 1 or 2; Grade ≥3 events were reported in 5/117 (4.3%) patients.

Table 37. Overview treatment-emergent adverse events by encephalopathy grouping - Phase 2 and All 200 mg patients (SAF) (Study 1826)

	Phase 2		
	50 mg (N=104)	200 mg (N=105)	All 200 mg* (N=117)
Number of TEAEs	22	20	24
Number of NCI grade 3/4/5 TEAEs	2	5	5
Number of Serious TEAEs	8	8	10
Number of patients with any TEAE, n (%)	20 (19.2%)	17 (16.2%)	20 (17.1%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	2 (1.9%)	5 (4.8%)	5 (4.3%)
Number of patients with any serious TEAE, n (%)	8 (7.7%)	7 (6.7%)	9 (7.7%)
Number of Patients who discontinued study treatment due to TEAEs, n (%)	0	1 (1.0%)	1 (0.9%)
Number of patients with any TEAE leading to a dose interruption/delay, n (%)	1 (1.0%)	3 (2.9%)	3 (2.6%)
Number of patients with any TEAE leading to a dose reduction, n (%)	1 (1.0%)	1 (1.0%)	1 (0.9%)
Number of patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	1 (1.0%)	1 (0.9%)
Number of patients with any TEAE resulting in death, n (%)	0	1 (1.0%)	1 (0.9%)

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; TEAE=Treatment Emergent Adverse Event
*All 200 mg (N=117) = Phase 1 200 mg patients (n=12) + Phase 2 200 mg patients (n=105)
Note: NCI grades were coded using CTCAE Version 5.0.

Potential motor dysfunction

In All 200 mg Patients, 20/117 (17.1%) patients experienced events of motor dysfunction. The most commonly reported terms (≥3 patients) were muscle spasms (9/117 [7.7%]), muscular weakness (7/117 [6.0%]) and dysphonia (4/117 [3.4%]). The majority of events were Grade 1 or 2; Grade ≥3 events were reported in 2/117 (1.7%) patients; there were no Grade 4 or 5 events. The Grade ≥3 events were Muscular weakness (2 patients, both Grade 3).

Potential sensory neuropathy

In All 200 mg Patients, 15/117 (12.8%) patients experienced events of sensory neuropathy. The most commonly reported terms (≥3 patients) were paraesthesia (7/117 [6.0%]) and peripheral sensory neuropathy (5/117 [4.3%]). The majority of events were Grade 1 or 2; Grade ≥3 events were reported in 1/117 (0.9%) patients; there were no Grade 4 or 5 events. The reported Grade ≥3 event was Paraesthesia (event occurred in a 56-year-old male on study day 17, one day after the 3rd dose [200 mg] of linvoseltamab and assessed as due to bone disease of underlying MM and not a neurotoxicity due to linvoseltamab). Of note, 10/15 (66.7%) of All 200 mg Patients with sensory neuropathy in Study 1826 had a medical history of a peripheral neuropathy, which was ongoing at study start and an additional 2/15 (13.3%) of All 200 mg Patients with sensory neuropathy in Study 1826 had a medical history of diabetes mellitus, which was ongoing at study start.

Other potential neurotoxicity event

In All 200 mg Patients, 48/117 (41.0%) patients experienced other potential neurotoxicity events. The most commonly reported terms (≥3 patients) were Headache (25/117 [21.4%%]), Insomnia (15/117 [12.8%%]), Dizziness (9/117 [7.7%]), Dysgeusia (4/117 [3.4%]), Lethargy (3/117 [2.6%]), and Anxiety (3/117 [2.6%]). The majority of events were Grade 1 or 2; Grade ≥3 events were reported in 4/117 (3.4%) patients; there were no Grade 5 events. The Grade ≥3 events were Grade 4 Spinal epidural haematoma and Hyperammonaemia encephalopathy, and Grade 3 Syncope and Headache.

- **Infections**

In All 200 mg Patients, 85/117 (72.6%) patients experienced a TEAE of infection. The most common infection by PT (≥10%) was COVID-19 (20/117 [17.1%]), Pneumonia (19/117 [16.2%]), and Upper respiratory tract infection (17/117 [14.5%]).

In Phase 2 50 mg Patients, infection was reported at a lower frequency than in All 200 mg Patients (64/104 [61.5%] vs. 85/117 [72.6%]. The most common infections by PT (>10%) were the same as those observed in All 200 mg Patients (COVID-19, Pneumonia, and Upper respiratory infection), with the addition of Urinary tract infection (14/104 [13.5%]) and Rhinovirus infection (12/104 [11.5%]).

In Phase 2 50 mg Patients, the incidence of infections appeared stable across time windows: 41.3% in 0 to <3 months, 34.0% in 3 to <6 months, 40% in 6 to <9 months, 43.6% in 9 to <12 months, and 46.7% in 12 to <15 months after initiating treatment. In contrast, in Phase 2 200 mg Patients, the incidence of infections decreased after 6 months in patients still receiving treatment: 52.4% in 0 to <3 months, 42.5% in 3 to <6 months, 31.1% in 6 to <9 months, 21.1% in 9 to <12 months, and 21.1% in 12 to <15 months after initiating treatment.

Exposure adjusted incidence rates of infections

In order to adjust for differences in exposure profiles between All 200 mg Patients and Phase 2 50 mg Patients, exposure-adjusted incidence rates (EAIRs) of infections were compared between these groups (**Table 38**).

This analysis showed that the EAIRs of all grade infections were similar between the two groups (in All 200 mg Patients: 237.92 per 100 PY vs. Phase 2 50 mg Patients: 252.39 per 100 PY). EAIRs of Grade 3 or 4 infections were also similar in All 200 mg Patients compared with the Phase 2 50 mg Patients: (in All 200 mg Patients: 77.74 per 100 PY vs. Phase 2 50 mg Patients: 76.17 per 100 PY).

However, EAIRs analysis accentuated the difference in frequency of Grade 5 infections: (in All 200 mg Patients: 11.75 per 100 PY vs. Phase 2 50 mg Patients: 6.31 per 100 PY).

By EAIRs, the most frequent infections were the same in All 200 mg Patients and Phase 2 50 mg Patients: Upper respiratory tract infections, Coronavirus infections, Lower respiratory tract and lung infections, and Urinary tract infections.

Table 38. Exposure-adjusted rate of most frequent treatment-emergent infections and infestations by high level term (≥5 patient-years in either phase 2 Cohort or All 200 mg Patients) (SAF) - Phase 2 and All 200 mg dose (Study 1826)

	Phase 2		All 200 mg* (N=117) nP/PY (nP per 100 PY)
High Level Term, n (%)	50 mg (N=104) nP/PY (nP per 100 PY)	200 mg (N=105) nP/PY (nP per 100 PY)	
Number of patients with any treatment-emergent infections and infestations [1]	64/25.4 (252.39)	75/32.5 (230.43)	85/35.7 (237.92)
Upper respiratory tract infections	19/59.8 (31.78)	25/58.2 (42.99)	31/65.9 (47.06)
Coronavirus infections	24/57.5 (41.73)	25/63.5 (39.35)	26/79.8 (32.59)
Lower respiratory tract and lung infections	16/70.2 (22.78)	16/69.7 (22.94)	20/82.2 (24.34)
Urinary tract infections	14/68.6 (20.41)	7/72.5 (9.65)	9/88.2 (10.20)
Bacterial infections NEC	7/76.6 (9.14)	6/75.7 (7.92)	8/92.7 (8.63)
Viral infections NEC	3/78.1 (3.84)	6/73.6 (8.16)	7/90.7 (7.71)
Candida infections	8/70.5 (11.35)	4/74.1 (5.40)	6/86.9 (6.91)
Escherichia infections	2/78.8 (2.54)	5/74.0 (6.76)	6/90.5 (6.63)
Influenza viral infections	5/77.0 (6.49)	6/73.4 (8.17)	6/91.0 (6.60)
Herpes viral infections	2/78.7 (2.54)	4/74.1 (5.40)	6/90.6 (6.62)
Cytomegaloviral infections	3/76.5 (3.92)	4/74.3 (5.39)	6/90.6 (6.62)
Pneumocystis infections	0/79.4 (0.00)	4/74.1 (5.40)	5/91.6 (5.46)
Rhinoviral infections	12/70.0 (17.14)	2/75.1 (2.66)	4/89.4 (4.47)
Pseudomonal infections	6/72.4 (8.29)	2/75.3 (2.66)	3/92.6 (3.24)
Streptococcal infections	7/74.7 (9.37)	1/76.4 (1.31)	2/91.9 (2.18)

[1] Based on MedDRA SOC: Infections and Infestations.
nP, number of patients with an event of interest; PY, patient-years; nP per 100 PY, number of patients with at least 1 event of interest per 100 patient-years.
*All 200 mg (N=117) = Phase 1 200 mg Patients (n=12) + Phase 2 200 mg Patients (n=105)
Note: For patients with event of interest, PY = (date of first on-treatment event of interest - 1st dose date+1)/365.25
Note: For patients without event of interest, PY=(Min (last dose date+30 days, death date, new multiple myeloma therapy date - 1, re-treatment date - 1, IPDE date -1, , cutoff date) - 1st dose date + 1)/365.25
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023.
The table is sorted by decreasing frequency in the All 200 mg dose.

