CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761400Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Original BLA, 351(a)
Application Number(s)	761400
Priority or Standard	Re-submission- class 2
Submit Date(s)	January 10, 2025
Received Date(s)	January 10, 2025
PDUFA Goal Date	July 10, 2025
Division/Office	Division of Hematologic Malignancies II / Office of Oncologic Diseases
Review Completion Date	July 1, 2025
Established/Proper Name	Linvoseltamab-gcpt
(Proposed) Trade Name	Lynozyfic
Pharmacologic Class	Human IgG4-based bispecific antibody that binds to CD3, a T-cell antigen associated with the T-cell receptor complex, and B cell maturation antigen (BCMA)
Code name	REGN5458
Applicant	Regeneron Pharmaceuticals, Inc.
Dosage form	• 5 mg/2.5 mL (2 mg/mL) single-dose vial • 200 mg/10 mL (20 mg/mL) single-dose vial
Applicant proposed Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population	Relapsed or refractory multiple myeloma (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population	Relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy, including a proteasome

	inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Recommended Dosing Regimen	(b) (4)

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMAMES=Division of Mitigation Assessment and Medication Error Surveillance
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management

Glossary

AE	adverse event
AR	adverse reaction
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
DHOT	Division of Hematology Oncology Toxicology
ETASU	elements to assure safe use
FDA	Food and Drug Administration
IND	Investigational New Drug
OPQ	Office of Pharmaceutical Quality
PI	prescribing information
PMR	postmarketing requirement
PPI	patient package insert (also known as Patient Information)
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Product: Linvoseltamab

Pharmacological Class: Linvoseltamab is a bispecific B-cell maturation antigen (BCMA)-directed and CD3-directed T-cell engager.

Proposed Indication: Linvoseltamab is a bispecific BCMA-directed and CD3-directed antibody indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) (b) (4)

Dosing Regimen: The recommended dosage of linvoseltamab is step-up doses (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of linvoseltamab under BLA 761400 for "the treatment of adult patients with RRMM who have received at least four prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody."

The review team determined that the benefit-risk was favorable for the recommended indication during the review of the initial BLA submission (refer to Assessment Aid, August 20, 2024). However, the FDA identified significant manufacturing issues precluding approval and a Complete Response was issued on August 20, 2024. The Applicant resubmitted the BLA on January 10, 2025. The Office of Product Quality (OPQ) determined that the manufacturing facilities issues have been resolved (Refer to OPQ memo dated June 11, 2025, for additional details).

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence. Substantial evidence of effectiveness for linvoseltamab was established in Study R5458-ONC-1826 (Study 1826), a phase 1/2 single-arm trial of linvoseltamab monotherapy in patients with RRMM. Phase 1 was the dose escalation portion and phase 2 included two cohorts to evaluate the safety and efficacy of two full dose levels: 50mg and 200mg. The trial included 105 patients treated in the Phase 2 portion of the study at the proposed registrational dose (200 mg) and had previously received 3 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb; 80 of these patients had received 4 or more prior lines of therapy and made up the primary efficacy population.

In the efficacy population (n=80), the median age was 71 years (range 37-83). Sixty-four percent of patients were male and 36% were female. The majority (69%) of patients were White, 14% were Black or African American, 13% were Asian, and 5.1% were of other races or had race not reported. Only 2.5% of patients were of Hispanic or Latino ethnicity. Patients had received a median of 5 prior lines (range 4, 13); 79% were triple-class refractory and 83% were refractory to their last line of therapy.

Efficacy was established based on an intermediate clinical endpoint of overall response rate (ORR), supported by duration of response (DOR). The ORR in the efficacy population was 70.0% (95% CI: 58.7%, 79.7%). With a median duration of follow-up of 11.3 months, the median DOR was not reached (NR). The estimated DOR rate was 92.6% (95% CI: 81.6, 97.2) at 6 months, 88.8% (95% CI: 76.7, 94.8) at 9 months, and 72.4% (95% CI: 54.1, 84.4) at 12 months.

The Applicant's proposed indication was for the treatment of adult patients with RRMM (b) (4) For purposes of accelerated approval, the therapy must demonstrate an advantage in the context of available therapies.

In Study 1826, only 21% of patients who received the proposed dose received 3 prior lines of therapy. Further, there are multiple two- and three-drug regimens approved for

patients with RRMM who have received 3 prior therapies, as well as for patients who have received 3 prior lines of therapy. Response rates with linvoseltamab are consistent with several regimens with regular approval for these populations including elotuzumab, lenalidomide, and dexamethasone (approved for 1-3 prior lines; ORR 79%) and daratumumab, carfilzomib, and dexamethasone (approved for 1-3 prior lines; ORR 84%), among others.

When considering currently available therapies for patients who received 4 or more prior lines of therapies, while several therapies and combinations of therapies are approved, only selinexor has regular approval for the treatment of adult patients with RRMM who have received 4 prior therapies and are refractory to 2 PIs, 2 IMiDs, and one CD38 monoclonal antibody, a more refractory patient population. The ORR for selinexor in this refractory patient population was 25.3% (95% CI 16.4, 36.0) and the DOR was 3.8 months (95% CI: 2.3, not estimable). Three bispecific antibodies (teclistamab, talquetamab, and elranatamab) have accelerated approved for the RRMM population with 4 prior lines of therapy, including a PI, IMiD, and anti-CD38 mAb. The two approved CAR T-cell products (idecabtagene vicleucel and ciltacabtagene autoleucel) have regular approval, however, these products have unique patient-specific manufacturing requirements which may preclude many patients with RRMM from receiving these therapies are generally not considered available therapies for this determination.

In the context of available therapies for a population of patients with RRMM who have received 4 or more prior lines of therapy, a meaningful advantage is demonstrated by the ORR, supported by durability of response, with linvoseltamab.

The 50 mg cohort from Phase 2 of Study 1826 provides confirmatory evidence in support of the new indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Multiple myeloma (MM) is a plasma cell malignancy that accounts for approximately 1% of all cancers and approximately 10% of hematologic malignancies (1). In the United States, approximately 32,000 new cases are diagnosed, and 13,000 patients die of multiple myeloma each year (1). Patients are diagnosed at a median age of 65 years (1). Despite the availability of multiple treatments, MM remains an incurable disease. Patients who have received multiple lines of therapy and treated with the major class of drugs, including a PI, IMiD and an anti-CD38 mAb, have poor outcomes.

Linvoseltamab is a BCMA-directed CD3 T-cell engaging bispecific monoclonal antibody. The data provided in support of the proposed indication are from Study 1826, a phase 1/2 single-arm, multicenter, multicohort trial evaluating linvoseltamab monotherapy in patients with relapsed or refractory MM (RRMM). The efficacy population included 80 patients who received 4 or more prior lines of therapy and were treated at the proposed dosing regimen. Patients had received a median of 5 prior lines of therapy (range 4-13). The ORR in the efficacy population was 70% (95% CI: 58.7, 79.7). At the time of the data cutoff of September 08, 2023, with median follow-up of 11.3 months in responders, the median duration of response (DOR) was not reached (95% CI: 12.2, NE). The estimated DOR rate was 92.6% at 6 months (95% CI: 81.6, 97.2), 88.8% at 9 months (95% CI: 76.7, 94.8), and 72.4% at 12 months (95% CI: 54.1, 84.4).

The primary safety population included patients treated at the proposed dosing regimens in phases 1 and 2 of study (n=117). The median duration of exposure to core treatment was 10.9 months (range 0.3-34.6 months). The most common adverse reactions (≥20%) were musculoskeletal pain, cytokine release syndrome (CRS), cough, diarrhea, upper respiratory tract infection, fatigue, pneumonia, nausea, and headache. The most common Grade 3 or 4 laboratory abnormalities (≥30%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, and decreased white blood cells. Serious adverse events (SAEs) occurred in 74% of patients. AEs leading to dose interruption occurred in 71% of patients, most commonly neutrophil decrease, and infections. AEs leading to treatment discontinuation occurred in 16%, most commonly infections.

The key safety concerns for linvoseltamab are CRS and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and neurologic toxicity were common occurrences in study population, occurring in 46% and 54% of patients, respectively. The first occurrence of CRS occurred after a step-up dose (SUD) in the majority of patients (42% of patients had a first occurrence of CRS after a SUD: 38% of patients after the initial 5 mg dose and 3.4% after the intermediate 25 mg dose). Neurologic toxicity included headache in 22% of patients, encephalopathy in 17%, insomnia in 12%,

and sensory neuropathy in 11%. A risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) to mitigate the risk of CRS and neurologic toxicity, including ICANS, along with a boxed warning for CRS and neurologic toxicity, including ICANS, is warranted to support the favorable benefit-risk of linvoseltamab. Other safety concerns include infections, neutropenia, and hepatotoxicity, along with CRS and neurologic toxicity, including ICANS, should be included in the Warnings and Precautions of the draft U.S. Prescribing Information (USPI). Review of safety data with longer follow-up at the time of resubmission demonstrated a safety profile consistent with that seen with the original data cutoff.

The proposed confirmatory trial is Study R5458-ONC-2245 (LINKER-MM3), "An Open- Label, Randomized, Phase 3 Study of Linvoseltamab (REGN5458; Anti-BCMA X Anti-CD3 Bispecific Antibody) Versus the Combination of Elotuzumab, Pomalidomide, and Dexamethasone (EPd), in Patients with Relapsed/Refractory Multiple Myeloma." The primary endpoint of Study 2245 is PFS in the CD38-exposed participants. The study was fully enrolled for the primary population (b) (4) as of April 1, 2025, with current ongoing enrollment (b) (4) The Applicant provided an update regarding status of the study. The readout of the primary PFS endpoint is planned to occur in Q2 2026. The Division considers the timelines and projections for study completion to be reasonable.

The Office of Product Quality determined that the manufacturing issues identified during the original BLA submission have since been resolved.

In patients with RRMM who have received 4 or more prior lines of therapy, linvoseltamab has a favorable benefit-risk balance, in the context of the REMS for the risks of CRS and neurologic toxicity, including ICANS, and is noted to demonstrate an advantage in the context of available therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MM is the second most common hematological malignancy. • Therapy for patients with RRMM has improved considerably over the years with approval of multiple new therapies with improvement in response rate and progression-free survival (PFS). • However, relapses are common, and MM remains incurable, with a 5-year survival rate of 57.9%.	• RRMM is a serious and life-threatening condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Multiple drugs approved for use in MM and numerous combination regimens are considered standard of care. • Potential treatments include alkylating agents, corticosteroids, PIs, IMiDs, mAbs, CAR T-cell therapies, and BCMA-directed or GPRC5D-directed bispecific antibodies. Of note, all approved bispecific antibodies are under Accelerated Approval • Patients who have received multiple lines of therapy including a PI, IMiD and an anti-CD38 monoclonal antibody have limited available effective treatment options and have poor outcomes.	• Despite the availability of multiple therapies, RRMM remains an incurable disease.
Benefit	• Assessment of substantial evidence of effectiveness was based on results from Study 1826, a single-arm trial of linvoseltamab monotherapy in patients with RRMM. • The primary efficacy population included 80 patients treated at the proposed dosing regimen in phase 2 who had received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. • The ORR in the efficacy population was 70% (95% CI: 59.2, 78.9). • With median follow-up of 11.3 months (95% CI: 10.2, 12.5) among responders, the median duration of response was not reached (95% CI: 12.2, NE). • The estimated DOR rate was 92.6% at 6 months (95% CI: 81.6, 97.2), 88.8% at 9 months (95% CI: 76.7, 94.8), and 72.4% at 12 months (95% CI: 54.1, 84.4).	• The ORR, supported by durability of response, demonstrated based on the results of the single-arm trial show evidence for effectiveness in this patient population. • Based on available data, linvoseltamab demonstrates an advantage in the context of available therapies for RRMM

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety was evaluated in 117 patients treated at the proposed dosing regimen (5 mg initial dose, 25 mg intermediate dose, 200 mg full dose) in phases 1 and 2. • Median duration of exposure was 10.9 months. • Fatal treatment-emergent adverse events (TEAEs) occurred in 12% of patients and SAEs occurred in 74% of patients. • The most common adverse reactions (≥20%) were musculoskeletal pain, CRS, cough, diarrhea, upper respiratory tract infection, fatigue, pneumonia, nausea, and headache. • Key safety concerns are CRS and neurologic toxicity, including ICANS. CRS occurred in 46% of patients, neurologic toxicity in 54%, and ICANS in 8%. • Other safety concerns include infections, neutropenia, and hepatotoxicity. • The assessment of safety with longer follow up (median of 53 weeks with resubmission vs. median of 47 weeks at original submission) demonstrated a consistent safety profile and no new safety signals.	• The safety profile of linvoseltamab in the indicated patient population is acceptable and is based on adequate duration of exposure. • With longer follow up (data submitted with current BLA submission), the safety assessment was generally consistent with that based on the original data cutoff and no new safety signals were identified. • Risk mitigation measures for the key safety concerns of CRS and neurologic toxicity, including ICANS, are: o Boxed warning in USPI to alert prescribers regarding the risks of CRS and neurologic toxicity, including ICANS. o Guidance in USPI to hospitalize patients for 24 hours after the initial dose and 24 hours after the intermediate dose. o Risk evaluation and mitigation

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		strategy (REMS) with elements to assure safe use (ETASU) A and B, to ensure that the healthcare providers are aware of the risks and the recommended risk mitigations measures to ensure the safe use of linvoseltamab in the post-market setting. • Warnings and Precautions (W&P) for the risk of hepatotoxicity was added. • The Division agrees with the Applicant's proposed W&P for the risks of infection, neutropenia, and CRS.

2 Therapeutic Context

Refer to Assessment Aid from original BLA submission (dated 8/20/2024) for an analysis of the condition (RRMM) and current treatment options.

3 Regulatory Background

Refer to Assessment Aid from original BLA submission (August 20, 2024) for a summary of regulatory interactions under IND 138791 and BLA 761400 that occurred through June 24, 2024. BLA 761400 was originally submitted on December 22, 2023. During the review cycle, manufacturing facility deficiencies were identified, which precluded approval. The Applicant resubmitted the BLA on January 10, 2025, as a complete response.

4 Nonclinical Pharmacology/Toxicology

Refer to Assessment Aid from original BLA submission (August 20, 2024).

5 Clinical Pharmacology

Refer to Assessment Aid from original BLA submission (August 20, 2024). The Applicant proposed minor changes to the dosing schedule. These are outlined in Section 6.4.

6 Statistical and Clinical and Evaluation

6.1. Review of Efficacy

Refer to Assessment Aid from original BLA submission (8/20/2024) for a detailed description of the clinical trial and endpoints of Study R-5458-ONC-1826, a phase 1/2 open-label study of the safety, tolerability, and anti-tumor activity of linvoseltamab in patients with RRMM who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 monoclonal antibody.

While the Applicant identified the pooled Phase 1 (n=12) and Phase 2 (n=105) populations who received the 200mg dose (n=117) who received at least 3 prior lines of therapy including a PI, IMiD, and a CD38 monoclonal antibody as the primary efficacy and safety population, the FDA's analysis of efficacy was based on the population from Phase 2 only (i.e., patients who received at least 4 lines of therapy, including a PI, IMiD, and an anti-CD38 antibody; n=80).

The FDA's primary evaluation of efficacy was based on the original data cutoff of September 8, 2023. Refer to the original Assessment Aid (Section 8.1) for results based on the original data cutoff, the assessment of efficacy in the context of available therapies, and description of statistical issues. Based on the totality of data, linvoseltamab demonstrated evidence of effectiveness in patients with RRMM who have received at least 4 lines of prior therapy.

With the resubmission, the Applicant provided updated efficacy data with a median duration of follow-up of 21.7 months (July 23, 2024, data cutoff). The FDA requested the updated datasets. The median DOR was 21.0 months (95% CI: 19.0, NE). The estimated DOR rate was 92.7% (95% CI: 81.8, 97.2) at 6 months, 90.9% (95% CI: 79.4, 96.1) at 9 months, and 79.4% (95% CI: 65.9, 88.1) at 12 months. Assessment of durability data with longer follow up demonstrates results consistent with the primary analysis.

As of April 1, 2025, the confirmatory trial is fully enrolled and the PFS primary endpoint readout is projected in Q2 2026; the Division considers the projection provided by the Applicant to be reasonable.

6.2. Review of Safety

The assessment of safety is based on patients in Study 1826 who received the 200 mg full dose in Phase 1 (n=12) and Phase 2 (n=105), for a total of 117 patients. Refer to the original FDA Assessment Aid for comments regarding acceptability of the safety database, safety results based on the original data cutoff, and analysis of adverse events of special interest (AESIs).

FDA conducted analysis of safety data based on the updated data cutoff, along with comparisons to data based on the original data cutoff.

Table 1 summarizes the exposure duration with the original and updated data cutoffs. The median duration of exposure was 5 weeks longer with the updated data cutoff.

Table 1: Summary of Exposure Duration

All 200 mg Patients (n=117)	Original Data Cutoff	Updated Data Cutoff
Data cutoff date	Sep 8, 2023	Jul 23, 2024
Median (range) exposure duration	47.4 (1 to 151) weeks	53.0 (1 to 194) weeks

Source: Applicant's BLA Resubmission Safety Update Report dated 10 Oct 2024.

As shown in Table 2 below, with additional follow up, the rates of AEs and dose modifications are generally consistent with the rates seen based on the original data cutoff. The rates of AEs with the updated cutoff were generally similar for most AEs. Minor differences in rates (>or =5%) was observed for URI, diarrhea, cough, and dyspnea with longer follow-up.

Table 2: Summary of Adverse Events

All 200 mg Patients (n=117) N%	Original Data Cutoff	Updated Data Cutoff
Any Grade TEAEs	117 (100)	117 (100)
Grade 3-4 TEAEs	96 (82)	102 (85)
Grade 5 TEAEs	19 (16)	20 (17)
Serious TEAEs	86 (74)	91 (78)
AE leading to dose Reduction	16 (14)	21 (18)
AE leading to dose interruption	83 (71)	90 (77)
AE leading to discontinuation	19 (16)	24 (20)

Source: FDA analysis; ADAE dataset

Table 3 summarizes the categories of deaths that occurred overall and within 30 days of the last dose at each data cutoff. At the updated data cutoff, 12 additional patients died on study, the majority of which were due to progressive disease, and there was no substantial increase in fatal TEAE rates with longer follow up.

Table 3: Summary of Deaths

All 200 mg Patients (n=117) N%	Original Data Cutoff	Updated Data Cutoff
Total Deaths	31 (26)	43 (37)
Category Adverse Event Progressive Disease Other	 19 (16) 12 (10) 0	 20 (17) 21 (18) 2 (1.7)
Death within 30 days of Last Dose	9 (8)	10 (9)[1]
Category Adverse Event Progressive Disease	 9 (8) 0	 10 (9) 0

Source: FDA Analysis; ADSL dataset and Study 1826 Narratives
[1] Includes 1 death that occurred after start of new anti-MM therapy.

As shown in Table 4 below, a minor increase in the incidence of SAEs was noted based on the updated data cutoff, primarily due to infections (pneumonia). The additional SAEs were primarily related to infection as noted in Table 4 below. No additional SAEs of CRS or IRRs were noted with the longer follow up.

Table 4: Treatment Emergent Serious Adverse Events in ≥4%

All 200 mg Patients (n=117) N%	Original Data Cutoff	Updated Data Cutoff
Any SAE	86 (74)	91 (77)
Immune System Disorders		
Cytokine Release Syndrome	32 (27)	32 (27)
Infusion Related Reaction	5 (4.3)	5 (4.3)
Infections and Infestations		
Pneumonia	28 (24)	37 (32)
Sepsis	12 (10)	16 (14)
COVID-19 Infection	8 (7)	9 (8)
Upper Respiratory Tract Infection	6 (5)	7 (6)
Urinary Tract Infection	5 (4.3)	8 (7)
Nervous System Disorders		
Encephalopathy	9 (8)	9 (8)
Renal and Urinary Disorders		

Acute Kidney Injury	6 (5)	6 (5)
Blood and lymphatic system disorders		
Febrile Neutropenia	5 (4.3)	6 (5)

Source: FDA Reviewer; ADAE dataset

The rates of neurologic toxicity, based on the nervous system and psychiatric disorders SOCs, was slightly higher based on the updated data cutoff (60% vs. 54%), with the most common types of neurologic toxicity being headache, encephalopathy, and sensory neuropathy. Rates of ICANS based on the updated data cutoff were the same as those seen with the original data cutoff (8%). Rates of ICANS and IRR/CRS are not expected to increase with longer follow up as these events generally occur during the priming and initial target dosing period.

As shown in Table 5 below, the rates of the most common TEAEs were similar across data cutoffs, with minor increases in rates of all grade dyspnea, pneumonia, and diarrhea, at the updated data cutoff. Differences in grouping methodology may have contributed to the slightly lower rate of upper respiratory tract infections seen at the updated data cutoff.

Table 5: Treatment Emergent Adverse Events (≥ 20%)

All 200 mg Patients (n=117) N%	**Original Data Cutoff**		**Updated Data Cutoff**	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	53	3.4	53	3.4
Immune system disorders				
Cytokine release syndrome	46	0.9	46	0.9
Respiratory, thoracic, and mediastinal disorders				
Cough	39	0	44	0
Dyspnea	21	0.9	26	1
Infections and infestations				
Upper respiratory tract infection	35	6	44	5
Pneumonia	28	21	31	25
Gastrointestinal disorders				
Diarrhea	35	1.7	42	2
Nausea	23	0	24	0
General disorders and administration site conditions				
Fatigue	34	0	36	0
Nervous system disorders				

All 200 mg Patients (n=117) N%	Original Data Cutoff		Updated Data Cutoff	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Headache	22	0.9	26	0.9

Source: FDA analysis; ADAE dataset

6.2.1. Integrated Assessment of Safety

With the BLA resubmission, the Applicant provided the updated safety data based on longer duration of exposure (a median of 6 weeks of additional exposure). Minor increases in the rates of TEAEs, treatment modifications, and infections were observed, which are not unexpected with longer treatment exposure. Given that these differences were generally minor and given that no new safety signals were identified, the safety data in the initial submission with a data cutoff date of Sept 8, 2023, will be included in the USPI.

The important risks of linvoseltamab are well-characterized and these risks are similar to those of approved BCMA-targeted therapies in MM populations: CRS, IRR, ICANS, infections (including opportunistic infections), and neutropenia. Refer to the original Assessment Aid for a summary of these AESIs seen with linvoseltamab.

Overall, the safety data is consistent with that of other BCMA-directed bispecific antibodies and is acceptable for the indicated patient population in the context of the REMS for the risks of CRS and neurologic toxicity, including ICANS.

6.3. Conclusions and Recommendations

Based on IRC-assessed ORR and supported by durability of response from Study 1826, linvoseltamab has demonstrated substantial evidence of effectiveness in patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. The available data indicate that linvoseltamab demonstrates a clinically meaningful advantage in the context of available therapies for the patient population.

The safety profile of linvoseltamab includes toxicities that are consistent with those seen with other bispecific antibodies, currently under accelerated approval, for the treatment of RRMM. These include CRS, neurologic toxicity including ICANS, infections, neutropenia, and hepatotoxicity. Updated safety data provided with the BLA resubmission in January 2025 did not demonstrate any substantial change in the overall safety profile of the drug, with no new safety signals identified. In the context of the (b) (4) indicated patient population and with a REMS program for the risks of CRS and neurologic toxicity, including ICANS, the risks are acceptable, and the overall benefit/risk is favorable.

The confirmatory trial has been fully enrolled, as of April 1, 2025, and the PFS primary

endpoint is projected to read out in Q2 2026; the Division considers this projection to be reasonable. Manufacturing issues that were identified at the manufacturing facility during the original review cycle have been resolved.

Based on the observed benefit of linvoseltamab, combined with the REMS and elements to assure safe use (ETASU) to mitigate the risks of CRS and neurological toxicity, including ICANS, the FDA's clinical and statistical teams recommend accelerated approval of linvoseltamab for the following indication: "for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody."

Labeling Recommendations

6.4. Prescription Drug Labeling

The table below provides high-level changes to the USPI; see the approval letter for final approved labeling.

Section	Applicant's Proposed Labeling	FDA's Revised Labeling
Boxed Warning	Included CRS, ICANS, and REMS information	FDA modified the BW to include CRS, neurologic toxicity, including ICANS, and the REMS information.
1 Indications and Usage	Treatment of adult patients with multiple myeloma who are either relapsed or refractory and received at least 4 prior lines of therapy (b) (4) including a PI, an IMID, and an anti-CD38 mAB	FDA did not agre (b) (4) FDA revised the indication to include adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy including a PI, an IMID, and an anti-CD38 monoclonal antibody.
2 Dosage and Administration	Included: Important Administration instructions (2.1); recommended dosage (2.2); recommended pretreatment medications (2.3); restarting after a dosage delay (2.4); management of adverse reactions (2.5); preparation and administration instructions (2.6).	FDA agreed with the proposed subsections with modifications, including: Adding a bullet to remind prescribers to administer LYOZYFIC according to the step-up schedule to reduce the incidence and severity of CRS (2.1); Adding a bullet to require hospitalization for the 24 hours after the first step-up dose and for 24 hours after the second step-up dose (2.1); Adding minimum dosing

		intervals for every 2 week and every 4-week dosing (2.2); Adding management recommendations for decreased hemoglobin to Table 5.
5 Warnings and Precautions (W&P)	Included W&P for: CRS, neurologic toxicity, including ICANS, the LYNOZYFIC REMS, infections, neutropenia, hepatotoxicity, and embryo-fetal toxicity.	FDA generally agreed but modified to remove any statements of negative data (b) (4) (b) (4)
6 Adverse Reactions	Included safety details from LINKER-MM1	FDA generally agreed with the data but modified some adverse reaction grouped terms and changed (b) (4) to "adverse reaction" to align with 21 CFR 201.57(c)(7).
12 Clinical Pharmacology	Included subsection 12.1 Mechanism of Action; (b) (4) Included pharmacokinetic details in 12.3 Pharmacokinetics;	FDA agreed with proposed text for mechanism of action in subsection 12.1. FDA modified subsection 12.2 to remove (b) (4) and instead included a statement to describe the dose-response association with independently assessed efficacy. Additionally, FDA removed (b) (4) FDA retained the statement noting that linvoseltamab-gcpt E-R relationships have not been fully characterized. In subsection 12.3, FDA added PK data related to ethnicity.

	Included immunogenicity data in subsection 12.6 Immunogenicity	FDA agreed with the data presented in subsection 12.6 Immunogenicity.
14 Clinical Studies	Included study design and results from LINKER-MM1	FDA did not agree (b) (4) [redacted] FDA limited the efficacy results to the indicated population (i.e., those who had received the 200 mg dosage and had been treated with at least 4 prior lines of therapy) to align 21 CFR 201.57(c)(15) which states that "…this section will describe the studies that support effectiveness for the labeled indication(s)…". This approach aligns with other recent bi-specific labels in relapsed/refractory multiple myeloma.

Other Prescription Drug Labeling

The Medication Guide was modified to align with changes made to the USPI. See the separate review in DARRTS by the Patient Labeling Team from the Division of Medical Policy Programs (DMPP).

7 Risk Evaluation and Mitigation Strategies (REMS)

A REMS will be issued to ensure the risks of linvoseltamab can be adequately managed in the post- market setting.

The specific goal of the Lynozyfic REMS is to mitigate the risk of cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), by ensuring prescribers are aware of the importance of monitoring for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to Lynozyfic.

Elements of the REMS for linvoseltamab will include a Communication Plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU include ETASU A (certification of prescribers) and ETASU B (certification of pharmacies and healthcare settings that dispense linvoseltamab). Under ETASU A, prescribers must obtain certification by enrolling and completing training regarding the risks of CRS and neurologic toxicity, including ICANS, must counsel patients on the risks, and provide them with a Patient Wallet Card. Under ETASU B, pharmacies and healthcare settings must be certified and verify that prescribers are certified before dispensing linvoseltamab.

As part of the REMS, the Sponsor must submit REMS Assessments 12 months from the date of the initial approval of the REMS and annually thereafter. Depending on the findings from formal assessment of the REMS, FDA may modify the REMS or consider other regulatory actions. In the future, if the REMS assessments and/or data from other sources indicates that prescribers have gained familiarity with the risks of CRS and neurologic toxicity with linvoseltamab and are taking appropriate actions to reduce and manage the risks, FDA may re-evaluate the REMS to determine if continuation of REMS is necessary.

Refer to the REMS review dated 6/30/2025 for additional details.

8 Postmarketing Requirements and Commitment

The review team recommends one PMR, an accelerated approval PMR to verify clinical benefit, given that accelerated approval is being recommended based on a single-arm trial. The confirmatory trial proposed to verify clinical benefit is the REGN5458-ONC-2245 trial, a Phase 3 randomized study of linvoseltamab vs. elotuzumab, pomalidomide, and dexamethasone, in patients with RRMM. The trial has been fully enrolled and the primary PFS endpoint is projected to read out in Q2 2026. Refer to action letter for milestone dates.

PMR: Complete a randomized clinical trial in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive linvoseltamab compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and key secondary endpoints should include overall response rate and overall survival. The trial should enroll a sufficiently representative study population to allow for generalizability of the results to the U.S. patient population with multiple myeloma.

Proposed Timelines

Final Protocol Submission:	12/2022 (completed)
Trial Completion:	12/2026
Final Report Submission:	06/2027

9 Division Director (DHOT) Comments

Not applicable.

10 Division Director (OCP) Comments

Not applicable.

11 Division Director (OB) Comments

Not applicable.

12 Division Director (Clinical) Comments

Not applicable.

13 Office Director (or designated signatory authority) Comments

Not applicable.

BLA 761400 Lynozyfic (linvoseltamab-gcpt)				

Signatures

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OOD: Office of Oncologic Diseases			
DHOT: Division of Hematology, Oncology, Toxicology			
OCP: Office of Clinical Pharmacology			
DPM: Division of Pharmacometrics			
DCPI: Division of Cancer Pharmacology I			

OB: Office of Biostatistics				
DBIX: Division of Biometrics IX				
DHM2: Division of Hematologic Malignancies 2				
OCE: Oncology Center of Excellence				

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/s/

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NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original BLA/NME
Application Number(s)	BLA 761400
Priority or Standard	Priority
Submit Date(s)	December 22, 2023
Received Date(s)	December 22, 2023
PDUFA Goal Date	August 22, 2024
Division/Office	Division of Hematologic Malignancies II/Office of Oncologic Diseases
Review Completion Date	August 19, 2024
Established Name	Linvoseltamab
(Proposed) Trade Name	Lynozyfic
Pharmacologic Class	Human IgG4-based bispecific antibody that binds to CD3, a T-cell antigen associated with the T-cell receptor complex, and B cell maturation antigen (BCMA)
Code name	REGN5458
Applicant	Regeneron Pharmaceuticals, Inc.
Formulation(s)	• 5 mg/2.5 mL (2 mg/mL) single-dose vial • 200 mg/10 mL (20 mg/mL) single-dose vial
Dosing Regimen	(b) (4)

	(b) (4) [redacted]
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with relapsed or refractory multiple myeloma (b) (4) [redacted]
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	N/A

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management

Glossary

AC	Advisory committee
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ALB	Albumin
ALT	Alanine aminotransferase
APRIL	Human A proliferation-inducing ligand
AST	Aspartate aminotransferase
AUC	Area under the curve
BAFF	Human B-cell activating factor
BCMA	B-cell maturation antigen
BLA	Biologics license application
BLQ	Below the limit of quantitation
BMI	Body mass index
BMPC	Bone marrow plasma-cell percentage
BOR	Best overall response
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit-Risk Framework
BsAb	Bispecific antibody
CAR	Chimeric antigen receptor
$C_{average}$	Average concentration of a drug
CAVGAVG	$C_{average}$ up until the time of event
CAVGWK14	$C_{average}$ at week 14
CBER	Center for Biologics Evaluation and Research
CD	Cluster of differentiation
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration of the drug
C_{min}	Minimum concentration of the drug
CL	Values for clearance
CMC	Chemistry, manufacturing, and controls
CMV	Cytomegalovirus
COA	Clinical outcome assessment

COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CRT	Clinical review template
CSR	Clinical study report
CSS	Controlled Substance Staff
C_{trough}	Concentration at end of dosing interval
CV	Coefficient of variation
DL	Dose level
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DMF	Drug master file
DOR	Duration of response
DS	Disease symptoms
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic common technical document
EMP	Extramedullary plasmacytoma
EOI	End of infusion
E-R	Exposure-Response
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FIH	First-in-human
FLC	Free-light chains
GCP	Good clinical practice
GHS	Global health status
GLP	Good laboratory practice
GOF	Goodness of fit
GPRC5D	G protein-coupled receptor, class C group 5 member D
GRMP	Good review management practice
HNSTD	Highest non-severely toxic dose
ICANS	Immune effector cell-associated neurotoxicity syndrome

ICH	International Conference on Harmonization
Ig	Immunoglobulin
IL	Interleukin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug
IPDE	Intra-patient dose escalation
IRC	Independent review committee
IRR	Infusion related reaction
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ISS	International Staging System
ITT	Intent to treat
IV	Intravenous
KM	Kaplan-Meier
KM	Concentration of half maximal rate
LDH	Lactate dehydrogenase
LS mean	Least square mean
LUC	Large unstained cells
mAb	Monoclonal antibody
Mean (SD)	Mean standard deviation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MM	Multiple myeloma
MRD	Minimal residual disease
N/A	Not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCT	National clinical trial
NDA	New drug application
NE	Not evaluable
NME	New molecular entity
NR	Not reached
NSG mice	NOD severe combined immune deficiency gamma mice
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	Objective response rate
OS	Overall survival

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBMC	Peripheral blood mononuclear cell
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PD	Progressive disease
PF	Physical functioning
PFS	Progression free survival
PJP	Pneumocystis jirovecii pneumonia
PI	Prescribing information
PI	Proteasome inhibitor
PK	Pharmacokinetics
PMC	Postmarketing commitment
PML	Progressive multifocal leukoencephalopathy
PMR	Postmarketing requirement
PopPK	Population PK
PPI	Patient package insert
PR	Partial response
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred term
Q	Inter-compartmental clearance
QoL	Quality of life
QW	Every week
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBCBL	Baseline red blood cell
REMS	Risk evaluation and mitigation strategy
RP2DR	Recommended phase 2 dose regimen
RRMM	Relapsed or refractory multiple myeloma
RSE	Residual Standard Error
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
sBCMA	Soluble BCMA
SC	Subcutaneous
sCR	Stringent complete response
SD	Stable disease

SEER	Surveillance, Epidemiology, and End Results program
SGE	Special government employee
SOC	Standard of care
SOC	System Organ Class
SPR	Surface plasmon resonance
STD10	Severely toxic dose in 10% of the animals
TCR	Tissue cross-reactivity
TEAE	Treatment-emergent adverse event
TK	Toxicokinetics
FTSE	Treatment side effects
TTR	Time to response
U.S.	United States of America
VC	Volume of distribution of the central compartment
Vd_{ss}	Volume of distribution at steady-state
VGPR	Very good partial response
V_{max}	Maximum nonlinear elimination rate
VP	Volume of distribution of peripheral compartment
WBC	White blood cell
WGT	Body weight
WOE	Weight of evidence

1 Executive Summary

1.1. Product Introduction

Product: Linvoseltamab

Pharmacological Class: Linvoseltamab is a bispecific B-cell maturation antigen (BCMA)-directed and CD3-directed T-cell engager.

Proposed Indication: Linvoseltamab is a bispecific BCMA-directed and CD3-directed antibody indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) (b) (4)

Dosing Regimen: The recommended dosage of linvoseltamab is step-up doses (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends a Complete Response for linvoseltamab under BLA 761400 for the treatment of adult patients with RRMM (b) (4)

Substantial evidence of effectiveness for linvoseltamab, for (b) (4) indication of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, was established in Study R5458-ONC-1826 (Study 1826), a phase 1/2 single-arm trial of linvoseltamab monotherapy in patients with RRMM and was based on an intermediate clinical endpoint, overall response rate (ORR), and was supported by duration of response (DOR). The trial included 117 patients treated across phases 1 and 2 of the study at the proposed registrational dose (200 mg) and had previously received a PI, an IMiD, and an anti-CD38 mAb; 80 of these patients had received 4 or more prior lines of therapy and made up the primary efficacy population.

In the efficacy population (n=80), the median age was 71 years (range 37-83). Sixty-four percent of patients were male and 36% were female. The majority (69%) of patients were White, 14% were Black or African American, 13% were Asian, and 5.1% were of other races or had race not reported. Only 2.5% of patients were of Hispanic or Latino ethnicity. Patients had received a median of 5 prior lines (range 4, 13); 79% were triple-class refractory and 83% were refractory to their last line of therapy.

The overall response rate (ORR) in the efficacy population was 70.0% (95% CI: 58.7%, 79.7%). With a median duration of follow-up of 11.3 months, the median DOR was not reached (NR). The estimated DOR rate was 92.6% (95% CI: 81.6, 97.2) at 6 months, 88.8% (95% CI: 76.7, 94.8) at 9 months, and 72.4% (95% CI: 54.1, 84.4) at 12 months.