Serious Infections

In All 200 mg Patients, 49/117 (41.9%) patients experienced serious infections. The most common serious infections (>3 patients) by PT were Pneumonia (15/117 [12.8%]), COVID-19 (8/117 [6.8%], COVID-19 pneumonia and *Pneumocystis jirovecii* pneumonia (each 5/117 [4.3%]). When assessing EAIRs of serious infections, the most common infections (>10.0 per PY) were Lower respiratory tract and lung infections and Coronavirus infections.

In Phase 2 50 mg Patients, the frequency of serious infections was 34.6% (36/104). The EAIRs of any serious infection were similar for Phase 2 50 mg Patients and All 200 mg Patients (72.45 per 100 PY and 74.27 per 100 PY respectively), and the most common infections by EAIR and HLTs (>10.0 per PY) were the same as in All 200 mg Patients.

Fatal Infections

In All 200 mg Patients, fatal infections comprised sepsis or septic shock (5/117 [4.3%] patients), COVID-19 pneumonia (3/117 [2.6%]), opportunistic infections (PML and PJP) (2/117 [1.7%] patients), and influenzal pneumonia (1/117 [0.9%] patient). The nature of infections in Phase 2 50 mg Patients was not different: they were COVID-19 (3/104 [2.9%] patients), septic shock (1/104 [1.0%] patient), opportunistic infection (PML) (1/104 [1.0%]).

Frequency and Severity of Opportunistic Infections

In All 200 mg Patients, 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 Polyomavirus infections (PML); 1 patient with CMV also experienced Candida infections (Oesophageal candidiasis) and Herpes viral infections (Ophthalmic herpes simplex). Overall, 7/117 (6.0%) had Grade 3 or 4 opportunistic infections and 2/117 (1.7%) patients also had a Grade 5 opportunistic infections.

The incidence of opportunistic infections was higher in All 200 mg Patients compared to Phase 2 50 mg Patients (12/117 [10.3%] vs 5/104 [4.8%]) mostly occurring during the first 3 months. Due to the incidence of PJP in Phase 2 200 mg patients, the protocol was amended. Amendment 7 added a recommendation to consider prophylaxis against PJP. As of the data cut for this analysis (08 Sep 2023), no additional cases of PJP have been reported.

The exposure-adjusted incidence analysis showed the same difference in the rate of opportunistic infections between All 200 mg Patients and Phase 2 50 mg as observed with unadjusted incidences. The exposure-adjusted rate of opportunistic infections was 13.61 per 100 PY in All 200 mg Patients and 6.54 per 100 PY in Phase 2 50 mg Patients, and the rate of Grade ≥3 opportunistic infections was 9.96 per 100 PY and 6.54 per 100 PY, respectively.

Progressive multifocal leukoencephalopathy (PML)

In Phase 2, 2 patients died due to PML. One patient was among the Phase 2 50 mg Patients; the other was among the Phase 2 200 mg patients. Time to onset was 912 and 455 days respectively. In the second case, the patient died approximately 6 weeks after the last dose of linvoseltamab.

- **Tumour lysis syndrome (TLS)**

In Phase 2 50 mg Patients, 1/104 (1.0%) patient had a Grade 3 event of TLS on study day 22, which was nonserious, not related to study drug, and resolved. The patient had disease progression before day 22 and died from disease progression on day 37.

In Phase 2 200 mg Patients, 2/105 (1.9%) patients had a Grade 3 event of TLS each. One started on study day 9, was serious (led to hospitalisation), related to study drug per investigator, and was not resolved at the time of death. The sponsor assessed the TLS as not related, because the patient had a pre-existing hyperuricaemia and treatment with rasburicase while the patient was not receiving anti-myeloma treatment. The other reported TLS occurred on study day 22, was nonserious, was assessed by the investigator as not related to study drug and was resolved. The patient had also marked disease progression on the same day as TLS was reported and urinary tract infection since day 20.

Other findings relevant to safety

- **Vital signs and Electrocardiograms**

Small variations in mean and median vital signs were seen over time, but none indicated a trend towards an overall increase or decrease. There were no clinically meaningful trends in mean or median changes from baseline during the study for ECG parameters in All 200 mg Patients, Phase 2 50 mg Patients, Phase 2 200 mg patients, and All study patients.

Adverse drug reactions in the SmPC

Adverse drug reactions (ADRs) were identified based primarily on the evaluation of TEAEs that occurred in the 117 RRMM patients who were administered the 5/25/200 mg dosing regimen of linvoseltamab monotherapy and received at least one dose of linvoseltamab (the "All 200 mg Patients"). Serious TEAEs, AESIs, and treatment-related TEAEs from other patients treated with linvoseltamab were also assessed to identify additional ADRs, if any. ADRs, proposed for inclusion in SmPC, met one or more of the following criteria:

- TEAEs that occurred in ≥10% of patients;
- Events reflecting important identified risks of linvoseltamab: CRS, ICANS, IRR, Infections;
- SAEs, AESIs, and events leading to discontinuation of linvoseltamab determined to be possibly related to linvoseltamab based on one or more of the following key considerations: plausible mechanism, frequency, important potential risks for linvoseltamab, risks for other BCMA×CD3 antibodies, investigator assessment of causality, relevant epidemiology of the TEAE in RRMM;
- Worsening of laboratory abnormalities to Grade 3 or 4 in ≥ 5% of patients.

In All 200 mg Patients, TEAEs were more frequently reported (>50%) in the SOCs of Infections and infestations (85/117 [72.6%] patients), Investigations (80/117 [68.4%] patients), Gastrointestinal disorders (71/117 [60.7%] patients), Respiratory, thoracic and mediastinal disorders (71/117 [60.7%] patients), Metabolism and nutrition disorders (70/117 [59.8%] patients), Musculoskeletal and connective tissue disorders (67/117 [57.3%] patients), General disorders and administration site conditions (66/117 [56.4%] patients), and Immune system disorders (64/117 [54.7%] patients) (**Table 39**).

Table 39. Adverse reactions in patients with relapsed or refractory multiple myeloma treated with linvoseltamab 200 mg in Study 1826

MedDRA System Organ Class	Adverse reaction	Frequency categories (All grades)	Any grade (%)	Grade 3 or 4 (%)
Infections and infestations	Pneumonia[a]	Very common	32	21
	COVID-19	Very common	17	7
	Upper respiratory tract infection[b]	Very common	30	2.6
	Urinary tract infection[c]	Very common	19	8
	Sepsis[d]	Common	8	3.4
	Cytomegalovirus infection[e]	Common	4.2	2.6
	Progressive multifocal leukoencephalopathy	Uncommon	0.9	0