For purposes of accelerated approval, the therapy must demonstrate an advantage in the context of available therapies. When considering currently available therapies, while several therapies and combinations of therapies are approved for RRMM, only Selinexor has regular approval for the treatment of adult patients with RRMM who have received 4 prior therapies and are refractory to 2 PIs, 2 IMiDs and one CD38 monoclonal antibody, a more refractory patient population. The ORR for selinexor in this refractory patient population was 25.3% (95% CI 16.4, 36.0) and the DOR was 3.8 months

(95% CI: 2.3, not estimable). Three bispecific antibodies (teclistamab, talquetamab, and elranatamab) have accelerated approved for the RRMM population with 4 prior lines of therapy, including a PI, IMiD, and anti-CD38 mAb. The two approved CAR T-cell products (idecabtagene vicleucel and ciltacabtagene autoleucel) have regular approval, however, these products have unique patient-specific manufacturing requirements and toxicity profiles which preclude many patients with RRMM from receiving these therapies.

The Applicant's proposed indication was for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) based on the population enrolled and the clinical trial results, the FDA considered the ORR, along with demonstration of durability of response, to provide data to support a clinically meaningful advantage in treatment effect in the context of available therapies (b) (4) patients with RRMM who have received at least 4 (b) (4) prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. The considerations (b) (4) included consistency with the population enrolled on the clinical trial and the context of available therapies (b) (4) On Study 1826, only 21% of patients who received the proposed dose received 3 prior lines of therapy. Further, there are multiple two- and three-drug regimens approved for patients with RRMM who have received 3 prior therapies, as well as for patients who have received 3 prior lines of therapy. Response rates with linvoseltamab are consistent with several regimens with regular approval for these populations including elotuzumab, lenalidomide, and dexamethasone (approved for 1-3 prior lines; ORR 79%) and daratumumab, carfilzomib, and dexamethasone (approved for 1-3 prior lines; ORR 84%), among others. In considering requirements to support accelerated approval, (b) (4) in the context of available therapies (b) (4) for a population of patients with RRMM who have received 4 or more prior lines of therapy, however, a meaningful advantage is demonstrated by the ORR, supported by durability of response, with linvoseltamab.

Substantial evidence of effectiveness was established with one adequate and well-controlled clinical investigation (results from the 200 mg cohort from Phase 2 of Study 1826) with highly persuasive results considered to be the scientific equivalent of two clinical investigations.

During the review of the BLA, the facilities review identified significant manufacturing issues. Due to these manufacturing issues, which preclude approval of linvoseltamab and are detailed further in the Office of Pharmaceutical Quality (OPQ) Executive Summary, the Division's recommendation is a Complete Response.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Multiple myeloma (MM) is a plasma cell malignancy that accounts for approximately 1% of all cancers and approximately 10% of hematologic malignancies (1). In the United States, approximately 32,000 new cases are diagnosed, and 13,000 patients die of multiple myeloma each year (1). Patients are diagnosed at a median age of 65 years (1). Despite the availability of multiple treatments, MM remains an incurable disease. Patients who have received multiple lines of therapy and treated with the major class of drugs, including a PI, IMiD and an anti-CD38 mAb, have poor outcomes.

Linvoseltamab is a BCMA-directed CD3 T-cell engaging bispecific monoclonal antibody. The data provided in support of the proposed indication are from Study 1826, a phase 1/2 single-arm, multicenter, multicohort trial evaluating linvoseltamab monotherapy in patients with relapsed or refractory MM (RRMM). The efficacy population included 80 patients who received 4 or more prior lines of therapy and were treated at the proposed dosing regimen. Patients had received a median of 5 prior lines of therapy (range 4-13). The overall response rate (ORR) in the efficacy population was 70% (95% CI: 58.7, 79.7). At the time of the data cut-off of September 08, 2023, with median follow-up of 11.3 months in responders, the median duration of response (DOR) was not reached (95% CI: 12.2, NE). The estimated DOR rate was 92.6% at 6 months (95% CI: 81.6, 97.2), 88.8% at 9 months (95% CI: 76.7, 94.8), and 72.4% at 12 months (95% CI: 54.1, 84.4).

The primary safety population included patients treated at the proposed dosing regimens in phases 1 and 2 of study (n=117). The median duration of exposure to core treatment was 10.9 months (range 0.3-34.6 months). The most common adverse reactions (≥20%) were musculoskeletal pain, cytokine release syndrome (CRS), cough, diarrhea, upper respiratory tract infection, fatigue, pneumonia, nausea, and headache. The most common Grade 3 or 4 laboratory abnormalities (≥30%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, and decreased white blood cells. Serious adverse events occurred in 74% of patients. AEs leading to dose interruption occurred in 71% of patients, most commonly neutrophil decrease and infections. AEs leading to treatment discontinuation occurred in 16%, most commonly infections.

The key safety concerns for linvoseltamab are CRS and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and neurologic toxicity were common occurrences in study population, occurring in 46% and 54% of patients, respectively. The first occurrence of CRS occurred after a step-up dose (SUD) in the majority of patients (42% of patients had a first occurrence of CRS after a SUD: 38% of patients after the initial 5 mg dose and 3.4% after the intermediate 25 mg dose). Neurologic toxicity included headache in 22% of patients, encephalopathy in 17%, insomnia in 12%, and sensory neuropathy in 11%. During the review process, it was determined that risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) to mitigate the risk of CRS and neurologic toxicity, including ICANS, along with a boxed warning for CRS and neurologic toxicity, including ICANS, would be warranted to support the favorable benefit-risk of linvoseltamab. Other safety concerns include infections, neutropenia, and hepatotoxicity, along with CRS and neurologic toxicity, including ICANS, should be included in the Warnings and Precautions of the draft U.S. Prescribing Information (USPI).

The proposed confirmatory trial is Study R5458-ONC-2245 (LINKER-MM3), “An Open- Label, Randomized, Phase 3 Study of Linvoseltamab (REGN5458; Anti-BCMA X Anti-CD3 Bispecific Antibody) Versus the Combination of Elotuzumab, Pomalidomide, and Dexamethasone (EPd), in Patients with Relapsed/Refractory Multiple Myeloma.” The primary endpoint of Study 2245 is PFS in the CD38-exposed participants. The Applicant provided an update regarding status of the study on August 8, 2024, stating that 154 of the planned (b) (4) patients (b) (4) had been enrolled; the projected trial completion date was reported to be Q2 2025, and the projected primary efficacy readout was projected to occur in Q2 2026. Based on the increase in enrollment from the time of BLA submission, at which point 8 patients had been enrolled to the trial, and the information supporting the Applicant’s projections, the Division considers the timelines and projections for study completion to be reasonable.

In patients with relapsed or refractory MM (RRMM) who have received 4 or more prior lines of therapy, linvoseltamab has a favorable benefit-risk balance, and is noted to demonstrate an advantage in the context of available therapies. Given the manufacturing issues, described further in the OPQ Executive Summary, which must be resolved prior to approval of linvoseltamab, the Agency’s recommended regulatory action for the application is a Complete Response.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Multiple myeloma (MM) is the second most common hematological malignancy. • Therapy for patients with RRMM has improved considerably over the years with approval of multiple new therapies with improvement in response rate and progression-free survival (PFS). • However, relapses are common, and MM remains incurable, with a 5-year survival rate of 57.9%.	• RRMM is a serious and life-threatening condition.
Current Treatment Options	• Multiple drugs approved for use in MM and numerous combination regimens are considered standard of care. • Potential treatments include alkylating agents, corticosteroids, PIs, IMiDs, mAbs, CAR T-cell therapies, and BCMA-directed or GPRC5D-directed bispecific antibodies. Of note, all approved bispecific antibodies are under Accelerated Approval • Patients who have received multiple lines of therapy including a PI, IMiD and an anti-CD38 monoclonal antibody have limited available effective treatment options and have poor outcomes.	• Despite the availability of multiple therapies, RRMM remains an incurable disease.
Benefit	• Assessment of substantial evidence of effectiveness was based on results from Study 1826, a single-arm trial of linvoseltamab monotherapy in patients with RRMM • The primary efficacy population included 80 patients treated at the proposed dosing regimen in phase 2 who had received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. • The ORR in the efficacy population was 70% (95% CI: 59.2,	• The ORR, supported by durability of response, demonstrated based on the results of the single-arm trial show evidence for effectiveness in this patient population • Based on available data, linvoseltamab demonstrates an advantage in the context of available therapies for RRMM

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	78.9). • With median follow-up of 11.3 months (95% CI: 10.2, 12.5) among responders, the median duration of response was not reached (95% CI: 12.2, NE). • The estimated DOR rate was 92.6% at 6 months (95% CI: 81.6, 97.2), 88.8% at 9 months (95% CI: 76.7, 94.8), and 72.4% at 12 months (95% CI: 54.1, 84.4).	
Risk and Risk Management	• Safety was evaluated in 117 patients treated at the proposed dosing regimen (5 mg initial dose, 25 mg intermediate dose, 200 mg full dose) in phases 1 and 2 of study. • Median duration of exposure was 10.9 months. • Fatal treatment-emergent adverse events (TEAEs) occurred in 12% of patients and serious adverse events (SAEs) occurred in 74% of patients • The most common adverse reactions (≥20%) were musculoskeletal pain, cytokine release syndrome (CRS), cough, diarrhea, upper respiratory tract infection, fatigue, pneumonia, nausea, and headache. • Key safety concerns are CRS and neurologic toxicity, including ICANS. CRS occurred in 46% of patients, neurologic toxicity in 54%, and ICANS in 8%. • Other safety concerns include infections, neutropenia, and hepatotoxicity	• The safety profile of linvoseltamab in the indicated patient population is acceptable and is based on adequate duration of exposure. • Risk mitigation measures that were considered during the review of this application for the key safety concerns of CRS and neurologic toxicity, including ICANS, were: o Boxed warning in USPI to alert prescribers regarding the risks of CRS and neurologic toxicity, including ICANS o Guidance in USPI to hospitalize patients for 48 hours after the initial dose and 24 hours after the intermediate dose o Risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) A and B, to ensure that the healthcare providers are aware of the risks and the recommended risk mitigations

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		measures to ensure the safe use of linvoseltamab in the post-market setting • Warnings and Precautions (W&P) for the risk of hepatotoxicity and expansion of the proposed W&P of ICANS to also describe neurologic toxicity will be considered upon resubmission • The Division agrees with the Applicant's proposed W&P for the risks of infection, neutropenia, and CRS

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section where discussed, if applicable
☐	The patient experience data that was submitted as part of the application, include:			
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]

	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

MM is a malignancy associated with the clonal proliferation of plasma cells. MM comprises approximately 13% of hematologic cancers. The median age of diagnosis is approximately 70 years. In 2023, there will be approximately 35,730 new cases of MM and 12,590 deaths due to this disease in the U.S. (American Cancer Society, 2023).

MM commonly presents with organ impairment such as renal dysfunction (due to filtered FLCs leading to cast nephropathy or amyloidosis, among other mechanisms), bone infiltration by malignant plasma cells, hypercalcemia, and hematopoietic suppression. Malignant plasma cells in patients with MM typically secrete high levels of monoclonal immunoglobulin (termed "M protein"), which can be detected in the blood, or monoclonal immunoglobulin light chain (termed Bence-Jones protein), which can be detected in the urine to diagnose and monitor the disease.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the condition.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Significant advances have been made in the treatment of MM, including approval of drugs with various mechanisms of action, including IMiDs (such as thalidomide, lenalidomide, and pomalidomide), PIs (such as bortezomib, ixazomib, and carfilzomib), nuclear export inhibitor therapy (selinexor), mAb therapies directed towards cell surface antigens such as CD38 (daratumumab and isatuximab) and SLAMF7 (elotuzumab), CD3 BsAb therapies targeting MM via cell surface antigens BCMA (teclistamab and elranatamab) and GPRC5D (talquetamab), and BCMA-directed genetically modified autologous CAR T-cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel). Due to the modest monotherapy activity of all agents (except BCMA- and GPRC5D-targeted immunotherapies), early line treatment often utilizes combinations including 2 to 4 active drugs including IMiDs, PIs, anti-CD38 antibodies, corticosteroids (such as dexamethasone), and/or alkylating agents.

A few novel therapies have recently been approved for treatment in patients with myeloma who have failed an anti-CD38 antibody, a PI, and an IMiD (NCCN, 2023). The most relevant approved therapies are summarized in Table 1 below.

Table 1: Applicant - Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval*	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Selinexor/ Dexamethasone (selective inhibitor of nuclear export)	Adult patients with RRMM who have received 4 or more prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 mAb.	FDA: 2020/Full Approval	Selinexor 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity in combination with dexamethasone 20 mg taken orally with each dose of selinexor on Days 1 and 3 of each week.	Open-label, single-arm study STORM **ORR:** 25.3% (95% CI: 16.4%, 36%) **sCR**: 1% **Median DOR:** 3.8 months (95% CI: 2.3, NE)	Selinexor is associated with significant AEs including thrombocytopenia, neutropenia, nausea, diarrhea, anorexia, hyponatremia, infections, neurological AEs. Infections of interest: upper respiratory tract infection, pneumonia, sepsis
Teclistamab (BCMAxCD3 BsAb)	Adult patients with RRMM with who have received 4 or more prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb	FDA: 2022/ Accelerated Approval	SC, Step-up dosing schedule 0.06 mg/kg on day 1, 0.3mg/kg on day 4, 1.5 mg/kg on day 7, then 1.5 mg/kg 1 week after first treatment dose and weekly thereafter	Single-arm study MajesTEC-1 (U.S. Cohort). **ORR:** 61.8% (95% CI: 52.1, 70.9) **≥CR:**28.2% **Median DOR:** NE (9.0, NE)	Teclistamab is associated with significant AEs including the following key AEs:CRS, Neurologic toxicity, ICANS, hepatotoxicity, serious infections, neutropenia, systemic-administration reactions, injection-site reactions.
Elranatamab (BCMAxCD3 BsAb)	Adult patients with RRMM who have received at least 4 prior lines of therapy	FDA: 2023/ Accelerated Approval	SC, Step-up dosing: 12 mg on day 1 32 mg on day 4 76 mg on day 8 (first treatment dose)	Single-arm, open-label study (MagnetisMM-3): **ORR:** 57.7% (95%CI: 47.3%, 67.7%)	Elranatamab is associated with significant AEs including the following key AEs: CRS,

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval*	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
	including a PI, IMiD, and an anti-CD38 mAb.		76 mg 1 week after first treatment dose and weekly thereafter through week 24 (For those with PR or better for at least 2 months): 76 mg on week 25 and Q2W thereafter, until disease progression or unacceptable toxicity	**CR or better:** 25.8% **Median DOR**: NR (95% CI: 12.0, NE)	neurologic toxicity, ICANS, serious infections, neutropenia, hepatotoxicity.
Talquetamab (GPRC5DxCD3 BsAb)	Adult patients with RRMM who have received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.	FDA:2023/ Accelerated Approval	SC, 2 Step-up dosing schedules 0.01 mg/kg on day 1, 0.06mg/kg on day 4, 0.4 mg/kg on day 7 (first treatment dose), then 0.4 mg/kg 1 week after first treatment dose and weekly thereafter OR 0.01 mg/kg on day 1, 0.06 mg/kg on day 4, 0.4mg/kg on day 7 0.8 mg/kg on day 10 (first treatment dose), then 0.8 mg/kg 2 weeks after the first treatment dose and Q2W thereafter. Continue until disease progression or unacceptable toxicity.	Single-arm, open-label study (MonumenTAL-1). **0.4 mg/kg weekly:** **ORR**: 73% (95% CI: 63.2%, 81.4%) **≥CR**: 26% **Median DOR**: 9.5 (95% CI: 6.5, NE) months **0.8 mg/kg Q2W:** **ORR**: 73.6% (95% CI: 63.0%, 82.4%) **sCR**: 20% **Median estimated DOR**: NE	Talquetamab is associated with significant AEs including the following key AEs: CRS, neurologic toxicity including ICANS, oral toxicity, weight loss, serious infections, cytopenias, skin reactions, hepatotoxicity.

*Accelerated approval or full approval
Source: Module 2.5 Clinical Overview, Table 3

In addition to the relevant approved therapies mentioned in Table 1, there are 2 CAR T-cell therapies that target the BCMA protein. Idecabtagene vicleucel received full FDA approval in 2021, demonstrating 72% ORR and 11.0 months median DOR. Ciltacabtagene autoleucel received full FDA approval in 2022, demonstrating 97.9% ORR and 21.8 months median DOR. Both drugs are associated with significant toxicity, including CRS, neurotoxicity, infections, prolonged cytopenia, and hypogammaglobulinemia.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's assessment of current treatment of patients who have received an anti-CD38 antibody, PI, and IMiD (triple class exposed). The FDA notes that the three bispecific antibodies approved for RRMM (teclistamab, talquetamab, and elranatamab) remain under accelerated approval. The FDA also notes that in addition to the therapies that are specifically indicated for patients who are triple class exposed, patients may also respond to therapies or combinations of therapies of the same classes already received in subsequent lines of therapy.

Treatment options for patients with RRMM are provided in Table 2.

Table 2: FDA – Treatment Options for Patients with RRMM

Elotuzumab with Rd	Regular (2015)	RRMM/1-3L
Elotuzumab with Pd	Regular (2018)	RRMM/≥2L, including lenalidomide and PI
Selinexor with dex+	AA (2019)*	RRMM/≥4L, including 2 PIs, 2 IMiDs, anti-CD38 mAb
Selinexor with Vd	Regular (2020)	RRMM/≥1L
Daratumumab-IV with Kd	Regular (2020)	RRMM/1-3L
Daratumumab-SC	Regular (2020)	RRMM/≥3L, including PI and IMiD or PI/IMiD double-refractory
Daratumumab-SC with Rd	Regular (2020)	RRMM/≥1L
Isatuximab with Pd	Regular (2020)	RRMM/≥2L, including lenalidomide and PI
Isatuximab with Kd	Regular (2021)	RRMM/1-3L
Daratumumab-SC with Pd	Regular (2021)	RRMM/≥1L, including lenalidomide and PI
Daratumumab-SC with Kd	Regular (2021)	RRMM/1-3L
Idecabtagene vicleucel (BCMA-CART)+	Regular (2021)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb

Ciltacabtagene autoleucel (BCMA CAR-T)+	Regular (2022)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb
Teclistamab-cqyv+	AA (2022)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb
Talquetamab+	AA (2023)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb
Elranatamab+	AA (2023)	RRMM/≥4L, including PI, IMiD, anti-CD38 mAb

* Accelerated approval converted to regular following verification of clinical benefit;

^ Accelerated approval of Panobinostat was withdrawn in 2021 due to lack of due diligence in verifying clinical benefit; Red text indicates approved regimens for patients with 4 or more prior lines of therapy including an IMiD, PI, and anti-CD38

+ Approved for the proposed patient population

Abbreviations: AA= accelerated approval, anti-CD38 mAb=anti CD38 monoclonal antibodies, dex= dexamethasone, IMiD=immunomodulatory drug, IV=intravenous, Kd=carfilzomib and dexamethasone, L=lines of therapy, Pd=pomalidomide and dexamethasone, PI=proteasome inhibitor, Rd=lenalidomide and dexamethasone, RRMM=relapsed refractory multiple myeloma, SC=subcutaneous, Vd=bortezomib and dexamethasone; not shown is melphalan flufenamide-accelerated approval granted February 26, 2021 but currently withdrawn from the US market. Also not shown is belantamab mafodotin which received accelerated approval in 2020 but was withdrawn from the US market.