MedDRA System Organ Class	Adverse reaction	Frequency categories (All grades)	Any grade (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
	Neutropenia	Very common	43	42
	Thrombocytopenia	Very common	20	15
	Anaemia	Very common	38	31
	Lymphopenia	Very common	12	11
	Febrile neutropenia	Common	7	7
Immune system disorders	Cytokine release syndrome	Very common	46	0.9
	Hypogammaglobulinemia	Very common	16	0.9
Metabolism and nutrition disorders	Decreased appetite	Very common	15	0.9
	Hyperuricaemia	Very common	10	1.7
	Hypophosphataemia	Very common	14	0.9
Psychiatric disorders	Insomnia	Very common	13	0
Nervous system disorders	Encephalopathy (excl. ICANS)[f]	Very common	16	3.4
	Musculoskeletal pain	Very common	52	3.4
	Pain[g]	Very common	22	1.7
	Motor dysfunction[h]	Very common	18	1.7
	Headache[i]	Very common	23	0.9
	ICANS[j]	Common	8	2.6
Vascular disorders	Hypertension	Very common	10	4.3
Respiratory, thoracic and mediastinal disorders	Cough	Very common	42	0
	Dyspnoea	Very common	23	0.9
	Nasal congestion	Very common	18	0
Gastrointestinal disorders	Diarrhoea	Very common	39	1.7
	Constipation	Very common	18	0
	Nausea	Very common	23	0
	Vomiting	Very common	20	0
Skin and subcutaneous tissue disorders	Rash[k]	Very common	19	2.6
General disorders and administration site conditions	Oedema[l]	Very common	21	0.9
	Pyrexia	Very common	17	0
	Fatigue[m]	Very common	36	0
	Chills	Very common	10	0
Investigations				
	Blood creatinine increased	Very common	12	0
	Weight decreased	Very common	10	0

MedDRA System Organ Class	Adverse reaction	Frequency categories (All grades)	Any grade (%)	Grade 3 or 4 (%)
	Transaminase elevation	Common	9.4	2.6
Injury, poisoning and procedural complications	Infusion related reactions[n]	Common	9	1.7

[a] Pneumonia includes atypical pneumonia, COVID-19 pneumonia, haemophilus infection, influenza, metapneumovirus infection, PJP, pneumonia, pneumonia cytomegaloviral, pneumonia fungal, pneumonia influenzal, and pneumonia viral.
[b] Upper respiratory tract infection includes acute sinusitis, bronchitis, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, rhinovirus infection, sinobronchitis, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
[c] Urinary tract infection includes cystitis, Escherichia urinary tract infection, klebsiella urinary tract infection, urinary tract infection, urinary tract infection bacterial, and urinary tract infection enterococcal, and urinary tract infection staphylococcal.
[d] Sepsis includes sepsis, septic shock, pseudomonal sepsis, streptococcal sepsis, Escherichia sepsis, and haemophilus sepsis.
[e] CMV infection includes cytomegalovirus infection reactivation, cytomegalovirus infection, and cytomegalovirus viraemia and excludes pneumonia cytomegaloviral.
[f] Encephalopathy includes agitation, amnesia, aphasia, cognitive disorder, confusional state, delirium, depressed level of consciousness, encephalopathy, memory impairment, mental status changes, mood altered, somnolence, toxic encephalopathy, and excludes ICANS.
[g] Pain includes ear pain, flank pain, groin pain, oropharyngeal pain, pain, and toothache.
[h] Motor dysfunction includes dysarthria, dysphonia, gait disturbance, muscle spasm, muscular weakness, and tremor.
[i] Headache includes headache and migraine.
[j] ICANS is based on adjudicated ICANS which were reported with the terms ICANS, depressed level of consciousness, encephalopathy, and toxic encephalopathy.
[k] Rash includes dermatitis acneiform, dermatitis contact, drug eruption, erythema, rash, rash erythematous, rash maculo-papular, rash pruritic, and stasis dermatitis.
[l] Oedema includes face oedema, lip oedema, localised oedema, oedema, and oedema peripheral.
[m] Fatigue includes fatigue, lethargy, and malaise.
[n] Infusion related reactions related to IVIG administration are not included.

2.6.8.4. Laboratory findings

Worsening postbaseline shifts from Grade ≤2 at baseline to Grade 3/4 post-baseline were commonly observed. In All 200 mg patient population, the most frequent Grade 3 or 4 abnormalities were anaemia (50/117, 42.7%), platelet count decreased (23/117, 19.7%) and neutropenia (53/117, 45.3%). Reports of these abnormalities as TEAEs were also very common. In All 200 mg Patients, 48/117 (41%) patients reported 105 events of any Grade neutropenia and 47/117 (40.2%) patients reported Grade ≥3 neutropenia: 21/117 (17.9%) with maximum Grade 3, 26/117 (22.2%) with maximum Grade 4 and none with Grade 5. In 2/117 (1.7%) patients, at least one event was serious. Febrile neutropenia was experienced in 9/117 (7.7%) patients treated with 200 mg linvoseltamab. Maximum severity was Grade 3 in 8/117 (6.8%), Grade 4 in 1/117 (0.9%) patients and Grade 5 in none.

- **Chemistry Laboratory Evaluations**

The majority of chemistry parameters had low proportions of participants that shifted from Grade ≤2 at baseline to Grade 3/4 post-baseline. In particular, chemistry parameters with ≥5% of participants with shifts from Grade ≤2 at baseline to Grade 3 or 4 post-baseline were limited to Hypophosphatemia (28/117, 23.9%). In All 200 mg Patients, 16/117 (13.7%) patients reported 26 TEAEs of any grade

hypophosphatemia (PT Hypophosphatemia) and 1/117 (0.9%) patients (840011026) reported Grade ≥3 hypophosphatemia (considered unrelated to linvoseltamab treatment by the investigator). Hypokalaemia occurred in 29/117 (24.8%) of All 200 mg Patients.

Of the liver function test categories, an increase in mean ALT and AST during the step-up dosing period, to approximately 3x the baseline value in Phase 2 50 mg Patients, and 2x the baseline value in Phase 2 200 mg Patients was observed, followed by return to baseline over the next 2 to 3 weeks.

In All 200 mg Patients, the most frequent Grade 3 or 4 abnormalities were AST increased (12/117, 10.3% patients) and ALT increased (8/117, 6.8% patients). Blood bilirubin increased was experienced in 16/117 (13.7%) including 3/117 (2.6%) with Grade 3 or 4 abnormalities.

Transaminase elevations associated with other laboratory values that met the biochemical definition of Hy's Law (ALT or AST ≥ 3x ULN and total bilirubin ≥2x ULN and ALP ≥ 2x ULN or missing) occurred in 1/117 (0.9%) participants.

In Phase 2 50 mg Patients, a higher proportion of patients had Grade 3 or 4 ALT increased laboratory abnormalities (15/104 [14.4%]) compared to All 200 mg Patients. Grade 3 or 4 AST increased (15/104 [14.4%]) and Blood bilirubin increased (3.8%) abnormalities were similar to All 200 mg Patients. There were 2 patients with Hy's Law biochemistries, and none of these were deemed due to direct linvoseltamab hepatotoxicity.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Table 40. Overview of treatment-emergent adverse events by age group – Core Treatment (SAF) – All 200 mg Patients

	All 200 mg Patients			
	Age <65 (N=44)	**Age 65-74 (N=42)**	**Age 75-84 (N=30)**	**Age ≥85 (N=1)**
Number of TEAEs	935	848	476	13
Number of NCI grade 3/4/5 TEAEs	175	158	104	3
Number of serious TEAEs	101	66	54	1
Number of serious TEAEs resulting in death	5	3	7	0
Number of serious TEAEs resulting in hospitalization or prolonged existing hospitalization	97	59	50	1
Number of life-threatening serious TEAEs	6	2	4	0
Number of serious TEAEs resulting in disability or incapacity	0	0	0	0
Number of serious TEAEs resulting in an important medical event	4	8	2	0
Number of patients with any serious TEAEs, n (%)	37 (84.1%)	29 (69.0%)	21 (70.0%)	1 (100%)
Number of patients with any serious TEAE resulting in death, n (%)	5 (11.4%)	3 (7.1%)	7 (23.3%)	0
Number of patients with any serious TEAE resulting in hospitalization or prolonged existing hospitalization, n (%)	37 (84.1%)	29 (69.0%)	21 (70.0%)	1 (100%)
Number of patients with any life-threatening serious TEAE, n (%)	4 (9.1%)	2 (4.8%)	3 (10.0%)	0
Number of patients with any serious TEAE resulting in disability or incapacity, n (%)	0	0	0	0
Number of patients with any serious TEAE resulting in an important medical event, n (%)	3 (6.8%)	6 (14.3%)	2 (6.7%)	0
Number of patients with any TEAE resulting in death, n (%)	5 (11.4%)	3 (7.1%)	7 (23.3%)	0
SMQ (narrow): Accidents and injuries, n (%)	11 (25.0%)	15 (35.7%)	3 (10.0%)	0
SMQ (narrow): Anticholinergic syndrome, n (%)	0	0	0	0
Sum of PTs: Postural hypotension, Falls, Black outs, Syncope, Dizziness, Ataxia, Fractures, n (%)	8 (18.2%)	13 (31.0%)	1 (3.3%)	0

MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, Preferred term; SAF, Safety analysis set; SMQ, Standardised MedDRA Queries; TEAE, Treatment-emergent adverse event.
Data cutoff as of 06 Jan 2024; Data extract as of 19 Feb 2024

- **Pregnancy and lactation**

There were no available data with linvoseltamab use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with linvoseltamab to assess whether linvoseltamab can cause fetal harm when administered to a pregnant woman. There are no available data regarding the presence of linvoseltamab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG has the potential to be secreted in human milk.