Source: FDA Analysis

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Linvoseltamab is a NME and is not currently marketed in the U.S. or outside of the U.S. BLA 761400 is being submitted for accelerated approval of linvoseltamab as monotherapy indicated for the treatment of adult patients with RRMM (b) (4)

The FDA's Assessment:
The FDA agrees with the Applicant's position, and notes that while the application was submitted for the indication noted above, the indication for which the Division considers the benefit/risk to be favorable is for the treatment of adult patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Key presubmission regulatory interactions related to BLA 761400 are summarized in Table 3.

Table 3: Applicant - Summary of Key Regulatory Interactions for BLA 761400

Date	Regulatory Interaction
19 Oct 2018	IND 138791 was opened with Study R5458-ONC-1826, *a FIH study of REGN5458 for the treatment of RRMM.*
06 Jun 2022	Orphan Drug Designation was granted to linvoseltamab for the treatment of MM (# DRU-2022-8820).
23 Mar 2023	FDA confirmed the BLA will be exempt from PREA requirement and the initial pediatric study plan is closed.
30 Mar 2023	Fast Track Designation granted for linvoseltamab for the treatment of patients with MM who have received an IMiD, a PI, and an anti-CD38 mAb.
18 Oct 2023	Type B pre-BLA meeting was held on 18 Oct 2023 and alignment was reached with the FDA on the proposed content and format of the planned REGN5458 BLA submission.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of regulatory interactions and also adds the following interactions and details regarding interactions:

- July 27, 2018: Pre-IND Written Responses Only (WRO) responses were issued. Topics addressed in the meeting included key elements of the R5458-ONC-1826 study, including the patient population, starting dose and dose escalation plan, and DLT criteria.
- September 21, 2018: New IND was submitted.
- October 19, 2018: Study was determined to be safe to proceed.
- March 11, 2021: Preliminary Breakthrough Therapy Designation (BTD) Request Advice Meeting was held.
    - The Agency informed the Sponsor that BTD would be premature, given the small sample size, lack of data in patients treated at the RP2D, and limited follow-up. The Agency advised the sponsor to request an EOP1 meeting to discuss future development and dose selection.
- April 23, 2021: WRO responses with feedback on the completed 5-week toxicology study and reproductive toxicology package were issued.
- August 23, 2022: Pre-Phase 3 Teleconference was held to discuss the proposed strategy to seek Accelerated Approval based on results from Study R5458-ONC-1826.
    - Dose/Regimen: FDA did not agree with proposed dose and requested additional data to support the proposed dose. FDA expressed concerns with proposal (b) (4) and requested data that the change would not result in loss of efficacy
    - Registrational Approach: FDA expressed concerns with proposal to seek Accelerated Approval based on a single-arm trial for RRMM and recommended consideration of a randomized trial. FDA stated that the proposed duration of follow-up would be insufficient and requested at least 9-12 months of follow-up from response.
    - Patient Population: FDA stated (b) (4) and requested that the Sponsor revise the protocol or provide justification for the threshold.
- May 15, 2023: WRO meeting minutes regarding analytical comparability of new drug product concentrations and microbial challenge data were issued.
- October 18, 2023: Additional details about the pre-BLA meeting and FDA perspectives are provided below;
    - FDA expressed concerns about the use of a single-arm trial to support Accelerated Approval, and reiterated the need for adequate DOR follow-up and for the confirmatory trial to be well underway.
    - FDA stated that adequacy of the safety database would be determined during the BLA review and that the acceptability of pooling patients who received the 200mg dose in phases 1 and 2 of study would depend on

whether there were differences in the populations, duration of follow-up, efficacy, and safety assessments between arms.
  - FDA stated that there was insufficient information provided about the (b) (4) test for minimal residual disease (MRD) in order to determine whether the data could be used to supplement missing data from the (b) (4) assay.
- February 16, 2023: Application Orientation meeting (AOM) for BLA 761400 was held.
- April 11, 2023: Mid-Cycle Communication Teleconference.
  - The FDA conveyed concerns about the risks of CRS, neurologic toxicity, and hepatic toxicity. The FDA also stated that additional items under review included the status of the confirmatory trial, adequacy of the hospitalization and monitoring requirements, the benefit-risk in for the proposed indication, the proposal to pool data for safety and efficacy between phases 1 and 2 of study, the adequacy of the MRD data, and the applicability of the data to the general U.S. patient population, given the limited enrollment of Hispanic/Latino patients.
- June 24, 2024: Late-Cycle Communication Teleconference
  - The FDA conveyed concerns about the risks of CRS and neurologic toxicity, and stated that determination of the appropriate risk mitigation measures was ongoing. The Sponsor inquired about the status of FDA review of the progress reports addressing the facility-related deficiencies. The FDA stated that review was ongoing and that the CMC team is amenable to an informal meeting with (b) (4)

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspected the Applicant for quality of study conduct and oversight, and three clinical sites that were selected by the clinical team due to high accrual (Dr. Naresh Bumma [Site #840009], Dr. Hans Lee [Site #840011], and Dr. Attaya Suvannasankha [Site #840012]). No issues warranting action were identified. The Applicant's site audit included selection, monitoring, and financial disclosures of research staff, study monitoring, safety reporting, data collection and handling, records retention, and electronic records. OSI determined that the Applicant's oversight and monitoring appeared to have been conducted adequately.

4.2. Product Quality

Refer to the OPQ Executive Summary for a description of the details of the manufacturing issues identified. The FDA OPQ team recommended Complete Response.

4.3. Clinical Microbiology

Refer to the OPQ Executive Summary for further details regarding the drug substance and product microbiology.

4.4. Devices and Companion Diagnostic Issues

Not Applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Linvoseltamab (also referred to as REGN5458) is an IgG4-based bispecific T-cell engaging antibody that binds to the CD3 receptor expressed on the surface of T-cells and B-cell maturation antigen (BCMA) expressed on the surface of multiple myeloma (MM) cells and some healthy B-lineage cells. The proposed indication is relapsed or refractory MM.

In vitro studies showed linvoseltamab bound to BCMA from humans (K_D = 437 pM) and cynomolgus monkeys (K_D = 24.6 nM), with no affinity towards rodent BCMA. Linvoseltamab bound to primary human and cynomolgus monkey T-cells with similar EC_{50} values, ranging between 120 nM to 193 nM. Based on these results, the cynomolgus monkey is the relevant animal species for toxicological studies with linvoseltamab.

Linvoseltamab induced concentration-dependent T-cell activation and cytotoxicity of myeloma cells in bone marrow samples from patients with MM. Administration of linvoseltamab reduced tumor growth in immunodeficient mice co-implanted with human PBMCs and either NCI-H929 (BCMA-high) or MOLP-8 (BCMA-low) MM cells. Linvoseltamab treatment resulted in elevated serum levels of IFN-γ and IL-2 at 4 hours after the first dose. Safety pharmacology parameters were evaluated in the toxicology studies in cynomolgus monkeys; there were no linvoseltamab-induced effects on the central nervous or respiratory systems. However, higher heart rates were observed over the course of the 5-week intravenous (IV) repeat-dose study. These assessments were not conducted during the 9 or 14-week repeat-dose study due to unscheduled deaths in the animals.

General toxicology studies were conducted in cynomolgus monkeys, a pharmacologically relevant species, to assess the toxicity and toxicokinetics (TK) of linvoseltamab. In the 5-week IV repeat-dose study, linvoseltamab was administered once weekly at doses of 0.1, 1, and 10 mg/kg followed by a 12-week recovery phase. Linvoseltamab was tolerated with clinical observations of emesis/vomitus (associated with mildly elevated C-reactive protein [CRP] and cytokines) and red or liquid feces; these findings occurred with high incidence at 1 and 10 mg/kg, and at 10 mg/kg these findings were still present at the end of the recovery phase. Linvoseltamab-related

statistically significant and dose-proportional decreases in lymphocytes may have been related to decreased lymphocyte cellularity, noted microscopically in the thymus and germinal centers of the spleen. The increased monocyte counts, large unstained cell (LUC) counts, and fibrinogen may have been associated with increased inflammatory cell infiltrates, noted microscopically in various tissues. Additional decreases in white blood cells occurred during the dosing phase along with slight decreases of the relative proportions of CD3, CD4, and CD8 T-cells that returned to control values during the recovery phase.

Decreases in total protein, albumin, globulin, calcium, and phosphorus were related to gastrointestinal (GI) abnormalities. The spleen, thymus, and gut associated lymphoid tissue (GALT)/Peyer's patch were the target organs of toxicity with significant increases in spleen and decreases in thymus weights. Changes in spleen and thymus weights were still present at the end of the recovery phase although with decreased magnitude. Linvoseltamab-related microscopic changes included decreased B-cell lineage lymphocyte populations and changes in cellularity in the target organs of toxicity.

A subsequent toxicology study was initially planned as a 26-week repeat-dose study with once weekly dosing at 1, 5, and 20 mg/kg; the FDA did not request the study to be 26 weeks in duration. The study protocol was amended due to the declining body conditions across all dose groups compared to control. Consequently, a decision was made to euthanize severely affected animals for humane reasons. For the remaining animals the study was then divided into a 9-week (20 mg/kg group) or 14-week (1 and 5 mg/kg groups) repeat-dose study, each followed by a 13-week recovery phase.

The animals showed adverse clinical signs that correlated with decreased body weight and food consumption that contributed to moribundity. In general, findings were similar in moribund and terminally sacrificed animals. Decreased B-cells and plasma cells likely contributed to decreased immunoglobulins causing secondary infections. Additionally, the most severely impacted animals showed a dose-dependent induction of CRP that correlated with increased IL-2, IL-6, and MCP-1. Decreases in circulating T-cells were also observed. An increase in cellularity was noted microscopically in various lymphoid organs, which along with the multi-organ inflammatory cell infiltration observed, are indicative of immune cell redistribution and infiltration.

Systemic exposure, as assessed by C_{max} and AUC_{tau}, increased proportionally with dose in both the 5-week and the 9/14-week toxicology studies. There were no sex-related differences in either study. Modest accumulation was observed in the 9/14-week study only. Evidence of an anti-drug antibody (ADA) response was observed in both studies, but exposure was maintained in 83% (30/36) of the animals in the 5-week study and 92% (33/36) of the animals in the 9/14-week study. The ADA responses did not significantly compromise the interpretability of either study.

The Applicant provided a weight of evidence (WOE)-based risk assessment to assess the potential for reproductive and developmental toxicities. The WOE risk assessment took into consideration the pharmacology of linvoseltamab, the expression and biology of the targets, and the effects observed in the repeat-dose toxicology studies. Linvoseltamab is expected to cause T-cell activation, cytokine release, and an associated inflammatory response that may adversely impact a pregnant woman or a developing fetus. Linvoseltamab may cross the placenta to a developing fetus; based on findings of B-cell depletion in the repeat-dose toxicology studies, in utero exposure to linvoseltamab may cause B-cell depletion in a developing fetus or a newborn. Due to the potential for linvoseltamab to cause embryofetal toxicities, the proposed product label advises female patients of reproductive potential to use effective contraception during treatment with linvoseltamab and for 3 months after the last dose. The recommendation for the duration of contraception use is based on the clinical pharmacokinetics (PK) of linvoseltamab, which exhibits nonlinear clearance. At the standard weekly dose of linvoseltamab, a 97% decrease from C_{max} was observed in a median time of 77.7 days after last dose.

There are no data on the presence of linvoseltamab in human milk, the effects on the breastfed child, or the effects on milk production. Linvoseltamab is an IgG4-based bispecific T-cell engaging antibody, and maternal IgG is known to be present in human milk. Because of the potential for serious adverse reactions in a breastfed child, the product label for linvoseltamab advises women not to breastfeed during treatment with linvoseltamab and for 3 months after the last dose. The recommended duration to avoid breastfeeding is also based on the clinical PK of linvoseltamab.

Linvoseltamab binds CD3 and BCMA and promotes the T-cell dependent elimination of BCMA-expressing cells; the Established Pharmacologic Class of linvoseltamab is “bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager”.

The nonclinical pharmacology, PK, and toxicology data submitted to BLA 761400 are adequate to support the approval of linvoseltamab for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant’s Position:

There are no referenced NDAs, BLA, or DMFs related to nonclinical pharmacology or toxicology for linvoseltamab.

5.3. Pharmacology

Primary pharmacology

Results from nonclinical studies demonstrate that linvoseltamab binds specifically to human and cynomolgus monkey BCMA, and is capable of bridging CD3 and BCMA expressed on effector and target cell surfaces, respectively, resulting in T-cell activation

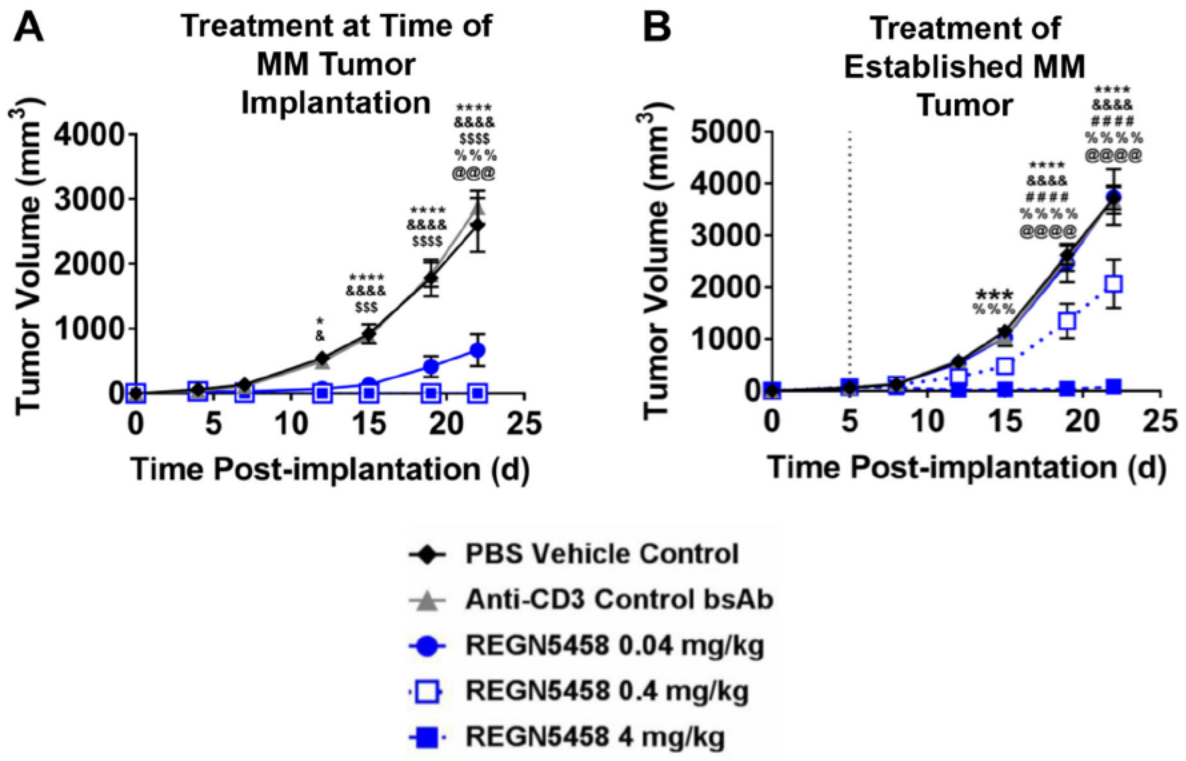
and directed cytotoxicity. Linvoseltamab-mediated cytotoxicity of MM cells, abnormal plasma cells that build up in the bone marrow, was demonstrated in vivo, where linvoseltamab treatment of mice bearing human MM tumor xenografts resulted in significantly reduced tumor growth, as well as ex vivo, where linvoseltamab-mediated autologous T-cell killing of some patient-derived MM cells.

In vivo studies were performed to evaluate the anti-tumor efficacy and minimum effective dose of linvoseltamab in immunodeficient NSG mice SC co-implanted with human PBMC and either NCI-H929 (BCMA-high) or MOLP-8 (BCMA-low) MM cells. Linvoseltamab was administered intraperitoneally either at the time of tumor implantation or 5 days after implantation to established tumors (NCI-H929 only; n=7 for all groups). Linvoseltamab efficacy was compared at 0.04, 0.4, and 4 mg/kg to a CD3-binding isotype control bsAb consisting of a non-binding arm and the same CD3-binding arm as in the linvoseltamab bsAb.

Immediate treatment of NCI-H929 tumors with linvoseltamab at 0.04, 0.4, and 4 mg/kg resulted in significantly reduced tumor growth compared with the CD3-binding isotype control bsAb (Figure 1A). Immediate treatment with 0.4 or 4 mg/kg (but not 0.04 mg/kg) linvoseltamab resulted in prolonged tumor clearance past the dosing period in all mice bearing NCI-H929 tumors.

Treatment of 5-day established NCI-H929 tumors with linvoseltamab at 0.4 and 4 mg/kg (but not 0.04 mg/kg) resulted in significantly reduced tumor growth compared with CD3-binding isotype control bsAb (Figure 1B). Compared with treatment at 0.4 mg/kg, treatment at 4 mg/kg resulted in significantly less tumor growth and in more tumor clearance, with prolonged tumor clearance observed past the dosing period in 1 out of 8 mice and 6 out of 8 mice in the 0.4 and 4 mg/kg dose groups, respectively.

Figure 1: Applicant - Linvoseltamab Reduces MM Tumor Growth in NSG Mice Bearing NCI-H929 Xenografts Co-Implanted with Human PBMC



(A) or treated after 5 days of tumor establishment (B) with linvoseltamab at doses of 0.04, 0.4, or 4 mg/kg, phosphate-buffered salinevehicle control, or anti-CD3 control bsAb (n=7 for all groups). The following symbols were used to indicate statistically significant differences: "$", "&", and "*" mark anti-CD3 control bsAb vs linvoseltamab at 0.04, 0.4, and 4 mg/kg, respectively; "@" and "%" mark linvoseltamab 0.04 mg/kg vs linvoseltamab at 0.4 and 4 mg/kg, respectively. Increasing numbers of symbols indicate increasing significance: 1x=P<0.05; 2x=P<0.01; 3x=P<0.001; 4x=P<0.0001.
Source: M2.6.2 Pharmacology Written Summary, Figure 1

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the primary pharmacology studies as described above. Additional details and clarifications regarding the studies are provided in the review below.