2.6.8.7. Immunological events

See Clinical Pharmacology section of this report.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with linvoseltamab.

2.6.8.9. Discontinuation due to adverse events

In All 200 mg Patients, 19/117 (16.2%) patients experienced TEAEs leading to study discontinuation. The most common PT ≥2 patients) that led to study drug discontinuation was COVID-19 pneumonia, Pneumocystis jirovecii pneumonia, and Pseudomonal sepsis (2/117 [1.7%] patients each). A total of 8/117 (6.8%) patients had treatment-related events that led to study drug discontinuation. In addition to the fatal cases (**Table 33**), there were Pneumocystis jirovecii pneumonia, Pseudomonal sepsis, Dilated cardiomyopathy, Immune effector cell-associated neurotoxicity syndrome, Pneumonitis (1 patient each).

In Phase 2 50 mg Patients, the incidence of TEAEs that led to study drug discontinuation was 12.5% (n=13/104).

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The safety data available for linvoseltamab stem from the ongoing Study 1826, including 282 subjects exposed to linvoseltamab monotherapy. Of these, 117 subjects were exposed to the proposed registrational dosage (termed "All 200 mg Patients" subset of the Safety Analysis Set), including patients treated with 200 mg full dose across Phase 1 (n= 12) and Phase 2 (n= 105), administered weekly for 12 doses, then biweekly (Q2W) and monthly (Q4W) after a minimum of 24 weeks of therapy for patients who achieved ≥VGPR. Supportive evidence is provided by the individual Phase 2 Cohorts, Cohort 1 50 mg full dose (n= 104) (hereafter referred as "Phase 2 50 mg Patients"), Cohort 2 200 mg full dose (n= 105) (hereafter referred to as "Phase 2 200 mg Patients"), and all Study patients treated in Study 1826, including both Phase 1 and Phase 2 (n= 282) (hereafter referred to as "All study patients").

Notably, Study 1826 is a single-arm trial, therefore there is no concurrent control group against which the safety profile could be compared, which limits a comprehensive assessment.

At the latest data cut-off date (DCO 06 Jan 2024), the median duration of follow-up for Phase 2 200 mg Patients was 14.06 months (and the median duration of follow up in All 200 mg Patients was 14.26 months.

Common adverse events, SmPC implications

In All 200 mg Patients, TEAEs were more frequently reported (>50%) in the SOCs of Infections and infestations (85/117 [72.6%] patients), Investigations (80/117 [68.4%] patients), Gastrointestinal disorders (71/117 [60.7%] patients), Respiratory, thoracic and mediastinal disorders (71/117 [60.7%] patients), Metabolism and nutrition disorders (70/117 [59.8%] patients), Musculoskeletal and connective tissue disorders (67/117 [57.3%] patients), General disorders and administration site conditions (66/117 [56.4%] patients), and Immune system disorders (64/117 [54.7%] patients). CRS was the most commonly observed individual TEAE and was reported in 54/117 (46.2%) of All 200 mg Patients. The other most common TEAEs (≥20% patients by PT) also included Anaemia (45/117 [38.5%], Cough (42/117 [35.9%]), Diarrhoea (41/117 [35.0%]), Fatigue (39/117 [33.3%]), Neutrophil count decreased (38/117 [32.5%]), Arthralgia (35/117 [29.9%]), Hypokalaemia (29/117 [24.8%]), Nausea (27/117 [23.1%]), and Headache (25/117 [21.4%]).

In All 200 mg Patients, 85/117 (72.6%) experienced Grade 3 or 4 TEAEs and 14/117 (12.0%) experienced Grade 5 TEAEs. The most common Grade 3 or 4 TEAEs (≥5%) by PT were events

reflecting decreases in hematologic parameters, as well as Pneumonia, Acute kidney injury, and COVID-19.

In All 200 mg Patients, 101/117 (86.3%) had a treatment-related TEAE, with 70/117 (59.8%) experiencing Grade ≥3 treatment related TEAE and 65/117 (55.6%) experiencing serious treatment related TEAEs. CRS as well as haematologic abnormalities were the most commonly reported treatment-related TEAEs.

There was a slightly higher rate of Grade ≥3 treatment-related TEAEs and treatment-related TEAEs leading to discontinuation in All 200 mg Patients compared to Phase 2 50 mg Patients (59.8% vs. 47.1% Grade ≥3 treatment-related TEAEs and 6.8% vs. 3.8% treatment-related TEAEs leading to discontinuation, respectively), generally driven by events in the Infections and infestations and Investigations SOCs. Treatment-related TEAEs leading to dose interruption/delay were also more frequent in All 200 mg Patients compared to Phase 2 50 mg Patients (50.4% vs. 31.7%, respectively).

The most common treatment-related SAEs (≥5% of patients) were Cytokine release syndrome (32/117 [27.4%]) followed by Pneumonia (15/117 [12.8%]), which were both anticipated risks for linvoseltamab. Three serious cases of cellulitis grade 3/4 in the 50 mg arm and one additional case in the 200 mg arm were noted. Due to the low overall incidence of serious events (4/221 [1.8%]) without life-threatening or fatal events, alternative aetiologies and the absence of dose correlation with an increase in severity or frequency of the event of cellulitis, cellulitis was not listed among ADRs for linvoseltamab.

There were 4 treatment-related TEAEs resulting in death in Phase 2: 1 in Phase 2 50 mg Patients (PML) and 3 in Phase 2 200 mg Patients (PML, Pseudomonal sepsis, and Pneumocystis jirovecii pneumonia).

When evaluating All study Patients (n= 282), no additional safety findings were identified.

At the latest data cut-off date (DCO 06 Jan 2024), no clinically relevant change in the overview of the safety profile of linvoseltamab was observed from the initial MAA submission, in terms of TEAEs, serious TEAEs, drug discontinuation, dose interruption/delay or dose reduction, consistently with expectations of a stable safety profile of All 200 mg Patients over longer follow up. No additional ADRs were identified, with the exception of *Weight decreased* which has been added to the ADR table in section 4.8 of the SmPC.

Adverse events of special interest

Cytokine Release Syndrome (CRS)

These events were mostly Grade 1 or 2, mostly occurred during the step-up period and were generally transient (median duration was reported as 16 hours at the last DCO). The CRS profile appeared to be independent of the dose (50 mg or 200 mg). There were no CRS events leading to discontinuation. Of the 54 patients who experienced CRS, 23/54 (42.6%) had recurrent CRS (23/117 [19.7%] in All 200 mg patients): all recurrent CRS events were Grade 1 (21/23 [91.3%] patients) or Grade 2 (2/23 [8.7%] patients) and there were no recurrent CRS events of Grade ≥3. Overall, 29/117 (24.8%) patients received treatment for the management of CRS after the infusion of linvoseltamab. The most common treatments were tocilizumab (22/117 [18.8%] patients) and corticosteroids (13/117 [11.1%] patients). 1/17 (5.9%) patients who received tocilizumab to treat a first episode of CRS experienced recurrence.

Overall, the observed characteristics of CRS events associated with linvoseltamab use is manageable with the warnings included in the SmPC. In Study 1826, the use of premedication was mandated according to a specific scheme provided in the protocol, which includes step-up dosing, 1st 200 mg dose and 2nd 200 mg dose. Pretreatment medications should be administered until two full doses are tolerated without CRS. Supportive measures, including the use of tocilizumab, were used for the

management of CRS in a substantial proportion of participants (29/117, 24.8%) and are also reflected in the SmPC.