Surface plasmon resonance (SPR) studies demonstrated linvoseltamab bound recombinant human BCMA protein with high affinity (K_D = 437 pM) and to recombinant cynomolgus monkey BCMA protein with lower affinity (K_D = 24.6 nM); linvoseltamab did not bind to rodent BCMA under the conditions tested.

The binding affinity of linvoseltamab to CD3 expressed endogenously on human and cynomolgus monkey T-cells was determined by flow cytometry; linvoseltamab bound human and cynomolgus monkey T-cells with similar EC_{50} values ranging between 120

nM to 193 nM. The CD3 protein sequence is poorly conserved between humans and rodents, and linvoseltamab is not expected to cross react with rodent CD3.

The capacity of linvoseltamab to mediate primary human T-cell-induced cytotoxicity and T-cell activation was evaluated in flow cytometry-based assays using NCI-H929 (BCMA-high) and MOLP-8 (BCMA-low) human MM target cell lines. Linvoseltamab mediated the cytolysis of NCI-H929 and MOLP-8 cells in the presence of primary human T-cells in a concentration-dependent manner with EC_{50} values of 108 pM to 139 pM. Linvoseltamab also mediated T-cell activation (as measured by CD25 upregulation) in both cell lines in a concentration-dependent manner; however, greater maximum percent cytolysis and T-cell activation were observed with NCI-H929 (BCMA-high) cells.

The T-cell-induced cytotoxicity assay described above was repeated using primary cynomolgus monkey T-cells and target cells that endogenously expressed human BCMA (NCI-H929) or human embryonic kidney 293T (HEK293T) cells which were engineered to express cynomolgus monkey BCMA (HEK293/MfBCMA). Linvoseltamab mediated the cytolysis of NCI-H929 and HEK293/MfBCMA cells in the presence of primary cynomolgus monkey T-cells with EC_{50} values of 17.7 pM and 883 pM, respectively.

The flow cytometry-based cytotoxicity and T-cell activation assay was repeated in the presence of human primary T-cells pretreated with dexamethasone. The EC_{50} values for linvoseltamab-mediated T-cell cytotoxicity and T-cell activation were reduced by dexamethasone pretreatment of T-cells, but the maximum percent cell killing was unaffected, suggesting higher concentrations of linvoseltamab could overcome the impact of dexamethasone treatment.

Human A proliferation-inducing ligand (APRIL) and human B-cell activating factor (BAFF) are endogenous BCMA ligands; binding to BCMA leads to the activation of signaling that results in B-cell activation, differentiation and maturation into plasma cells, and long-term plasma cell survival. The ability of APRIL, BAFF, or soluble BCMA (sBCMA) to block the interaction of linvoseltamab with BCMA on BCMA-expressing cells was assessed using a NFAT reporter bioassay. Results showed that sBCMA and APRIL inhibited linvoseltamab-mediated NFAT signaling with IC_{50} values of 756 pm and 1.22 nM, respectively; however, BAFF did not block linvoseltamab-mediated T-cell activation under the conditions tested.

The capacity of linvoseltamab to mediate cytotoxicity of primary MM cells was evaluated using (1) autologous patient T-cells or (2) non-autologous healthy donor T-cells; flow cytometry was used to evaluate cell viability and T-cell activation. Most of the primary MM cells from newly diagnosed and relapsed/resistant patients were sensitive to linvoseltamab in the presence of autologous T-cells; cells that were not sensitive to linvoseltamab in the presence of autologous T-cells were killed in the presence of healthy donor T-cells.

The in vivo antitumor activity of linvoseltamab was evaluated in immunodeficient NSG mice subcutaneously co-implanted with human PBMCs and either NCI-H929 (BCMA-high) or MOLP-8 (BCMA-low) MM cells; linvoseltamab doses of 0.4 mg/kg and 4 mg/kg were effective at reducing tumor growth (see Applicant's Figure 1). T-cell activation was assessed in response to linvoseltamab treatment by measuring the serum concentration of inflammatory cytokines. Linvoseltamab induced higher levels of IFN-γ, IL-2, IL-4, and IL-8.

Secondary Pharmacology

The Applicant's Position:

Secondary studies have not been conducted.

The FDA's Assessment:
The FDA agrees.

Safety Pharmacology

Safety pharmacology evaluations were integrated into a GLP-compliant repeat-dose toxicology study conducted in cynomolgus monkeys using linvoseltamab (R5458-TX-17179). These evaluations included measurement of cardiac conduction by Jacketed External Telemetry™, as well as assessment of hemodynamics (heart rate and blood pressure), respiratory function (breaths/minute and pulse oximetry), and central nervous system 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.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the safety pharmacology endpoints evaluated as part of the GLP-compliant 5-week repeat-dose toxicology study in cynomolgus monkeys. The FDA notes higher heart rates were observed over the course of the 5-week IV repeat-dose toxicology study. Females at 10 mg/kg presented a 25% higher mean heart rates without statistical significance (+25 bpm) and a single female presented an increase of +75 bpm (+63%) compared to control. During the recovery phase, males at 10 mg/kg presented a 20% higher mean heart rates without statistical significance (+21 bpm) with one male presenting an increase of +91 bpm (+123%) compared to control.

Safety pharmacology endpoints were not evaluated as part of the GLP-compliant 9 or 14-week repeat-dose toxicology study in cynomolgus monkeys due to the high mortality rate in the animals.

5.4. ADME/PK

The Applicant's Position:

The concentration-time profiles of linvoseltamab are characterized by a brief distribution phase followed by a linear beta-elimination phase at concentrations sufficient to saturate the target-mediated elimination pathway and a subsequent nonlinear terminal elimination phase at the lower linvoseltamab concentrations. During the repeat-dose GLP toxicology studies, continuous exposure to total linvoseltamab was observed for the majority of the linvoseltamab-treated monkeys at doses ≥0.1 mg/kg throughout the 5-, 9-, and 14-week treatment periods and linvoseltamab concentrations were detected throughout the 12- and 14-week recovery periods, respectively.

Across the repeat-dose studies, dose proportional increases in C_{max} and exposure (AUC_{tau}) were observed, indicating linear kinetics. The kinetics of linvoseltamab following multiple dosing were as predicted based on single dose linvoseltamab PK data. Accumulation of linvoseltamab was observed following multiple dosing during the treatment period, as indicated by a 1.8- to 3.7-fold increases in C_{trough} values across all dose groups in the 5-week and 9- or 14-week studies. In the 9- or 14-week study, steady-state was achieved by approximately the eighth dose in all groups.

Furthermore, immunogenicity of linvoseltamab was low in the single dose PK studies and moderate to high in the repeat-dose studies and dose dependent, with a higher effect of ADA observed at low DLs. The apparent presence of ADA did not adversely affect the ability to characterize the PK or safety profiles of linvoseltamab and is not considered predictive of immunogenicity in humans.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

The review below provides additional information and some clarifications regarding the data presented by the Applicant.

Type of Study	Major Findings
A 5-Week Intravenous Infusion Toxicity and Toxicokinetic Study in Cynomolgus Monkeys With a 12-week Dose-Free Recovery Phase (study	Monkeys (5-week repeat-dose) • Systemic exposure, as assessed by C_{max} and AUC_{tau}, increased proportionally with dose from 0.1 to 10 mg/kg after doses 1 and 5 (weeks 1 and 5). • No significant differences were observed in total linvoseltamab concentrations in serum between males and females (after exclusion of ADA impacted values). • A formal ADA assay was not conducted; the presence of ADAs was inferred by inspection of the individual concentration-time profiles. An ADA response was detected in 36% (13/36) of the animals during the dosing period. However, linvoseltamab exposure was maintained in 83% (30/36) of the animals during the dosing period. • The ADA response did not significantly compromise the interpretability of the study.

Type of Study	Major Findings
R5458-TX-17179) A 9 or 14-Week Intravenous Injection Toxicity and Toxicokinetic Study in Sexually Mature Cynomolgus Monkeys with a 13-Week Recovery Phase (study R5458-TX-20118)	**Table 4: FDA - Summary of Mean Toxicokinetic Parameters in the 5-Week Repeat-Dose Monkey Study**

Linvoseltamab TK Parameters *											
Parameter	Unit	Dose	0.1 mg/kg			1 mg/ kg			10 mg/kg		
			N	Mean	SD	N	Mean	SD	N	Mean	SD
C_{max}	µg/mL	1	12	2.23	0.295	12	19.9	3.87	12	239	24.2
		5	9	3.16	0.899	9	22.8	7.99	12	370	42.2
t_{max}	h	1	12	0.527	0.0202	12	1.19	1.57	12	2.54	6.97
		5	9	0.972	1.35	9	4.13	7.93	12	0.532	0.0206
AUC_{tau}	day•(µg/mL)	1	12	6.07	1.13	12	52.9	9.85	12	724	61.8
		5	7	12.3	5.47	9	77.1	37.4	12	1510	284
Terminal $t_{1/2}$	day	5	4	7.45	2.94	5	7.72	1.46	6	6.48	1.01

AUC = Area under the concentration-time curve; AUC_{tau} = AUC calculated during the dosing interval; C_{max} = Peak concentration; h = Hours; N = Number of animals; SD = Standard deviation; t_{max} = Time to C_{max}; Terminal $t_{1/2}$ = Elimination half-life estimated in the recovery period * Concentrations considered to be impacted by ADAs were excluded from 5 animals in the 0.1 mg/kg group, 5 animals in the 1 mg/kg group and 3 animals in the 10 mg/kg group

Monkeys (9 or 14-week repeat-dose)

- Systemic exposure, as assessed by C_{max} and AUC_{tau}, increased proportionally with dose.
- C_{max} increased 1.8- to 3.7-fold from the first to the thirteenth dose for the 1 and 5 mg/kg dose groups, and 3.6-fold from the first to the ninth dose for the 20 mg/kg dose group, indicating accumulation of linvoseltamab.
- No significant differences were observed in total linvoseltamab concentrations in serum between males and females.
- ADAs were detected using a bridging immunoassay. An ADA response was detected in 47% of animals (9/12, 4/12, and 4/12 animals in the 1, 5, and 20 mg/kg groups, respectively) treated with linvoseltamab. However, linvoseltamab exposure was maintained in 92% (33/36) of the animals during the dosing period.
- The presence of ADAs correlated with faster elimination of linvoseltamab, specifically in the 1 mg/kg group. However, samples affected by ADAs were not excluded from TK analyses.
- The ADA response did not significantly compromise the interpretability of the study.

Type of Study	Major Findings

Table 5: FDA - Summary of Mean Toxicokinetic Parameters in the 9 or 14-Week Repeat-Dose Monkey Study

Linvoseltamab TK Parameters											
Parameter	Unit	Dose	1 mg/kg			5 mg/kg			20 mg/kg		
			N	Mean	SD	N	Mean	SD	N	Mean	SD
C_{max}	µg/mL	1	12	21.9	6.27	12	120	34.2	12	507	105
		6	12	42.3	17	12	237	131	12	975	239
		13	10	29.1	25.6	8	199	77.3	0	NC*	NC*
t_{max}	h	1	12	0.41	1.13	12	0.736	1.52	12	2.37	2.02
		6	12	1.39	1.93	12	3.71	6.68	12	1.39	1.93
		13	10	0.475	1.24	8	0.573	1.38	0	NC*	NC*
AUC_{tau}	day•(µg/mL)	1	12	78.8	28	12	394	79.9	12	1910	374
		6	12	184	111	12	930	296	12	4960	1320
		13	10	124	139	4	1200	383	0	NC*	NC*

AUC, Area under the concentration-time curve; AUC_{tau}, AUC calculated during the dosing interval; C_{max}, Peak concentration; h, Hours; N, Number of animals; NC, Not calculated; SD, Standard deviation; t_{max}, time to C_{max} Notes: For Groups 2 and 3, N = 4 animals/sex/group through Day 95, then N = 2 animals/sex/group through Day 183, with the exception of time points beyond unscheduled necropsy of 2 animals in Group 2 and 9 animals in Group 3; For Group 4, N = 4 animals/sex/group through Day 64, then N = 2 animals/sex/group through Day 154, with the exception of time points beyond unscheduled necropsy of 4 animals; * Analysis for the 9th dosing interval for 20 mg/kg IV dose group was not performed, as only C_{trough} samples were collected after the sixth dosing interval.

5.5. Toxicology

5.5.1. General Toxicology

The nonclinical safety profile of linvoseltamab was evaluated in cynomolgus monkeys utilizing a weekly IV dosing regimen consistent with the intended clinical dosing paradigm. Studies included a GLP 5-week repeat-dose toxicology study and an intended chronic (26-week) toxicology study that was ultimately shortened to 9- or 14-weeks due to decreased tolerability of the drug during prolonged treatment. In addition to the described in vivo evaluations, the ex vivo TCR of linvoseltamab to fetal and adult tissue panels from humans and monkeys was evaluated in support of the safety evaluation (see Table 6).

The toxicologic evaluation of linvoseltamab demonstrated that administration to monkeys results in a persistent and progressive inflammatory response, which limited the tolerability of the drug during prolonged treatment. While the observed inflammatory response led to secondary toxicity that limited the long-term evaluation of linvoseltamab, no other adverse direct target-organ toxicity was observed in the monkeys, consistent with the restricted expression profile of BCMA and the high affinity and specificity of linvoseltamab, which is further evidenced by the lack of unexpected/off-target cross-reactivity in the conducted ex vivo evaluations. Overall, considering that the drug-related effects noted in the nonclinical safety studies have not been observed in the clinical trials and can be effectively mitigated in clinical settings (e.g., monitoring of

inflammatory conditions), these data fully support the continued clinical evaluation and registration of linvoseltamab.

Table 6: Applicant - Summary of Linvoseltamab Toxicology Program

Study Type and Duration (Compliance)	Study Number	Species	Linvoseltamab Dose (Administration Route)	Dosing Frequency (Total Number of Doses)
Repeat-dose Toxicology Studies				
5-week toxicology study with a 12-week recovery period (GLP)	R5458-TX-17179	Cynomolgus monkey (*Macaca fascicularis*)	0, 0.1, 1, or 10 mg/kg (IV)	QW for 5 weeks (total of 5 doses)
9- or 14-week toxicology study with a 13-week recovery period (GLP)[a]	R5458-TX-20118	Cynomolgus monkey (*Macaca fascicularis*)	0, 1, 5, or 20 mg/kg (IV)	QW for 9- or 14-weeks (total of 9- or 14- doses, respectively)[a]
Other Studies				
Tissue cross-reactivity study (GLP)	R5458-TX-17162	Normal human and cynomolgus monkey tissues	2 and 10 µg/mL (ex vivo)	NA
Tissue cross-reactivity study (GLP)	R5458-TX-21227	Selected fetal human and cynomolgus monkey tissues	2 and 5 µg/mL (ex vivo)	NA

[a] This study was initially intended to evaluate the safety profile of linvoseltamab when administered QW for 26 weeks. However, due to declining clinical condition that necessitated early euthanasia of a number of animals across dose groups for animal welfare reasons, the study protocol was amended, and the study was stopped after 9 (20 mg/kg group) or 14 (1 and 5 mg/kg groups) weeks.
Source: Module 2.6.6 Toxicology Written Summary Table 1

The FDA's Assessment:

The FDA agrees with the Applicant's overall assessment of the general toxicology studies; however, the review below provides additional information and some clarifications regarding the data presented by the Applicant. A detailed review of the 5-week and 9/14-week general toxicology studies are included.

General toxicology studies with linvoseltamab were conducted in cynomolgus monkeys based on the results of in vitro binding and functional activity studies. Linvoseltamab does not bind BCMA in rodents. General toxicology studies in rodents would not provide meaningful information and are not warranted to support a BLA.

Study title / Study number: REGN5458: A 5-Week Intravenous Infusion Toxicity and Toxicokinetic Study in Cynomolgus Monkeys With a 12-Week Dose-Free Recovery Phase / R5458-TX-17179

Key Study Findings

- Clinical observations were limited to emesis/vomitus (associated with mildly elevated CRP and cytokines), and red or liquid feces.
- Findings consistent with the expected pharmacology of linvoseltamab included changes in circulating lymphocytes, clinical pathology changes indicative of an inflammatory response, microscopic changes including decreased B-cell lineage lymphocyte populations, and microscopic inflammatory infiltrates.
- Linvoseltamab-related increases in heart rates were observed at 10 mg/kg in females at the end of dosing and in one male at 10 mg/kg at the end of recovery with no microscopic correlates.
- The HNSTD was 10 mg/kg corresponding to a C_{max} of 370 µg/mL and AUC_{0-t} of 1510 µg*day/mL. The linvoseltamab half-life ranged from 6.5 to 7.7 days.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (control), 0.1, 1, or 10 mg/kg/dose Once weekly for 5 weeks (Days 1, 8, 15, 22, and 29) A 12-week recovery phase was included at the end of the last dosing cycle
Route of administration:	IV infusion (30 minutes)
Formulation/Vehicle:	(b)(4) mM Histidine pH 6.0, (b)(4)% sucrose, and (b)(4)% polysorbate 80
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	6/sex/group
Age:	31 to 49 months old
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Fecal and vomitus abnormalities incidence was higher in 1 and 10 mg/kg monkeys during the dosing phase. The incidence decreased during the recovery phase except for 10 mg/kg monkeys. Numerous veterinary interventions occurred during the study to control GI disruption, dehydration and to provide extra food supplements. Scabs were present in various locations on the body for several monkeys at all dose levels during the dosing and recovery phases with uncertain relationship to linvoseltamab.
Body Weights	No linvoseltamab-related alterations in body weight or body weight gain occurred during the dosing or recovery phases.
Food Consumption	Low qualitative food consumption was noted in 10 mg/kg male monkeys with no correlating effect on body weights.
Ophthalmoscopy	Unremarkable
Physical Examinations, Vital Signs, Blood Pressure	No linvoseltamab-related abnormalities were noted during the physical examinations, assessment of vital signs, or blood pressure measurements.