Neurotoxicity (including immune effector cell associated neurotoxicity syndrome/ICANS)

ICANS was reported in 9/117 (7.7%) of All 200 mg Patients. 2.6% of patients had Grade 3 ICANS and no Grade 4 or 5 ICANS events were reported (a single Grade 4 ICANS was reported in a Phase 2 50 mg Patient). ICANS events were mostly concurrent with CRS or IRR and primarily occurred during the first day after dosing. The ICANS profile appeared to be independent of the administered dose (50 mg or 200 mg).

Similar to CRS, the ICANS events were mostly of limited duration (median duration was 2 days, range: 1-11 days), but supportive treatment including tocilizumab was used in most subjects developing ICANS. These are described in detail in the SmPC. All ICANS events were resolved as of the latest DCO (06 Jan 2024), except for 1 patient.

Assessment of events of potential encephalopathy, motor dysfunction, sensory neuropathy, and any other neurologic or psychiatric events did not reveal any other important neurotoxicity of linvoseltamab.

Regarding the events of "sensory neuropathy", this event was reported in 15/117 (12.8%) of All 200 mg Patients. The most commonly reported terms were paraesthesia (7/117 [6.0%]) and peripheral sensory neuropathy (5/117 [4.3%]). Whether a history of sensory neuropathy may represent an increased risk of a sensory neuropathy ADR, it should be noted that more than half of All Study Patients (159/282) had a history of sensory neuropathy and there is insufficient evidence that patients with past medical history of sensory neuropathy were more at risk of neuropathy recurrence with linvoseltamab treatment.

Infusion-Related Reactions (IRR)

IRR events associated with linvoseltamab were reported in 9.4% (11/117) of All 200 mg Patients. IRR events were mostly Grade 1 or 2, with 1.7% (2/117) of patients experiencing a Grade 3 event. IRR occurred mostly during the initial doses. No patient discontinued treatment due to IRR. All patients with IRR recovered and no patient discontinued due to IRR at the updated DCO (06 Jan 2024). As IRR may be clinically indistinguishable from manifestations of CRS, prescribers are advised in the SmPC to manage both events in the same way.

Infections

In All 200 mg Patients, 85/117 (72.6%) patients experienced a TEAE of infection. Most of the cases were considered as serious (43% at the last DCO) including 40/117 (36% at the last DCO) Grade 3 or 4 infections and 11/117 (9.4%) with fatal outcome because of the infectious event.

The overall rate of infections was lower in Phase 2 50 mg Patients than in All 200 mg Patients (64/104 [61.5%] vs. 85/117 [72.6%], respectively) as well as fatal infections occurred less frequently in Phase 2 50 mg Patients than in All 200 mg Patients (5/104 [4.8%] vs. 11/117 [9.4%], respectively).
The incidence of opportunistic infections was higher in All 200 mg Patients compared to Phase 2 50 mg Patients (12/117 [10.3%] vs 5/104 [4.8%]), mostly occurring during the first 3 months. The exposure-adjusted incidence rates (EAIR) analysis showed the same difference in the rate of opportunistic infections between All 200 mg Patients and Phase 2 50 mg Patients, as observed with unadjusted incidences (in All 200 mg Patients: 13.61 per 100 PY vs. Phase 2 50 mg Patients: 6.54 per 100 PY).

Incidence by 3-month windows showed a higher incidence of infections in All 200 mg Patients than in Phase 2 50 mg Patients, especially in the first 3 months of treatment. This difference eased during the following 3 months and reversed in patients who had been treated for more than 6 months.

Similarly, incidence by 3-month windows showed a higher incidence of fatal infections in All 200 mg Patients in the first 6 months of treatment (especially the first 3 months of treatment) than over subsequent time. Meanwhile, the incidence of fatal infections was stable in the Phase 2 50 mg Patients. Indeed, after 6 months, the incidence of fatal infections was sporadic and occurred at a similar incidence in both dose groups.

Improvements in lymphocytes over time were more prominent in All 200 mg Patients than in Phase 2 50 mg Patients, as a reflection of greater disease control evidenced by the better efficacy outcomes in the All 200 mg Patients compared with the Phase 2 50 mg Patients. Regarding the decrease in immunosuppression with the decrease in dosing frequency, the marked decrease in infections in All 200 mg Patients after 6 months coincided with the switch from Q2W to Q4W dosing in the great majority of patients continuing in this group. This raises the possibility that the decrease in infections may also be related to the decrease in linvoseltamab exposure at this time point. However, even after the switch to Q4W dosing, both overall exposure to linvoseltamab and C_{trough} levels were still higher in All 200 mg Patients than in Phase 2 50 mg Patients, as reflected in the exposure-adjusted incidence of infection for each dosing frequency.

Regarding COVID-19, it is recognised that its impact on clinical safety in immunocompromised RRMM patient population is difficult to assess. Attention is needed in these patients after COVID-19 infection to treat adequately and quickly the possible other infection. Recommendation to vaccinate against COVID-19 has been added to updated PI.

Due to the incidence of PJP in Phase 2 200 mg patients, the protocol was amended. Amendment 7 added a recommendation to consider prophylaxis against PJP. As of the data cut for this analysis (08 Sep 2023), no additional cases of PJP have been reported. Specific recommendations have been included in the SmPC.

Two cases of PML have been reported (one in each cohort): both cases of PML were related to study drug linvoseltamab, based on temporal association and lack of alternative aetiologies. Both cases occurred in patients with profound decreased CD4 counts at baseline. The information on PML has been included in section 4.4 of the SmPC, under the "Infection" subsection and appropriately reflected in the package leaflet.

Additional recommendations for vaccination, including use of live vaccines, have been provided in the SmPC.

The prescriber must discuss the risks of linvoseltamab therapy with the patient. Patients should be provided with the Patient Card, and instructed to carry it at all times, and show it to all of their healthcare professionals. The Patient Card describes the common signs and symptoms of CRS and ICANS and provides instructions on when a patient should seek immediate medical attention, provides monitoring instructions, and has the prescribing physician's contact details.

Occurrence of TLS was limited to one subject in Phase 2 50 mg Patients and 2 cases in Phase 2 200 mg Patients. Based on current evidence, the risk of TLS with linvoseltamab can be considered limited.

Regarding adverse events by age groups, the data provided and the small number of patients in the age subgroups do not allow any definitive conclusions.

At the time of the initial submission, 42/117 (35.9%) of the total analysis population had received ≥12 months of study treatment. Of the 61 Phase 2 200 mg Patients who had completed at least 24 weeks on-study, 59 (96.7%) achieved a BOR of VGPR or better and were eligible for transition from Q2W to

Q4W. Of these, 56 (91.8%) patients transitioned from Q2W to Q4W and received treatment for a mean (SD) of 22.89 (11.795) weeks after the transition.

After transitioning to Q4W dosing, only 18/61 (29.5%) had ≥6 months of exposure, and 4/61 (6.6%) had ≥9 months of exposure to linvoseltamab. To better understand the change in the safety profile over time, the applicant provided the incidence of AEs (any grade and Grade 3/4) in participants who switched from QW to Q2W and Q4W dosing. A decrease in incidence of TEAEs occurred in parallel with the decrease in frequency of linvoseltamab administration and as responses deepen. The data support the applicant's position that the deep and sustained disease control resulting from continued treatment with 200 mg at the studied regimen leads to improved health status, reflected by a decreasing incidence of TEAEs and grade≥3 TEAEs.

The currently available safety data does not point to any specific safety concerns associated with longer-term administration, but the very limited sample size should be taken into consideration, and robust conclusions cannot yet be made.

Deaths

The incidence of TEAEs resulting in death (at any time after last dose) was 12.0% (14/117). In 9.4% (11/117) of patients, the fatal TEAE was an infection, mostly occurred within the first 3 months of treatment. In Phase 2 50 mg Patients, a lower proportion of patients experienced a TEAE leading to death (9/104, 8.7% of patients) compared to All 200 mg (14/117, 12%); this was accounted for by a lower rate of infections leading to death (5/104, 4.8%). Therefore, an increased rate of TEAEs leading to death was observed in the All 200 mg set compared to the Phase 2 50 mg cohort. This difference was primarily driven by a higher rate of fatal TEAEs in the Infections and Infestations SOC, and almost two-thirds of all the fatal infections occurred in the first 3 months from treatment start. After the initial 6 months, a low incidence of fatal infections was observed in both cohorts. In the absence of controlled data, disentangling the contribution of dose and lack of efficacy/disease progression to the risk of early death due to infection is not feasible.