<table>
<tr><td>ECG</td><td>On Day 29, females at 10 mg/kg presented 25% higher mean heart rates without statistical significance (+25 bpm) with a single female presenting an increase of +75 bpm (+63%) compared to controls. On Day 81 of the recovery phase, males at 10 mg/kg presented 20% higher mean heart rates without statistical significance (+21 bpm) with a single male presenting an increase of +91 bpm (+123%) compared to controls. These higher rates were considered linvoseltamab-related based on the magnitude of differences with controls. No linvoseltamab-related changes in PR interval, QRS duration, QT interval, corrected QT (QTc) interval or abnormal ECG waveforms or arrhythmias were observed during the dosing phase or recovery phase in any dose group compared to control.</td></tr>
<tr><td>Body Temperature</td><td>Unremarkable</td></tr>
<tr><td>Neurological Examinations</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Linvoseltamab-related decreases in erythrocytes, hemoglobin, hematocrit, and lymphocyte counts, and increases in fibrinogen and monocyte and LUC counts, were observed in males and/or females at the end of the dosing phase. Decreased lymphocyte counts correlated with decreased lymphocyte cellularity, noted microscopically in the thymus and germinal centers of the spleen. The increases in fibrinogen and monocyte and LUC counts may have been associated with increased inflammatory cell infiltrates, noted microscopically in various tissues.

All hematology changes were reversible by the end of the recovery phase.

Table 7: FDA - Linvoseltamab-Related Hematology Changes (% Change from Control) - Terminal
<table>
<tr><th rowspan="2">Parameter</th><th colspan="6">Linvoseltamab (mg/kg)</th></tr>
<tr><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><th>0.1</th><th>1</th><th>10</th><th>0.1</th><th>1</th><th>10</th></tr>
<tr><td>Erythrocytes</td><td>-1%</td><td>-6%</td><td>-4%</td><td>-8%</td><td>-16%</td><td>-15%</td></tr>
<tr><td>Hematocrit</td><td>0%</td><td>0%</td><td>-9%</td><td>-8%</td><td>-17%</td><td>-19%</td></tr>
<tr><td>Hemoglobin</td><td>2%</td><td>1%</td><td>-9%</td><td>-3%</td><td>-14%</td><td>-17%</td></tr>
<tr><td>Basophils</td><td>78%</td><td>233%</td><td>44%</td><td>-33%</td><td>-20%</td><td>-47%</td></tr>
<tr><td>Eosinophils</td><td>35%</td><td>153%</td><td>371%</td><td>-14%</td><td>14%</td><td>103%</td></tr>
<tr><td>Large Unstained Cells</td><td>47%</td><td>207%</td><td>293%</td><td>7%</td><td>97%</td><td>28%</td></tr>
<tr><td>Leukocytes</td><td>61%</td><td>74%</td><td>26%</td><td>-10%</td><td>-24%</td><td>-50%</td></tr>
<tr><td>Lymphocytes</td><td>61%</td><td>108%</td><td>-47%</td><td>-36%</td><td>-55%</td><td>-74%</td></tr>
<tr><td>Monocytes</td><td>30%</td><td>11%</td><td>106%</td><td>-27%</td><td>-8%</td><td>-4%</td></tr>
<tr><td>Neutrophils</td><td>65%</td><td>23%</td><td>114%</td><td>9%</td><td>-4%</td><td>-37%</td></tr>
<tr><td>Platelets</td><td>48%</td><td>0%</td><td>-22%</td><td>22%</td><td>-3%</td><td>3%</td></tr>
<tr><td>Reticulocytes</td><td>54%</td><td>96%</td><td>101%</td><td>-12%</td><td>11%</td><td>-11%</td></tr>
</table></td></tr>
</table>

	Fibrinogen	4%	10%	31%	7%	14%	56%
Bone Marrow Smear Evaluation	At terminal sacrifice females in the 10 mg/kg dose group showed linvoseltamab-related minimally higher total myeloid cell count (percent and absolute) and minimally higher myeloid to erythrocyte ratio. This suggests an increase of inflammatory cell infiltrates, noted microscopically in various tissues but reversible by the end of recovery.						
Immunophenotyping	Linvoseltamab-related statistically significant and dose-proportional decreases in lymphocytes, monocytes, and white blood cells were generally noted at 24 hours postdose on Day 1 at all dose levels. Lymphocyte decreases were also evident at 96 hours postdose on Day 1 and on Day 36, the end of dosing. Values were similar to control during recovery. Statistically significant decreases in mean absolute numbers of total T-cells, helper T-cells, and cytotoxic T-cells were noted at all dose levels on Day 1 at 24 hours postdose and remained decreased at 96 and 168 hours postdose on Day 1, and 24 hours postdose on Day 22. Linvoseltamab-related marked and generally statistically significant, but non-dose-proportional, decreases in mean absolute numbers and relative proportions of total B-cells, plasma cells, NK cells, and monocytes were noted at 24 or 96 hours postdose on Day 1.						
Clinical Chemistry	Linvoseltamab-related decreases in albumin and globulin appeared similar in proportion because the albumin:globulin ratio was unaffected. Decreased serum proteins may have reflected protein loss via the GI tract as fecal abnormalities were prevalent clinical signs. Decreased calcium was likely related to decreased albumin (decreased protein-bound fraction of calcium). All findings were resolved by the end of recovery except decreased albumin in 10 mg/kg males and 1 mg/kg females which exhibited partial recovery. Linvoseltamab-related elevations in CRP reflected an inflammatory/acute phase response and were likely related to increased inflammatory cell infiltrates, noted microscopically in various tissues. Decreased albumin persisted in select animals at the end of the recovery phase; all other clinical chemistry changes were fully reversible by the end of the recovery phase. **Table 8: FDA - Linvoseltamab-Related Clinical Chemistry Changes (% Change from Control) - Terminal**						

Parameter	Linvoseltamab mg/kg					
	Males			Females		
	0.1	1	10	0.1	1	10
Albumin/Globulin	12%	0%	-7%	2%	5%	-7%
Albumin	-2%	-2%	-27%	2%	-13%	-17%
Globulin	-12%	-10%	-23%	-9%	-25%	-22%

	Protein	-6%	-5%	-25%	-2%	-18%	-19%
	C Reactive Protein	71%	171%	1929%	-11%	1244%	3056%
	Calcium	5%	8%	-8%	2%	-4%	-5%
	Triglycerides	-8%	39%	120%	-5%	125%	183%
	Urea Nitrogen	-13%	-7%	-12%	12%	-2%	-8%
Urinalysis	Unremarkable						
Gross Pathology	At terminal sacrifice, linvoseltamab-related large spleen was observed in a 10 mg/kg male that corresponded with increased lymphocyte cellularity in the white pulp, and large mandibular lymph node was observed in a 10 mg/kg female that corresponded with increased lymphocyte cellularity of the paracortex. Scabbing of the skin/subcutis in various body locations was observed in a 10 mg/kg female that corresponded with serocellular crusts associated with an underlying ulcer. At recovery sacrifice, linvoseltamab-related rough surface of the spleen was noted in a 10 mg/kg female that corresponded with increased lymphocyte cellularity of the follicles. Scabs with corresponding microscopic findings were present in ≥0.1 mg/kg females and in a 1 mg/kg male.						
Organ Weights	Linvoseltamab-related increased spleen weights were observed at ≥0.1 mg/kg in both sexes that generally corresponded with microscopic findings of increased cellularity of lymphocytes in the follicles/PALs and increased CD3 staining. These findings were still present after recovery in ≥0.1 mg/kg males and in 10 mg/kg females. Linvoseltamab-related decrease in thymus weight was observed at 10 mg/kg in both sexes that generally corresponded with microscopic findings of decreased lymphocyte cellularity and decreased CD3 staining of the thymus cortex and/or decreased CD20 staining of the thymus medulla. At the recovery sacrifice, decreased thymus weights were present in ≥0.1 mg/kg males and corresponded with decreased cellularity of the cortex in 10 mg/kg males. Thyroid/parathyroid weight was decreased in ≥0.1 mg/kg males at terminal sacrifice with no microscopic correlates. These findings were also present in males at recovery sacrifice. The relation to linvoseltamab administration is uncertain. **Table 9: FDA - Linvoseltamab-Related Organ Weight Changes (% Change from Control) - Terminal**						

Organ/Tissue	Linvoseltamab (mg/kg)					
	Males			Females		
	0.1	1	10	0.1	1	10
Thyroid/Parathyroid	-13%	-48%	-25%	3%	2%	15%
Spleen	17%	34%	241%	53%	144%	77%
Thymus	17%	22%	-58%	-14%	28%	-45%

Histopathology

Linvoseltamab target organs of toxicity included the spleen, thymus, mesenteric and mandibular lymph nodes, bone marrow, urinary bladder and GALT/Peyer's patch. Increased cellularity was shown in the bone marrow with an increase in CD3 and decrease in CD20 staining. Linvoseltamab also induced inflammation as observed by the increased inflammatory cell infiltrates in various tissues across all dose groups. Cellular inflammation was also observed in the submucosa of the GI tract and urinary bladder. These findings were generally reversible at the end of the recovery phase.

Table 10: FDA - Linvoseltamab-Related Histopathology Changes - Terminal

Organ/Tissue	Finding	Severity	Linvoseltamab (mg/kg)							
			Males				Females			
			0	0.1	1	10	0	0.1	1	10
Spleen		# Animals	3	3	3	3	3	3	3	3
	CD138 staining, decreased	Mild		1				1		
		Moderate				3		1	2	3
		Total		1		3		2	2	3
	CD20 staining, decreased, follicle/red pulp	Minimal							1	2
		Mild				2				1
		Moderate				1				
		Total				3			1	3
	CD3 staining, increased, follicle/PALs	Minimal						2		1
		Mild				2			3	1
		Moderate				1				1
		Total				3		2	3	3
	Cellularity, decreased, lymphocyte, germinal center	Minimal				3		1		
		Mild	1						1	1
		Moderate		1						
		Total	1	1		3		1	1	1
	Cellularity, increased, lymphocyte, white pulp	Minimal			2	1		2		1
		Mild							2	1
		Moderate				2			1	1
		Total			2	3		2	3	3
Bone marrow, sternum		# Animals	3	3	3	3	3	3	3	3
	CD20 staining, decreased	Minimal						1	1	
		Mild							2	
		Moderate				3				3
		Total				3		1	3	3
	CD3 staining, increased	Minimal			1	3			2	2
		Total			1	3			2	2

		Cellularity, increased	Minimal			2	2			3	
			Mild								1
			Total			2	2			3	1
		Lymphoid nodule	Minimal							1	1
			Total							1	1
	Thymus		**# Animals**	3	3	3	3	3	3	3	3
		CD138 staining, decreased	Mild		2	1				2	
			Moderate			1	2		1	1	2
			Total		2	2	2		1	3	2
		CD20 staining, decreased, medulla	Mild								1
			Moderate				1				1
			Marked								1
			Total				1				3
		CD3 staining, decreased, cortex	Mild				1			1	
			Moderate				1			1	
			Marked								1
			Total				2			2	1
		Cellularity, decreased, lymphocyte	Minimal								1
			Mild							1	
			Moderate				2			1	
			Marked								1
			Total				2			2	2
	Lymph node, mandibular		**# Animals**	3	3	3	3	3	3	3	3
		Cellularity, decreased, lymphocyte, germinal center	Minimal						1		
			Mild		1		1			3	
			Moderate				2				3
			Total		1		3		1	3	3
		Cellularity, increased, paracortex	Minimal							1	1
			Total							1	1
		Infiltrate, neutrophils, increased	Mild							1	
			Total							1	
		Normal		3	2	3		3	2		
			Total	3	2	3		3	2		
	Urinary bladder		**# Animals**	3	3	3	3	3	3	3	3
		Infiltrate, eosinophils, increased	Minimal				1				
			Total				1				
		Infiltrate, mononuclear cell	Minimal					1			
			Total					1			
		Inflammation, mixed cell	Minimal				1				
			Mild								1
			Total				1				1

		Normal		3	3	3	1	2	3	3	2
			Total	3	3	3	1	2	3	3	2

Cytokine Analysis	Linvoseltamab-related transient increases in IFNγ, IL-2, IL-6, IL-10, and IL-15 were generally present at 4 hours postdose on Day 1 at ≥1 mg/kg in both sexes. No increases in TNFα were observed. The increases generally resolved by 24 hours postdose. There were generally no increases in cytokines after dosing on Days 8, 15, 22, or 29, or during the recovery phase.
Toxicokinetics	The TK information is presented and discussed in the ADME/PK section.
Anti-Drug Antibodies	The ADA information is presented and discussed in the ADME/PK section.

Study title / Study number: REGN5458: A 9 or 14-Week Intravenous Injection Toxicity and Toxicokinetic Study in Sexually Mature Cynomolgus Monkeys with a 13-Week Recovery Phase (GLP) / R5458-TX-20118

Key Study Findings

- A generalized and progressive inflammatory response was observed after repeated dosing, which is consistent with the expected pharmacologic activity of linvoseltamab. Associated deteriorating clinical conditions prompted the unscheduled sacrifice of some animals and the premature termination of dosing for surviving animals during Week 9 for the 20 mg/kg group and during Week 14 for the 1 and 5 mg/kg groups.
- Clinical observations included weight loss, decreased activity, inappetence, emesis, and liquid feces.
- Evidence of linvoseltamab-related immune system activation included elevations in CRP and plasma cytokines (IL-2, IL-6, and MCP), immunophenotyping changes, and multi-organ inflammatory infiltrates.
- Positive bacteria cultures were obtained from blood and tissue swabs in early sacrificed animals, but a correlation between infection due to decrease B-cells and plasma cells could not be determined.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (control), 1, 5, or 20 mg/kg/dose Once weekly for 14 weeks (0, 1, and 5 mg/kg groups) Once weekly for 9 weeks (20 mg/kg group) A 13-week recovery period was included at the end of the last dosing cycle
Route of administration:	IV injection (slow bolus)
Formulation/Vehicle:	(b)(4) mM Histidine pH 6.0, (b)(4) % sucrose, and (b)(4) % polysorbate 80
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	6/sex/group
Age:	5 to 10 years old

Deviation from study protocol affecting interpretation of results:	None
Comment on study design	The study was initially scheduled as a 26-week repeat-dose IV injection toxicity and toxicokinetic study. However, the protocol was amended because the animals were showing weight loss and declining body conditions across all dose groups compared to control, but more severely in the 20 mg/kg group. Consequently, a decision was made to prematurely euthanize animals for humane reasons. The last dose of the 20 mg/kg group was administered during Week 9, and the terminal and recovery necropsies for this group were conducted on Day 64 and Day 154, respectively. Dosing for groups administered 1 and 5 mg/kg were terminated at Week 14, and the terminal and recovery necropsies for these groups were conducted on Day 95 and Day 183, respectively.

Observations and Results: changes from control

Parameters	Major findings
Mortality	Unscheduled euthanasia was conducted due to significant weight loss. The following linvoseltamab-related findings were observed in these animals: • Microscopic findings, including multi-organ inflammatory infiltrates. • Bacteria growth from tissue swabs (thorax and abdomen) or blood samples. • Macroscopic findings, including adhesion of several tissues in the abdominal cavity, fluid retention, liver discoloration, enlarged spleen and thickness and discoloration of lungs, heart, pericardium and diaphragm. **Table 11: FDA - Unscheduled Deaths**

Moribund Sacrifice			
Dose	**Males**	**Females**	**Total**
1 mg/kg	1	1	2
5 mg/kg	4	5	9
20 mg/kg	1	3	4

Body Weights	Linvoseltamab-related decreases in body weights were observed in both males and females across all dosed groups with a maximum decrease of 30% compared to control. **Table 12: FDA - Linvoseltamab-Related Body Weight Changes (% Change from Control) - Terminal**

Linvoseltamab (mg/kg)	
Males	**Females**

<table>
<tr><td></td><td>
<table>
<tr><th>1</th><th>5</th><th>20</th><th>1</th><th>5</th><th>20</th></tr>
<tr><td>-13%</td><td>-18%</td><td>-11%</td><td>-20%</td><td>-26%</td><td>-30%</td></tr>
</table>
Terminal body weight % change from control has been combined in a single row to represent animals terminated at Day 64 (20 mg/kg group) and the animals terminated at Day 95 (0, 1, and 5 mg/kg groups)
</td></tr>
<tr><td>Food Consumption</td><td>Inappetence was observed across all dose groups and correlated with decreases in body weight. Quantitative food consumption values were not provided.</td></tr>
<tr><td>Ophthalmoscopy</td><td>Not conducted during the dosing phase due to unscheduled deaths. Unremarkable during the recovery phase.</td></tr>
<tr><td>Physical Examinations</td><td>Besides the decline in body condition there were no linvoseltamab-related changes on physical examination parameters.</td></tr>
<tr><td>ECG</td><td>Not conducted during the dosing phase due to unscheduled deaths. Unremarkable during the recovery phase.</td></tr>
<tr><td>Blood Pressure</td><td>There were no linvoseltamab-related effects on blood pressure in the 1 mg/kg dose group. Due to the unscheduled deaths, linvoseltamab-related effects on blood pressure in the 5 mg/kg and 20 mg/kg dose groups were undetermined.</td></tr>
<tr><td>Respiratory Rate</td><td>There were no linvoseltamab-related effects on respiratory rate in the 1 mg/kg dose group. Due to the unscheduled deaths, linvoseltamab-related effects on respiratory rate in the 5 mg/kg and 20 mg/kg dose groups were undetermined.</td></tr>
<tr><td>Arterial Blood Gas</td><td>Linvoseltamab-related changes were noted in the female animals in the 5 mg/kg dose group. Increases in carbon dioxide and bicarbonate concentrations were observed at Week 13. These findings were partially reversible at the end of the recovery phase.</td></tr>
<tr><td>Neurological Examinations</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Dose-related decreases in erythrocytes, hemoglobin, and hematocrit were observed in males and females at the end of the dosing phase. These decreases in red blood cell mass along with the variable reticulocyte response (data not shown) were suggestive of hemorrhage and reduced or ineffective erythropoiesis. Considerable inter-animal variation in lymphocyte and neutrophil counts were observed during the dosing phase and may have been related to ongoing inflammatory processes. Only changes in lymphocyte counts persisted at the end of the recovery phase.
Table 13: FDA - Linvoseltamab-Related Hematology Changes (% Change from Control) - Terminal
<table>
<tr><th rowspan="3">Parameter</th><th colspan="6">Linvoseltamab (mg/kg)</th></tr>
<tr><th colspan="3">Male</th><th colspan="3">Female</th></tr>
<tr><th>1</th><th>5</th><th>20</th><th>1</th><th>5</th><th>20</th></tr>
<tr><td>Erythrocytes</td><td>-13.6%</td><td>-12.2%</td><td>-17.4%</td><td>-7.2%</td><td>-13.1%</td><td>-30.7%</td></tr>
<tr><td>Hemoglobin</td><td>-15.3%</td><td>-16.8%</td><td>-20.3%</td><td>-4.0%</td><td>-20.8%</td><td>-38.0%</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>Hematocrit</td><td>-14.5%</td><td>-14.5%</td><td>-17.3%</td><td>-4.9%</td><td>-19.5%</td><td>-35.2%</td></tr><tr><td>Neutrophils</td><td>-4.2%</td><td>57.4%</td><td>177.0%</td><td>0.2%</td><td>-5.2%</td><td>107.5%</td></tr><tr><td>Lymphocytes</td><td>19.0%</td><td>69.7%</td><td>-10.2%</td><td>53.8%</td><td>-51.9%</td><td>-62.0%</td></tr></table> Terminal hematology % change from control has been combined in a single table to represent animals terminated at Day 64 (20 mg/kg group) and the animals terminated at Day 95 (0, 1, and 5 mg/kg groups)
Clinical Chemistry	Increases in alkaline phosphatase (ALP), CRP, and triglycerides were observed at ≥1 mg/kg during the dosing phase. The increase in CRP is consistent with an ongoing inflammatory/acute phase response and correlates with increases in cytokines. There was complete recovery of ALP and triglycerides, but there was only partial recovery of CRP. The decreases in albumin and globulin, and corresponding decrease in total protein, may reflect the overall poor clinical condition of the animals. Partial to full recovery of albumin, globulin, and total protein was observed. **Table 14: FDA - Linvoseltamab-Related Clinical Chemistry Changes (% Change from Control) - Terminal** <table><tr><th rowspan="3">Parameter</th><th colspan="6">Linvoseltamab (mg/kg)</th></tr><tr><th colspan="3">Male</th><th colspan="3">Female</th></tr><tr><th>1</th><th>5</th><th>20</th><th>1</th><th>5</th><th>20</th></tr><tr><td>Alkaline Phosphatase</td><td>207.5%</td><td>371.3%</td><td>1123.4%</td><td>0.0%</td><td>160.6%</td><td>878.8%</td></tr><tr><td>Albumin</td><td>-21.4%</td><td>-26.2%</td><td>-31.8%</td><td>-7.7%</td><td>-25.6%</td><td>-38.5%</td></tr><tr><td>Globulin</td><td>-27.6%</td><td>-37.9%</td><td>-25.0%</td><td>-16.1%</td><td>-35.5%</td><td>-17.2%</td></tr><tr><td>Total protein</td><td>-25.0%</td><td>-30.6%</td><td>-28.9%</td><td>-11.6%</td><td>-29.0%</td><td>-29.4%</td></tr><tr><td>C Reactive Protein (increased)#</td><td>4/5</td><td>2/3</td><td>5/5</td><td>0/5</td><td>1/1</td><td>5/5</td></tr><tr><td>Triglycerides</td><td>73.3%</td><td>53.3%</td><td>88.9%</td><td>18.6%</td><td>39.5%</td><td>165.6%</td></tr></table> Terminal clinical chemistry % change from control has been combined in a single table to represent animals terminated at Day 64 (20 mg/kg group) and the animals terminated at Day 95 (0, 1, and 5 mg/kg groups); # number of animals with finding out of the number of animals examined
Urinalysis	Unremarkable
Immunophenotyping	Linvoseltamab-related changes during the dosing phase included decreases in the absolute count of total T-cells, T-helper cells, and T-cytotoxic cells in the peripheral blood. There were also decreases in absolute counts of total B-cells in the peripheral blood and bone marrow. The decreases in T-cells are consistent with the observed multi-organ infiltrates while the decreases in B-cells are consistent with expected pharmacologic activity of linvoseltamab. Partial to full recovery of all immunophenotyping changes were observed at the end of the recovery phase. A definitive assessment of the impact of linvoseltamab on plasma cells could not be determined due to the low frequency of this cell population.