Laboratory parameters

Changes in haematological parameters are commonly observed in MM patients, and in the absence of a control group, the relative effect of linvoseltamab vs. disease-associated changes cannot be robustly assessed.

In All 200 mg Patients, 96/117 (82.1%) patients experienced at least 1 new or worsened hepatic laboratory abnormality. The most frequent Grade 3 or 4 abnormalities were AST increased (12/117 [10.3%] patients) and ALT increased (8/117 [6.8%] patients). The changes in liver parameters (ALT and AST elevation) seem to be transient, with an increase observed during the step-up dosing and mean ALT and AST levels maintained at baseline levels over the rest of the treatment period.

Three cases (1 case in All 200 mg Patients and 2 cases in Phase 2 50 mg Patients) met the criteria for Hy's Law biochemistries. None of these were deemed due to direct linvoseltamab hepatotoxicity.

At the updated DCO (06 Jan 2024) in All 200 mg Patients, 58/117 (49.6%) and 109/117 (93.2%) patients experienced at least 1 new or worsened grade 3 or 4 RBC or platelet and WBC laboratory abnormality, respectively. Relevant information related to the risk and management of neutropenia is now reflected in the proposed SmPC in section 4.4.

The percentage of patients who experienced hypogammaglobulinemia in All 200 mg Patients was 21/110 (19.1%) between 0 to <3 months, 29/75 (38.7%) between 3 to <6 months, and 25/71 (35.2%) between 6 to <9 months. Hypogammaglobulinemia was observed in All 200 mg Patients in every 3-month period out to <21 months. Relevant information related to the risk and management of hypogammaglobulinemia has been added to the SmPC in section 4.4.

In All Study Patients (n= 282), a total of 14 patients (5%, 6.03 per 100 patient-years) experienced second primary malignancy at the updated DCO (06 Jan 24). No new safety signals related to second primary malignancies associated with linvoseltamab have been identified.

Additional safety data needed in the context of a conditional MA

Considering that Study 1826 remains an ongoing study, further data from subsequent data locks is expected, including a final CSR for Study 1826 when available. Furthermore, to support eventual conversion to a full MA, adequate data from the ongoing Phase 3 study (Study 2245, LINKER-MM3) will be required.

Due to the limited follow-up, uncertainties remain on the long-term safety of linvoseltamab at the proposed dose regimen and schedule. In this regard, the applicant has committed to provide comprehensive data from the final analysis of pivotal study 1826 and from the randomised controlled Phase III study 2245 as specific obligations in the context of the proposed CMA.

2.6.10. Conclusions on the clinical safety

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- The final CSR for Study R5458-ONC-1826 (LINKER-MM1) should be provided
- The final study report from study R5458-ONC-2245 (LINKER-MM3) investigating the efficacy and safety of linvoseltamab monotherapy vs. elotuzumab plus pomalidomide and low-dose dexamethasone in adults with relapsed/refractory multiple myeloma should be provided.

2.7. Risk Management Plan

2.7.1. 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

2.7.2. Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
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				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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-tumour 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

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures
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

Safety Concern	Risk Minimisation Measures
	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 potential CRS and/or IRR for 24 hours after the end of the infusion of the first step-up dose and after the 2nd step-up dose if CRS is experienced after the first step-up dose are provided in SmPC Section 4.2. • Instructions for all patients to remain in close proximity to the treatment centre with a caregiver for the 24-hour monitoring period is provided in SmPC Section 4.2. • 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. • Patients/carers should inform their doctor or nurse immediately if they have signs of CRS as described in PIL Section 2. • Patients should be monitored for 24 hours after 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. **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:** • 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

Safety Concern	Risk Minimisation Measures
	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 for 24 hours after the end of the infusion of the first step-up dose and after the 2nd step-up dose if ICANS is experienced after the first step-up dose are provided in SmPC Section 4.2. • Instructions for all patients to remain within close proximity of the treatment centre with a caregiver for the 24-hour monitoring period is provided in SmPC Section 4.2. • 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 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. • 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. • 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. **Additional risk minimisation measures:** • Patient card
Serious Infections	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PIL Section 2

Safety Concern	Risk Minimisation Measures
	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 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 medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of MM. **Additional risk minimisation measures:** • Patient card
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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, LYNOZYFIC (linvoseltamab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is pursuing for linvoseltamab a conditional marketing authorisation (CMA) "*as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma (R/R MM) who have received at least 3 prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (anti-CD38 mAb)*".

Multiple myeloma (MM) is a chronic and incurable malignancy characterised by the proliferation of neoplastic plasma cells in the bone marrow and accounts for approximately 1-2% of all cancers. Median age at diagnosis is comprised between 65 and 74 years, with subjects aged ≤ 50 years being just 10% of the whole MM population. Patients with MM can present with signs/symptoms related to either direct infiltration of tissues by neoplastic plasma cells (e.g. anaemia, osteolytic bone lesions and hypercalcaemia) or the consequences of the deposition of monoclonal immunoglobulins (Igs) or free Ig light chains produced by MM plasma cells in organs and tissues (e.g. renal failure, peripheral neuropathy, light-chain amyloidosis).

MM is characterised by a chronic, relapsing/remitting behaviour with progressive resistance to all active compounds. Novel treatments introduced in the last 20 years have improved life expectancy for patients with MM, and the estimated 5-year survival rate now exceeds 50%. However, despite significant therapeutic advances, approximately 10% of patients die within 1 year of diagnosis, early deaths due to disease progression or treatment toxicity are still a clinically relevant issue, and approximately 40% and 62% of patients are not able to proceed to 2nd and 3rd line treatment, respectively.

3.1.2. Available therapies and unmet medical need

Several compounds are currently approved in the EU for the treatment of MM. Immunomodulators (IMiDs, e.g. lenalidomide, thalidomide and pomalidomide), proteasome inhibitors (PIs, e.g. bortezomib, carfilzomib and ixazomib) and anti-CD38 monoclonal antibodies (anti-CD38 mAbs, e.g. daratumumab, isatuximab) form the backbone of most regimens indicated for the treatment of newly diagnosed and relapsed or refractory MM (R/R MM). While the choice of the frontline treatment is usually based on eligibility to autologous stem cell transplant (ASCT), the treatment of subjects with relapsed or refractory disease is less standardised. Several agents/combinations are approved for the treatment of R/R MM and can be used sequentially with the aim of reducing cross-resistance and maximising clinical benefit, especially in terms of prolonged disease control. Several factors such as age, comorbidities, persisting toxicity from previous treatments, prior exposures, type and depth of response to previous lines of therapy, type of progression (e.g. biochemical relapse vs. clinical relapse) and treatment availability guide treatment choice in R/R MM. As a general rule, responses become shorter, and their clinical relevance reduced with increasing lines of therapy.

Real-world data showed that the outcomes of subjects with MM who are "tripe-class refractory" (TCR, i.e. who are refractory to at least one IMiD, one PI and one anti-CD38 mAb) were unsatisfactory: the real-world ORR in this setting did not exceed 30%, the median PFS was approximately 3 to 5 months, and the median OS was less than 1 year. Several products are currently authorised in the EU for the

treatment of "triple-class exposed" (TCE) patients, including selective inhibitors of nuclear export (i.e. selinexor [Nexpovio]), peptide conjugated alkylating agents (i.e. melphalan flufenamide [Pepaxti]), anti-BCMA CAR T cell advanced therapies (i.e. idecabtagene vicleucel [Abecma] and ciltacabtagene autoleucel [Carvykti]), and T cell engaging bispecific monoclonal antibodies (i.e. teclistamab and elranatamab targeting CD3 and BCMA, and talquetamab targeting CD3 and GPRC5D), yet no curative treatment is currently available. An unmet medical need for additional options for subjects in the advanced setting of relapse is acknowledged.

3.1.3. Main clinical studies

Pivotal efficacy and safety evidence supporting this CMA application comes from one, open-label, uncontrolled, first-in-human, Phase I/II study (study R5458-ONC-1826, also referred to in this report as study 1826).

3.2. Favourable effects

At the time of the most updated data cutoff date (DCO 06 Jan 2024), n=117 patients were included in the All 200 mg analysis set. The Objective response rate (ORR) by IRC in the All 200 mg set was 70.9% (95%CI 61.8, 79.0), which significantly exceeded the pre-specified threshold for efficacy (i.e. 31%).