<table>
<tr><td>Gross Pathology</td><td>Macroscopic findings observed in the 20 mg/kg dose group included capsular thickening and pale discoloration of the spleen, adhesion/discoloration of the liver, adhesion of the lungs, and fluid in the abdominal cavity. One male also displayed a mass in the abdominal skin (umbilical hernia) that histologically correlated with inflammation in the skin and peritoneum. Increased spleen size was observed in one animal in the 5 mg/kg dose group. Partial recovery of these changes was observed at the end of the recovery phase; however, two males in the 20 mg/kg dose group had adhesion, discoloration, and rough surface in the liver that correlated with inflammatory changes.</td></tr>
<tr><td>Organ Weights</td><td>Linvoseltamab-related organ weight changes in the 20 mg/kg dose group include increased liver and kidney weights in two males, and increased spleen weight in three males and three females. Increased spleen weight was also observed in one animal in each the 1 and 5 mg/kg dose groups. The increased spleen weights correlated microscopically with increased cellularity. The organ weights were generally comparable to control by the end of the recovery phase; however, increased spleen weight persisted at the end of the recovery phase.</td></tr>
<tr><td>Histopathology</td><td>Table 15: FDA - Summary of Histopathology Findings - Terminal
<table>
<tr><th colspan="3">Terminal</th></tr>
<tr><th>Dose (mg/kg)</th><th>Time Point</th><th>Findings</th></tr>
<tr><td>Control, 1 and 5</td><td>Day 95</td><td>Peritonitis in the intestines and kidneys.

Generalized inflammation of parenchymal cells in liver, gallbladder, kidneys, heart, and skeletal muscle.

Increased cellularity and extramedullary hematopoiesis in the bone marrow, spleen, and lymph nodes.</td></tr>
<tr><td>20</td><td>Day 64</td><td>Peritonitis in the stomach, intestines, liver, kidneys, spleen, pancreas, mesenteric lymph node, testes, uterus, cervix, and urinary bladder.

Pleuritis in the lungs, heart, and aorta. Generalized inflammation of the parenchymal cells in the liver, gallbladder, kidneys, spleen, heart, skeletal muscle, and skin.

Increased cellularity and extramedullary hematopoiesis in the in the bone marrow, spleen, lymph nodes, GALT, adrenal glands, heart, and kidneys.</td></tr>
</table>
Table 16: FDA - Summary of Histopathology Findings - Recovery
<table>
<tr><th colspan="3">Recovery</th></tr>
<tr><th>Dose (mg/kg)</th><th>Time Point</th><th>Findings</th></tr>
<tr><td>Control, 1 and 5</td><td>Day 183</td><td>Peritonitis in stomach and intestines.

Generalized inflammation of parenchymal cells in liver, gallbladder, and kidneys.

Increased cellularity in the spleen.</td></tr>
</table></td></tr>
</table>

	20	Day 154	Peritonitis in the stomach, intestines, and heart. Pleuritis in the lungs. Generalized inflammation of parenchymal cells in liver, gallbladder, kidneys, and skeletal muscle. Increased cellularity in bone marrow, spleen, and lymph nodes.
Cytokines	Linvoseltamab-related increases in the cytokines IL-2, IL-6, and MCP-1 were observed 4 hours after treatment on Day 1, with the highest increases in the 20 mg/kg dose group. Only the increase in IL-6 was dose-dependent. Slight elevations in IL-6 and MCP-1 persisted through Day 92. Levels of all cytokines returned to baseline by the end of the recovery phase.		
Special Evaluation	**Table 17: FDA - Immunohistochemistry on Histopathology Examination Findings**		

Immunohistochemistry on Histopathology Examination		
Target	**Cell Type**	**Findings**
Bone marrow (sternal/femoral)	↑ CD4, CD8, or CD20	Increased bone marrow cellularity
Spleen	↑ CD4 or CD8	Increased cellularity of the red/white pulp
Mesenteric lymph node	↑ CD8	Increase cellularity of the follicles/medulla
Stomach, esophagus, intestines, urinary bladder, uterus, peritoneum, heart, and lungs	↑ CD4, CD8, CD20, or CD68	Inflammatory lesions with fibroplasia in the serosa and submucosa
Kidneys and liver	↑ CD4, CD8, CD20, or CD68	Sinusoidal/perivascular mixed inflammatory cell infiltration in the liver and interstitial mononuclear cell infiltration and capsular fibroplasia in the kidneys

Toxicokinetics	The TK information is presented and discussed in the ADME/PK section.
Anti-Drug Antibodies	The ADA information is presented and discussed in the ADME/PK section.

5.5.2. Genetic Toxicology

The Applicant's Position:

According to the ICH Guideline (ICH, 2012), the standard genotoxicity studies routinely conducted for small-molecule pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals. Antibodies, such as linvoseltamab, are not expected to interact directly with DNA or other chromosomal material. Therefore, no genotoxicity studies were conducted with linvoseltamab.

The FDA's Assessment:

The FDA agrees.

5.5.3. Carcinogenicity

The Applicant's Position:

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 (ICH, 2009).

The FDA's Assessment:
The FDA agrees.

5.5.4. Reproductive and Developmental Toxicology

Embryo-fetal developmental toxicology studies with linvoseltamab were not conducted as such studies are expected to have limited value in communicating risks to patients with MM diagnosis where the median age of diagnosis is ~70 years. In lieu of conducting additional in vivo studies to assess reproductive toxicology risk, a weight-of-evidence review of potential hazards associated with targeting both BCMA-expressing B cells and plasma cells and CD3 has been completed.

Briefly, review of the literature suggests that BCMA-expressing cells are dispensable for normal pregnancy and embryo-fetal development including normal lymphoid tissue development (Xu, 2001), and published reports on several marketed B-cell modulating drugs showed no adverse effects in preclinical embryo-fetal developmental or pre- and postnatal developmental toxicology studies (Auyeung-Kim, 2009) (Vaidyanathan, 2011). Therefore, while linvoseltamab exposure during pregnancy may result in fetal B-cell and plasma-cell cytopenias based on its mechanism of action, due to limited BCMA expression in the embryo or fetus the risk of associated lymphopenias is low.

The FDA's Assessment:
The FDA agrees with the Applicant's WOE-based approach for the assessment of reproductive and developmental toxicity. There is no BCMA gene or protein expression in human reproductive organs; therefore, the risk of on-target/off-tumor toxicity in these tissues is relatively low. Linvoseltamab causes T-cell activation that could result in cytokine release syndrome (CRS) in humans. The WOE risk assessment referenced published literature supporting that CRS can cause adverse pregnancy outcomes, specifically by disrupting the regulation of inflammatory signals during the establishment of pregnancy, pregnancy maintenance, and parturition. The WOE risk assessment also referred to published literature that showed a reduction of B-cells does not appear to affect preclinical embryo-fetal development or pre- and postnatal development.

Linvoseltamab is an IgG4-based bispecific antibody and may be present in milk; a breastfed child may be exposed to linvoseltamab via lactational transfer.

The approval of BLA 761400 does not rely on product-specific published literature.

5.5.5. Other Toxicology Studies

Tissue Cross-Reactivity

In 2 GLP TCR studies (Table 6), linvoseltamab was applied to cryosections from panels of normal human and cynomolgus monkey tissues and selected fetal human and cynomolgus monkey tissues. The demonstrated specific reactivity of linvoseltamab with the positive control material and the lack of specific reactivity with the negative control material, as well as the lack of reactivity of the control article, indicated that the assays were sensitive, specific, and reproducible.

Across 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.

Immunotoxicology

Parameters to evaluate the potential for any drug-related effects on the immune system were incorporated into the repeat-dose toxicology studies conducted in monkeys. Consistent with its intended pharmacology, administration of linvoseltamab resulted in reversible reductions in B cells and elimination of plasma cells in peripheral blood, bone marrow, and lymphoid organs (mesenteric lymph node, spleen, and/or GI tract). In addition, likely corresponding with pharmacologic activity and/or the observed inflammatory response, reversible and non-adverse decreases in absolute T-cell numbers were observed.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the other toxicology studies. The FDA notes the linvoseltamab staining profiles of human and cynomolgus monkey tissues were generally comparable.

X X

Liz Garcia-Peterson, PhD
Primary Reviewer

Michael Manning, PhD
Secondary Reviewer

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:
Linvoseltamab is a bispecific T-cell engaging antibody that binds to the CD3 receptor expressed on the surface of T-cells and B-cell-maturation antigen (BCMA) expressed on the surface of multiple myeloma cells, 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 target cell, resulting in T-cell activation and generation of a polyclonal cytotoxic T-cell response. This leads to redirected lysis of the targeted cells, including malignant multiple myeloma B-lineage cells. The Applicant is seeking approval of linvoseltamab for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) (b) (4)

The proposed dosage regimen is shown in **Table 18** below (hereafter referred as 5/25/200 mg).

Table 18: FDA - Linvoseltamab Dosing Schedule

Dosing Schedule	Day[a]	Linvoseltamab Dose	Duration of Infusion	
Step-up Dosing Schedule	Day 1	Step-up dose 1	5 mg	4 hours
	Day 8	Step-up dose 2	25 mg	
	Day 15	First treatment dose	200 mg	
Weekly Dosing Schedule	One week after Day 15 treatment dose and once weekly from Week 4 to Week 13 for 10 treatment doses	Second and subsequent treatment doses	200 mg	1 hour for the second treatment dose, and 30 minutes for subsequent doses[b]
Biweekly (Every 2 Weeks) Dosing Schedule	Week 14 and every 2 weeks thereafter	Subsequent treatment doses	200 mg	30 minutes
Patients who have achieved and maintained VGPR or better and received at least 16 doses of 200 mg				
Every 4 Weeks Dosing Schedule	At Week 24 or after and every 4 weeks thereafter		200 mg	30 minutes

[a] Weekly doses should be at least 5 days apart.
[b] For patients who experienced CRS with the previous dose of linvoseltamab, the duration of infusion should be maintained at the duration of the previous infusion; reduce the duration of infusion sequentially in subsequent doses in patients who do not experience CRS (e.g., 4 hours, 1 hour, then 30 minutes).

Source: Table 1 of the revised Linvoseltamab labeling by FDA.

The efficacy of linvoseltamab was evaluated in patients with RRMM in Study R5458-ONC-1826 (Study 1826). Efficacy was established based on objective response rate (ORR) of 70% (95% CI: 60-78) following the proposed 5/25/200 mg dosage regimen. The key review issues are focused on the evaluation of dose selection, recommendations for restarting therapy after dose delay, and drug-drug interaction (DDI) due to cytokine release. The key review issues with specific recommendations/ comments are summarized below in **Table 19.**

Table 19: FDA – Key Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of efficacy comes from the clinical study Study 1826. The proposed dosage regimen (5/25/200 mg) is supported by the ORR of 70% (95% CI: 60-78%).
General dosing instructions	The proposed dosage regimen (5/25/200 mg) is selected with the following rationale: • The step-up dosing schedule of 5/25 mg helps to mitigate cytokine release syndrome (CRS) risk in the subsequent full therapeutic doses. • The incidence of any Grade and Grade ≥2 CRS decreased with each subsequent step-up dose. • There was no trend for any Grade or Grade ≥2 CRS across soluble BCMA (sBCMA) quartiles. • Efficacy and the pharmacodynamic (PD) marker sBCMA appeared to reach a plateau at dose levels 200 mg every week (QW) and above • The proposed dosage regimen demonstrated clinically meaningful ORR and an acceptable safety profile in patients enrolled in study 1826. • Responses were maintained or improved following the treatment dose when it was transitioned from QW to every 2 weeks (Q2W), and then to every 4 weeks (Q4W) dosing intervals in patients who achieved and maintained VGPR or better at or after Week 24, which provided the supportive evidence of efficacy of the proposed dosage regimen. • Multivariate dose-response analysis did not identify any efficacy or safety concerns with the proposed 5/25/200 mg dosage in patients with RRMM.
Dosage recommendations for restarting therapy after dose delay	The proposed dosage recommendation for restarting therapy after dose delay mitigate CRS risk and is supported by: • No increase in the risk of CRS following dose delays shorter than the proposed cut-offs for re-priming for all but one dose delay scenario, which is supported by PK-based criterion. • Based on the totality of data including population pharmacokinetic (popPK) simulation, clinical data, and labeling recommendations on

	premedication treatment, the proposed recommendations for restarting therapy after a dose delay are acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	There is no dose adjustment recommended for subpopulations based on age, body weight, sex, race (White [n=205], Black or African American [n=44], or Asian [n=18]), ethnicity (Hispanic or Latino [n=22], not Hispanic or Latino [n=251]), mild to moderate renal impairment, or mild hepatic impairment in patients with RRMM.
Drug-drug interactions	• Linvoseltamab administration resulted in the transient release of cytokines, which may suppress cytochrome P450 (CYP) enzymes and increase concomitant drug concentrations. Increased exposure of CYP450 substrates is most likely to occur from initiation of the linvoseltamab step-up dosing schedule up to 14 days after the first 200 mg dose, and during and after CRS. • Monitor for toxicity of drugs that are CYP450 substrates where minimal concentration changes may lead to serious adverse reactions.
Immunogenicity •	Anti-linvoseltamab antibodies (ADA) were developed in 1% (2/192) of patients treated with linvoseltamab.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement with the FDA-recommended revisions to the labeling.

Recommendations:
The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761400. This BLA is approvable from a clinical pharmacology perspective.

Postmarketing Requirements and Commitments
None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The evaluation of the clinical pharmacology of linvoseltamab via IV administration to support this BLA application is based on:

- The single pivotal Study R5458-ONC-1826, a phase 1/2, open-label, FIH study to assess the safety, tolerability, anti-tumor activity, PK, PD (biomarkers), and immunogenicity (ADA) of linvoseltamab in patients with RRMM
- Characterization of the PK, PD, and immunogenicity of linvoseltamab
- The E-R analyses for efficacy and safety to support the proposed 5/25/200 mg regimen for RRMM

In adult patients with RRMM, linvoseltamab was administered via IV infusion over 0.5 to 4 hours over a broad range of doses (3 to 800 mg). The disposition of linvoseltamab was concentration- and time-dependent.

Linvoseltamab primarily distributes in the vascular system with an estimated steady-state volume of distribution of 7.05 L (33.6%) (geometric mean [CV% of geometric mean]).The total clearance of linvoseltamab is composed of linear and nonlinear components. The linear clearance estimate was consistent with proteolytic clearance values typically reported for a BsAb. The target-mediated (nonlinear) clearance pathway was described by a concentration- and time-dependent clearance term in the PopPK analysis. 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 consistent with a reduction in the tumor burden (malignant plasma cells) by linvoseltamab. Following the last 200 mg QW dose, the predicted time required for linvoseltamab concentrations to decline to 3% of the median C_{max} was ~11 weeks. Due to presence of nonlinear and time-dependent clearance, dose proportionality (during the step-up regimen as well as during administration of 50 and 200 mg full doses) of linvoseltamab, concentrations differed over the duration of treatment.

Covariate analysis showed that albumin, IgG, total FLC, sex, and baseline body weight had statistically significant effects on linvoseltamab exposure. However, baseline albumin and IgG had a greater impact on linvoseltamab exposures compared to sex or body weight.