Results from sensitivity analyses were consistent with the primary analysis: the ORR by Investigator assessment was 69.2% (95%CI 60.0, 77.4) and the ORR by IRC only based on MM laboratory data was 71.8% (95%CI 62.7, 79.7).

The following response rates could be observed: the VGPR or better rate and the CR or better rate (CRR) by IRC were 63.2% (95%CI 53.8, 72.0) and 49.6% (95%CI 40.2, 59.0), respectively. Minimal residual disease (MRD) data showed that 41.4% of patients who achieved ≥CR reached a MRD negative status by either NGS or flow cytometry.

Subgroup analyses for ORR showed that response rates were generally consistent across the majority of the pre-specified subgroups, and clinically relevant ORRs could be observed irrespectively of e.g. age, ethnicity, baseline ECOG PS score and cytogenetic risk. With respect to the proposed indication, consistent ORRs could also be observed in triple- (ORR 80%) or penta-exposed patients (71%), as well as in patients who were triple- (ORR 74%) or penta-refractory (ORR 68%).

Responses were usually induced with a median time to response (TTR) by IRC in the All 200 mg set of 0.95 months (range 0.5, 6.3) and deepened over time (median TTCR 8.49 months; range 1.6, 14.1).

With a median follow-up of approximately 14 months, the median DoR by IRC in the All 200 mg set was 29.4 months (95%CI 19.2.0, NE), yet KM estimates suggested that ~81% of responders could still be relapse/progression free after 12 months from treatment start. The median DoR by Investigator assessment was 20.9 months (95%CI 16.6, NE).

The median Progression-free survival (PFS) by IRC in the All 200 mg set was not reached (95%CI 17.3, NE), yet KM estimates indicated that ~70% of subjects were expected to be alive and progression-free 12 months after treatment initiation.

3.3. Uncertainties and limitations about favourable effects

Clinical data supporting this application comes from one single arm, open-label, uncontrolled, Phase I/II study, which limits the strength of evidence, as relevant time-to-event endpoints such as PFS and OS cannot be evaluated in this setting.

MM is characterised by high clinical and biological heterogeneity, yet the number of subjects who received linvoseltamab at the dose regimen proposed for marketing authorisation was too limited to allow for reliable evaluation of treatment effect in specific subgroups.

The current follow-up in the Phase 2 200 mg cohort is considered too limited to adequately characterise long-term clinical benefit with linvoseltamab when administered according to the dose and schedule proposed for marketing authorisation. This is of relevance since in clinical practice linvoseltamab is expected to be continued until disease progression/excessive toxicity in a malignancy characterised by a chronic behaviour. The applicant has committed to provide the final CSR for study 1826.

A 50mg and 200mg "full dose" regimens were investigated in Phase 2 yet, due to subsequent protocol amendments, major imbalances in previous treatment lines and refractoriness status could be observed across Patients in the Phase 2 50 mg cohort were more heavily pre-treated than 200 mg patient group, which complicates the interpretation of clinical efficacy results from Phase 2. Furthermore, both groups have different follow-up time, which adds more limitations on favourable effects evaluation.

Limited follow-up and exposure after transitioning to the less frequent Q4W administration schedule did not allow to thoroughly assess the impact on long-term disease control of such potentially convenient "de-intensified" regimen in optimal responders.

Confirmation of the efficacy of linvoseltamab is expected to be provided through the randomised trial R5458-ONC-2245 [LINKER-MM3].

3.4. Unfavourable effects

Treatment-emergent adverse events (TEAEs) were reported in all subjects, with at least one Grade 3 to Grade 4 event in over 80% of All 200 mg Patients. TEAEs were more frequently reported (>50%) in the SOCs of Infections and infestations, Investigations, Gastrointestinal disorders, Respiratory, thoracic and mediastinal disorders, Metabolism and nutrition disorders, Musculoskeletal and connective tissue disorders, General disorders and administration site conditions and Immune system disorders.

The most common TEAEs included CRS (45/117 [46.2%]), anaemia (45/117 [38.5%], cough (42/117 [35.9%]), diarrhoea (41/117 [35.0%]), fatigue (39/117 [33.3%]), neutrophil count decreased (38/117 [32.5%]), arthralgia (35/117 [29.9%]), hypokalaemia (29/117 [24.8%]), nausea (27/117 [23.1%]), and headache (25/117 [21.4%]).

The most common Grade 3 or 4 TEAEs (≥5%) by PT were events reflecting decreases in hematologic parameters, as well as Pneumonia, Acute kidney injury, and COVID-19.

At least 1 event of any grade CRS was reported in 54/117 (46.2%) of All 200 mg Patients. Most events occurred during the step-up stage of dosing and were Grade 1 (35%) or Grade 2 CRS (10.3%). Median time to onset was 11.04 hours, and median event duration was 14.81 hours (16 hours at the last DCO). CRS was frequently managed with supportive measures, including tocilizumab.

ICANS occurred in 9/117 (7.7%) patients; 2.6% of patients had Grade 3 ICANS and no Grade 4 or 5 ICANS events were reported. The median time to onset was 1.0 days and the median duration of adjudicated ICANS was 2.0 days.

IRR was common. IRR events associated with linvoseltamab were reported in 9.4% of All 200 mg Patients. IRR events were mostly Grade 1 or 2, with 1.7% of patients experiencing a Grade 3 event. IRR occurred mostly during the initial doses. No patient discontinued treatment due to IRR.

Cytopenic events were reported in the majority of subjects. As TEAEs, Grade ≥3 neutropenia was reported in 40.2% patients (42% at the last DCO), whereas febrile neutropenia was experienced in 7.7% of patients treated with 200 mf linvoseltamab.

At the last DCO (06 Jan 2024), serious infections occurred in 43% of patients who received linvoseltamab at the recommended dose, with Grade 3 or 4 infections in 36%. Infections that were fatal within 30 days of the last dose occurred in 4% of patients. Serious opportunistic infections occurred in 6% of patients. Two cases pf progressive multifocal leukoencephalopathy (PML) occurred in patients receiving linvoseltamab.

3.5. Uncertainties and limitations about unfavourable effects

The key uncertainty is related to the nature of the Study 1826 as a single-arm study. The total number of subjects studied to date enables a reasonable characterisation of the overall safety profile and common adverse events, but the lack of a concurrent control group in a heavily pre-treated patient population with multiple disease-associated complications severely limits the ability to robustly assess the safety profile of linvoseltamab.

The limited duration of treatment and follow-up complicates assessment of any longer-term effects for a treatment that is foreseen to continue until disease progression. The uncertainty is particularly pertinent related to effects that have a high underlying prevalence in the relevant patient population, i.e. cytopenias and infections.

Additional safety data are expected with the provision of the final CSR of study 1826 and from the randomised trial R5458-ONC-2245[LINKER-MM3].

3.6. Effects Table

Table 41. Effects Table for linvoseltamab as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received three prior lines of therapy including an Anti-CD38 Antibody, a proteasome inhibitor, and an immunomodulatory agent (Data Cut-Of: 6 January 2024)

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
ORR	Percentage of participants with a confirmed PR or better according to the 2016 IMWG Response Criteria by IRC	% (95%CI)	70.9 (61.8, 79.0)	Data from open-label, uncontrolled, Phase I/II study, with limited number of subjects (n=105) receiving linvoseltamab at the dose regimen proposed for MA. CRR (95% CI): 49.6	Study 1826 All 200 mg analysis set
DOR	Median time from first documented evidence of PR or	Months (95%CI)	31.4 (21.6, NE)		

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
	better until the earliest date of documented PD per IMWG, or death due to PD			(40.2, 59.0) Follow-up in the pivotal Phase 2 200 mg cohort is considered too limited to characterise long-term clinical benefit with linvoseltamab	
Unfavourable Effects					
CRS	Any grade	%	46.2	No control arm Grade 3 or 4: 0.9%	Study 1826
ICANS			7.7	No control arm Grade 3 or 4: 2.6%	
Infections			43	No control arm Grade 3 or 4: 36%	
Neutropenia			43	No control arm Grade 3 or 4: 42%	

Abbreviations: ORR: objective response rate; DOR: duration of response; IMWG: International Myeloma Working Group; IRC: Independent Review Committee, CCI: Confidence Interval; MA: Marketing authorisation; CRR: Complete response rate; PD: progressive disease; SC QW: subcutaneous once a week; NE: not estimable; CRS: cytokine release syndrome; ICANS: Immune effector cell-associated neurotoxicity syndrome

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy data from uncontrolled study 1826 showed that treatment with linvoseltamab resulted in high ORRs (exceeding the pre-specified 31% efficacy threshold and meeting protocol-specified criteria to reject the null hypothesis in both Phase 2 cohorts): responses were rapidly induced and a high rate of complete remissions was observed, which is of clinical relevance in a population of patients characterised by extensive exposure to anti-MM agents and widespread refractoriness.

Although the long-term efficacy and safety of linvoseltamab are not yet thoroughly characterised because of limited follow-up (linvoseltamab is intended to be administered until disease progression or excessive toxicity), short-term DoR data from the Phase 2 200 mg cohort and DoR data from the supportive 50 mg cohort hinted at the potential for durable responses, which is of value in such advanced clinical setting.

Subgroup analyses showed that response rates were generally consistent across the majority of the pre-specified subgroups, and clinically relevant ORRs could be observed irrespectively of age, cytogenetic risk, and refractoriness status.

Overall, the efficacy of linvoseltamab is considered of potential clinical relevance and in line with the results observed with other bispecific mAbs in the same clinical setting.

Based on the totality of the safety data, the key risks for linvoseltamab are CRS, neurological toxicity including ICANS, and infections, as these events have the potential to be life-threatening or fatal if not properly managed. CRS and ICANS were reversible and manageable with appropriate premedication and standard therapies. The SmPC includes management guidelines for CRS and ICANS that are largely consistent with those used in Study 1826, and this approach is endorsed.

The high underlying prevalence of infections and cytopenias in RRMM patients complicates the assessment of any contributory role of linvoseltamab for these complications. Regarding infections, the reported events were early, mainly within 3 months after starting therapy. They comprised a substantial amount of bacterial sepsis, but also infections usually associated with significant levels of immunosuppression, such as CMV reactivations, PJP, PML and other opportunistic infections, including fungal diseases. Moreover, the infection profile is confounded by the highly dynamic COVID-19 landscape during the conduct of Study 1826.

3.7.2. Balance of benefits and risks

Based on the available efficacy data, showing a high rate of deep and potentially durable responses in a heavily pretreated population, linvoseltamab might represent an additional "off-the-shelf" alternative for patients in advanced settings of relapsed and refractory MM.

The toxicity profile of linvoseltamab overall aligns with what is expected in this class of compounds, and the key uncertainty is related to small number of patients treated and the short follow-up. In this respect, the safety profile of linvoseltamab may still be evolving and updated data have been requested to cover the expected exposure in clinical practice.

The benefit/risk of linvoseltamab is considered positive to support a CMA and further post-authorisation data are required.

3.7.3. Additional considerations on the benefit-risk balance

The basis of evidence supporting this application comes from one single arm, open-label, uncontrolled, Phase I/II study. The strength of evidence supporting B/R conclusions is, therefore, limited. The reduced sample size in the pivotal All 200 mg analysis set and the limited follow-up at the DCO did not allow to thoroughly characterise the efficacy and safety profile of linvoseltamab especially in the longer term. Moreover, MM is a chronic disease and clinical benefit evaluations would ideally require the demonstration of significant improvements in clinically relevant time-to-event endpoints.

Similarly for safety, while the current data are in line with the expected mechanism of action of the product, the number of patients exposed and duration of follow-up precludes from a comprehensive characterisation of the safety profile of linvoseltamab.

Overall, the data provided are regarded as sufficient for CMA but not comprehensive due to lack of interpretable time-to-event endpoints to determine treatment benefit and the duration of follow-up.

Conditional marketing authorisation

In view of the unmet medical need and clinical results available, and since comprehensive data on the product are not available at this stage, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. The applicant is planning to provide comprehensive confirmatory data from a Phase III, open-label, randomised, controlled study (study 2245) comparing linvoseltamab monotherapy at the same dose regimen proposed for this MAA vs elotuzumab plus pomalidomide and low-dose dexamethasone (EPd).

  The clinical trial application for study 2245 has been approved on September 2023, and enrolment is ongoing (FPFV September 2023).

  To further characterise the long-term clinical benefit with linvoseltamab when administered according to the dose and administration regimen proposed for marketing authorisation, the applicant has also committed to submit the final CSR for study 1826 (Q1 2027).
- Unmet medical need will be addressed. MM is currently incurable and its clinical course is characterised by a remitting/relapsing behaviour with progressive acquired resistance to all available classes of active compounds. In later lines of relapse, as targeted by the claimed indication for linvoseltamab, treatment options are limited because of widespread multi-class refractoriness (e.g. to one or more PIs, IMiDs and anti-CD38 mAbs).

  With all the intrinsic limitations in the provided unadjusted indirect comparisons, the efficacy potential of linvoseltamab as observed in study 1826 is considered to exceed that of selinexor (Nexpovio), as shown in the very late RR MM population (100% penta-refractory) enrolled in the registrational Phase 2 STORM and that of melphalan flufenamide (Pepaxti), as shown in triple-class refractory patients who had received at least 3 prior lines of therapies and who had no ASCT or progressed more than 36 months after an ASCT in the HORIZON study. Other options within the therapeutic indication claimed by linvoseltamab are the TCE bispecific mAbs talquetamab, teclistamab and elranatamab, all currently conditionally approved. Based on the provided simplistic indirect comparisons, the efficacy of linvoseltamab in the target population appears to be at least in line with the other bispecific mAbs and thus, address the unmet medical need of patients in advanced settings of RR MM at least to the same extent as those products.

  Idecabtagene vicleucel (ide-cel, Abecma) and ciltacabtagene autoleucel (cilta-cel, Carvykti) are anti-BCMA CARTs that were initially granted CMA for the treatment of adult patients with RR MM who have received at least three prior therapies. Recently, comprehensive data from Phase III studies in earlier lines of R/R MM were provided, demonstrating a statistically significant and clinically relevant improvement in PFS. However, it is acknowledged that linvoseltamab would represent an "off-the-shelf" option that is immediately available to the patients, whereas CARTs are autologous advanced medicinal products that need complex manufacturing procedures with an intrinsic risk of significant delay or failure. Further, the controlled distribution of CARTs implies that their administration is often limited to highly specialised centres and to patients who are sufficiently "fit" to withstand the manufacturing "turn-around" times, which might not always be acceptable in the case of rapidly progressing MM. Based on these considerations, linvoseltamab is still considered a suitable option to fulfil an unmet medical need for those patients who are not sufficiently fit for CARTs and/or require immediate treatment.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. MM is the second most common haematologic malignancy and, based on the known epidemiology, a significant number of patients is expected to be ineligible to anti-BCMA CARTs, which represent the current efficacy "gold-standard". Based on the available data, the efficacy and safety of linvoseltamab are at least in line with those of other

bispecific mAbs that are currently conditionally approved in the EU and can represent an additional off-the-shelf alternative in a population with limited treatment options. A significant number of patients may, therefore, potentially benefit from treatment with linvoseltamab over the period between CMA and full approval, and immediate availability is considered of public health interest.

3.8. Conclusions

The overall benefit/risk balance of LYNOZYFIC is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that LYNOZYFIC is not similar to Talvey, Carvykti, Abecma, Farydak, Blenrep, Ninlaro and Kyprolis within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of LYNOZYFIC is favourable in the following indication(s):

as 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 monoclonal antibody, and have demonstrated disease progression on the last therapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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 cytokine release syndrome (CRS) and immune-effector cell-associated neurotoxicity syndrome (ICANS). The patient card also includes a warning message for healthcare professionals treating the patient that the patient is receiving LYNOZYFIC, which may cause CRS or 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 that 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to further characterize the duration of response and long-term safety in subjects with multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, the MAH shall submit the final study report of R5458-ONC-1826, a phase 1/2, open-label, first-in-human study of linvoseltamab monotherapy in participants with RRMM.	January 2027
In order to confirm the efficacy and safety of linvoseltamab 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	June 2027

Description	Due date
proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy; the MAH shall submit the results of study R5458-ONC-2245, an open-label phase 3 randomized active controlled study designed to evaluate the efficacy and safety of linvoseltamab monotherapy versus elotuzumab, pomalidomide and dexamethasone (EPd) in participants with RRMM who have received 1 to 4 prior lines of therapy including a proteasome inhibitor and lenalidomide.	

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that linvoseltamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.