E-R analyses for efficacy with all treatment doses from phase 1 and phase 2 parts of Study 1826, which included a range from 0.3 to 800 mg full doses of linvoseltamab indicated that the probability of achieving ORR and CR increased with linvoseltamab exposure in a sigmoidal pattern, and substantial clinical response (71.7%) was predicted at exposures consistent with the median exposure ($C_{average}$) of 200 mg dosing regimen, supporting the selection of the 200 mg regimen for the treatment of RRMM . Further analysis of the effect of linvoseltamab exposure on PFS and OS for the patients in phase 2 (50 mg and 200 mg dose groups) indicated that the relationships between drug concentration and PFS as well as OS were described by monotonically increasing functions and were statistically significant.

E-R analysis of CRS suggest that median exposures 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, supporting the choice of the initial dose of 5 mg in the step-up regimen. There was no exposure related trend observed for the incidence of opportunistic infections of any grade possibly due to low number of events overall. E-R relationships for time to first infections grade ≥3 and neutropenia grade ≥3 indicate that increasing linvoseltamab exposure decreases the rate and hazard for these safety endpoints. However, the analyses may be influenced by the many first events occurring during the first few weeks of treatment. These events may not be related to linvoseltamab exposure but are rather more likely related to baseline patient characteristics and improving disease status.

Linvoseltamab exhibited PD responses in line with its mechanism of action, including transient distribution of T cells, T-cell activation, and associated transient cytokine

elevation, as well as a decrease (following an initial increase) in concentrations of total sBCMA in serum. CD19+ B cells in whole blood and involved FLC also declined following multiple cycles of treatment with linvoseltamab.

Immunogenicity was low across the 55 patients with RRMM in phase 1, the 137 patients with RRMM in phase 2, and the 192 patients in all patients combined.

The Applicant's Position:

The clinical pharmacology findings including PK, PD, E-R analyses of various efficacy and safety endpoints, and immunogenicity analyses support the proposed posology of linvoseltamab.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of clinical pharmacology assessment with regard to PK and PD assessment. Refer to Section 6.3.1 for details.

Dose-response analyses generally supported the safety and efficacy of the proposed 5/25/200 mg dosage. The Applicant's exposure-response (E-R) conclusions are relatively uncertain due to the following significant limitations:

- Exposure in the E-R analysis is likely confounded by factors such as duration of treatment, dose modifications, and patient response.
- Linvoseltamab activity is expected to be driven by the concentration of free drug, rather than total drug. The Applicant's E-R analysis used total drug exposure rather than free drug exposure and did not provide adequate justification to support their approach.

Refer to Section 6.3.2.2 and Appendices 19.4.2.3 and 19.4.2.6 for the detailed dose-response assessment of efficacy and safety, respectively. Refer to Appendix 19.4.1.2 for additional details regarding free versus total linvoseltamab concentration.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The recommended dose regimen for linvoseltamab includes step-up doses (b) (4)

Rationale for Selection of Step-Up Dose

Several step-up regimens with doses ranging from 1 mg to 32 mg preceding the full doses were evaluated in the phase 1. 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. This 5/25 mg step-up regimen as well as appropriate premedication (eg, use of dexamethasone) at the initiation of linvoseltamab therapy was shown to have an acceptable CRS profile and was implemented in phase 2 in both cohorts. The experience with this regimen in Phase 1 allowed Phase 2 to proceed without any split dosing.

The 5/25 mg step-up dosing regimen showed an acceptable safety profile in phase 2 and thus is selected as the optimal step-up regimen of linvoseltamab in patients with RRMM.

Rationale for Selection of Registrational Dose

A distinctively informative feature of the linvoseltamab development program is the investigation of 2 clinically active doses (50 and 200 mg full doses). The information generated at the 50 mg (N=104) and 200 mg (N=105) as part of the Phase 2 exploration, while not randomized, controlled, nevertheless allowed dose selection with greater certainty and improved characterization of the recommended dose with robust risk/benefit balance.

Clinically meaningful efficacy for the treatment of RRMM has been observed with the selected full dose of 200 mg preceded by the selected step-up dosing regimen 5/25 mg. The 200 mg dose regimen consistently demonstrated better efficacy than the 50 mg dose regimen in high-risk group; current data showed generally higher efficacy with the 200 mg dose in these groups: high-risk cytogenetics, ISS stages II/III, presence of EMP, penta-refractory status, age ≥75, and sBCMA ≥400 ng/L. Superior efficacy was demonstrated through multiple endpoints including ORR, CR, and PFS. And although OS wasn't conclusively superior with the 200 mg dose vs the 50 mg dose, a trend was apparent. Analyses of safety indicate that the recommended regimen for RRMM is tolerable in patients and is suitable for registration and differences in AEs between the 200 mg and 50 mg regimen were mostly due to early AEs that may have reflected baseline differences between the cohorts; these differences resolved and sometimes reversed as better disease control was achieved with the 200 mg dose vs the 50 mg dose.

The E-R analysis with ORR data from both dose escalation and dose expansion phases of Study 1826 indicated that ORR increased with drug exposure with an ORR of 72% for the 200 mg dosing regimen achieved at the median $C_{average}$ of 200 mg dosing regimen and superior efficacy at the 200 mg dose compared to the 50 mg dose, which supports the selection of the 200 mg dosing regimen for the treatment of RRMM. While the exposures associated with 200 mg Q2W and 200 mg Q4W were lower than the 200 mg QW regimen by design (with both being higher than the 50 mg Q2W exposure),

responses continued to deepen over time after transition from Q2W to Q4W doses. Responses were maintained with reduced dose frequency in phase 2 200 mg.

Evaluation of the effect of linvoseltamab exposures in the phase 2 patients with 50 mg or 200 mg dosing regimens on PFS and OS by time-to-event analyses indicated statistically significant relationships between linvoseltamab exposures on both PFS and OS. Decreased risks of progression and death were predicted for the patients in the 200 mg dosing regimen compared to the 50 mg dosing regimen.

The safety profiles were generally consistent in patients with both 200 mg and 50 mg full doses, with a higher incidence of TEAEs of infections leading to death in All 200 mg patients. As alluded to above, these occurred primarily in the first 3 months of treatment and reversed after 6 months as greater disease control was achieved with 200 mg vs 50 mg. The safety profile of the proposed regimen of linvoseltamab appears consistent with the mechanism of action of linvoseltamab and/or the AEs expected in a pretreated population with RRMM.

The Applicant's Position:

Data for both efficacy and safety along with E-R analyses of efficacy and relevant safety endpoints support the selection of the proposed registrational dose of 200 mg.

The FDA's Assessment:

The FDA agrees that the proposed linvoseltamab 5/25/200 mg dosage regimen is acceptable for the general patient population in regards to the proposed indication. Data supporting the recommended dosage regimen are described in detail below in Section 6.3.2.2.

Dose-response analyses generally supported the safety and efficacy of the proposed 5/25/200 mg dosage. The Applicant's E-R conclusions are relatively uncertain due to use of total drug exposure rather than free drug exposure and confounding factors such as duration of treatment, dose modifications, and patient response. Refer to Section 6.3.2.2 and Appendices 19.4.2.3 and 19.4.2.6 for the detailed dose-response assessment of efficacy and safety, respectively. Refer to Appendix 19.4.1.2 for additional details regarding free versus total linvoseltamab concentration.

6.2.2.2. Therapeutic Individualization

Data:

Linvoseltamab concentration data from all patients with RRMM evaluated in Study 1826, both phase 1 (3 mg to 800 mg) and phase 2 (50 mg and 200 mg) portion were utilized to assess the effect of intrinsic factors on the PK, using the PopPK model and covariate analysis.

Covariate analysis showed that body weight (44.2 to 171 kg), sex, albumin (15 to 48 g/L), and IgG (0.3 to 64.5 g/L), had a statistically significant effect on linvoseltamab exposure. However, baseline albumin and IgG had a greater impact on linvoseltamab

exposures compared to sex or body weight. In the population PK analysis, renal impairment, hepatic impairment, and age were not found to be statistically significant covariates affecting linvoseltamab exposure.

The Applicant's Position:

Given the totality of the data based on results from the linvoseltamab PopPK analysis, together with subgroup analysis for the efficacy and safety, no clinically meaningful covariate was identified that warrants dose adjustment for linvoseltamab.

The FDA's Assessment:
The FDA agrees with the Applicant's position that no alternative dosage is recommended according to patient covariates based on age, body weight, sex, race (White, Black, or Asian), ethnicity (Hispanic/Latino or not Hispanic/Latino), mild to moderate renal impairment, and mild hepatic impairment in patients with RRMM. See detailed discussion in Section 6.3.2.3.

6.2.2.3. Outstanding Issues

Data:

Not Applicable

The Applicant's Position:

Not Applicable

The FDA's Assessment:
The FDA agrees with the Applicant's position that there are no outstanding issues for this BLA submission.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Pharmacokinetics

- During step-up dosing (weeks 1 and 2) in the lower dose cohorts, the split dose regimens (1 to 32 mg in week 1; 3 to 96 mg in week 2) produced dose dependent increase in concentrations of total linvoseltamab in serum. Following IV infusion, C_{max} was observed at the EOI, with the highest weekly C_{max} in week 1 and week 2 observed after the second split dose. Generally, at any given timepoint during the first 2 weeks, concentrations were approximately dose proportional.
- The concentration-time profiles from phase 1 cohorts which evaluated full doses of 3 to 800 mg linvoseltamab, showed increase in concentrations of total linvoseltamab with increasing DL, as well as accumulation upon multiple dosing. Based on available data near the end of the QW dosing period over the 6 to 800

mg dose range, mean C_{trough} at week 16 ranged from 0.798 to 504 mg/L with a mean C_{max} at week 16 that ranged from 2.46 to 705 mg/L. After the dose frequency reduced from QW to Q2W at week 16, as expected, there was generally a modest decline in C_{trough} to week 24 across the dose groups.

- In the 200 mg dose group in Phase 2 cohort 2, patients who achieved ≥VGPR after 24 weeks of treatment with linvoseltamab transitioned from a Q2W to a Q4W dosing. As expected, median concentrations of total linvoseltamab declined in the Q2W to Q4W subgroup upon dose schedule change from Q2W to Q4W; at week 48 in the 200 mg Q2W to Q4W subgroup median concentrations of total linvoseltamab were approximately 60% lower than median concentrations for patients in phase 2 at the end of Q2W dosing interval (Week 24).
- 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. Over the course of this per protocol treatment regimen, C_{max} and C_{trough} increased 2.4-fold and 4-fold, respectively, from week 3 to week 13. Dosing with 200 mg Q4W started at week 24 and 97% of the steady-state estimated by C_{trough} was achieved by weeks 44 to 48. The C_{trough} and $C_{average}$ at steady-state (200 mg Q4W) were 10% and 24% relative to the respective values at week 13.

Population Pharmacokinetics

- Concentrations of linvoseltamab in serum were well described by a 2-compartment distribution model with parallel linear and nonlinear (Michaelis-Menten) clearance processes. Random effects were included on CL, VSS (as a single shared random effect on VC and VP), Q, and Vmax. The structural model included time-varying effects of IgG and ALB on linear CL and within-patient change in FLC on Vmax.
- The populations CL, VC, Q, VP, Vmax, and KM were, 0.2022 L/day, 4.125 L, 0.6721 L/day, 3.029 L, 8.278 nmol/L/day, and 99.78 nmol, respectively.
- Significant effects on exposure due to baseline IgG and ALB levels were identified.

Exposure-Response Relationship

- In the E-R response analyses of the pooled phase 1 and phase 2 data, increasing linvoseltamab exposure was significantly associated with an increased ORR, with the proposed registrational dosing regimen (200 mg) showing a 3.67-fold or 1.97-fold higher ORR compared to the 50 mg regimen, when response is grouped by ORR or ≥CR, respectively.
- Patients receiving a 200 mg dose compared to those receiving a 50 mg dose are predicted to have an approximate mean 49.5% decrease in risk of progression or death at any given point in time based on the PFS endpoint, and similarly on average an approximate mean of 33.8% decrease in OS at any given point in time when assessing the phase 2 data only. Additionally, there was a substantial overlap in the significant covariates found for PFS, OS, and ORR. DOR was not

associated with any exposure metric, however DOR may be related to the health status of the patients in terms of a lower RBCBL associated with a lower hazard.

- An increase in incidence of CRS in the first week with increase in linvoseltamab exposures (C*max*) at week 1 was observed (doses ranging from 1 to 32 mg) in data from phase 1 and phase 2. E-R relationships for time to first infections grade ≥3 and neutropenia grade ≥3 indicate that increasing linvoseltamab exposure decreases the rate and hazard for these safety endpoints while opportunistic infections (of any grade) do not show any trend with increase in exposures.

Summary of Pharmacodynamics

The PD responses to linvoseltamab were characterized by transient change in T-cell counts and T-cell activation, as well as transient cytokine elevation, which are all consistent with the mechanism of action for linvoseltamab. Rapid and pronounced B-cell depletion in blood was generally found within the first 4 weeks of linvoseltamab administration, regardless of the step-up regimen studied or clinical response status (responder vs non-responder). At doses in the phase 2 study, prolonged B-cell suppression was observed over the treatment period. Involved FLC concentrations in serum showed rapid decline in concentrations following linvoseltamab treatment and reached its nadir approximately 12 weeks following treatment and remained low during treatment. Dosing interval switch from Q2W to Q4W did not have an impact on the overall FLC level.

- High interpatient variability in cytokine concentrations was observed but time profiles of interferon-gamma, IL-2, and IL-6 were nevertheless similar in nature. Based on observed concentrations in serum, cytokine release appeared to be transient. In the dose groups that used the 5 mg/25 mg regimen during step-up dosing, maximum concentrations mostly occurred in the first 2 weeks of dosing and appeared to be attenuated upon subsequent administration. As transient cytokine release is a typical consequence of T-cell activation, the cytokine data are consistent with the effects of linvoseltamab on T-cell activation.

Immunogenicity

- Immunogenicity was low across the 55 patients with RRMM in phase 1, the 137 patients with RRMM in phase 2, and the 192 patients in all patients combined.
- All treatment-emergent ADA responses were of low titer. During treatment with linvoseltamab administered IV, the incidence of treatment-emergent ADA was 1.8% (1/55) in patients in phase 1, 0.7% (1/140) in patients in phase 2, and 1.0% (2/195) overall. Neutralizing antibodies were not assessed in this study. There was no effect of immunogenicity on linvoseltamab PK profiles observed in the 2 patients with treatment-emergent ADA responses.

The Applicant's Position:

Overall, the clinical pharmacology data adequately characterized the PK, PD, and immunogenicity of linvoseltamab. The E-R analyses for efficacy and safety support the proposed 5 mg/25 mg/200 mg dosing regimen in patients with RRMM.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position. General pharmacology and PK characteristics of linvoseltamab are summarized in **Table 20**.

Table 20: FDA - Linvoseltamab General Pharmacology and Pharmacokinetic Characteristics

General Information	
Pharmacokinetic characteristics	
Steady-state exposure at the proposed dosing regimen	Geometric mean (CV%) of linvoseltamab maximum concentration of 127 mg/L (51%) is achieved after the first dose of the Q2W dosing regimen (i.e., the 12th dose of 200 mg).
Dose proportionality	Linvoseltamab C_{trough} increased more than proportionally over a dose range of 96 mg to 800 mg (0.48 to 4 times the recommended full dose).
Distribution	The steady-state volume of distribution of linvoseltamab was 7.05 L (33.6%).
Elimination	Linvoseltamab clearance decreased over time because its elimination is mediated by two parallel processes: a linear, non-saturable catabolic process and a nonlinear, saturable target-mediated pathway. Linvoseltamab clearance is 0.68 L/day (52.2%) at baseline and 0.43 L/day (83.8%) at steady state (Week 48) following the 5/25/200 mg dosage. Linvoseltamab is expected to be metabolized into small peptides by catabolic pathways.
Bioanalytical Assay for PK	See Section 19.4.3 for detailed summary on validated range, accuracy, precision, and stability of the PK assay.
Specific Population	
Intrinsic Factors	No dose adjustments are recommended for subpopulations based on age (37 to 91 years), body weight (44 to 172 kg), sex, race (White, Asian, or Black), or ethnicity (Hispanic/Latino or not Hispanic/Latino) in patients with RRMM.
Immunogenicity	
In Study 1826, 1% (2/192) of patients who received the linvoseltamab developed anti-linvoseltamab antibodies.	
Pharmacodynamic Characteristics	
Pharmacodynamics	Transient elevations of circulating cytokines IL-2, IL-6, IL-10, TNF-α, and IFN-γ was observed at all dose levels starting from 1 mg (0.005 times the recommended dosage). After administration of the recommended dosage of linvoseltamab, elevations of circulating cytokines were observed during the step-up dose regimen (5 mg/25 mg) and the first full 200 mg dose.

	Transient elevations of total sBCMA in serum were observed after the start of treatment with linvoseltamab, which generally increased with dose and reached plateau at 200 mg or higher (i.e., Dose levels [DL] 7-9). After achieving maximum predose concentrations at around week 5, concentrations of total sBCMA concentrations declined, and by week 8 predose concentrations were lower than baseline in some of the dose groups, especially at dose levels 96 mg or higher.
Dose-Response for Efficacy	Multivariate dose-response analysis did not identify any concerns with the proposed 200 mg QW dosage in patients with RRMM. Dose finding was conducted in patients with RRMM across full dose levels from 3 to 800 mg. Efficacy estimates appeared to increase with increases of the full dose and appeared to be plateaued at dose levels at 200 mg or higher. After accounting for other covariates, a higher full dose amount was associated with better ORR, CR rate, and PFS in patients with RRMM who received at least one full dose of 50 mg QW or 200 mg QW; while no association was identified between OS and full dose amount in patients who received at least one full dose that ranged from 3 mg to 800 mg.
Dose-Response for Safety	The dose-response analysis did not identify any concerns with the proposed 5/25/200 mg dosage in patients with RRMM. After accounting for other patient and disease characteristics, the full dose amount was not identified as a significant covariate on the risk of any grade infusion-related reaction (IRR), TEAE leading to dose modification, any grade infection, Grade ≥2 infection, Grade ≥3 neurotoxicity (method 2), Grade ≥3 neutropenia, Grade ≥3 anemia, Grade ≥3 thrombocytopenia, or Grade ≥3 leukopenia. However, the rate of safety events at each dose may be confounded by longer duration of follow-up at lower doses (e.g., 50 mg QW) compared to relatively higher doses (e.g., 200 mg QW).

Pharmacokinetics

Clinical Pharmacology findings included data from Study 1826. The results of this study provided adequate characterization of linvoseltamab PK.

Linvoseltamab PK exposures following recommended dosing schedule are presented in **Table 21**.

Table 21: FDA - Geometric Mean (% CV) Exposure Following the Recommended Dosage of Linvoseltamab

Dosing Period	C_{max} (mg/L)	C_{trough} (mg/L)	C_{avg} (mg/L)
First 200 mg weekly dose	52.7 (37.2%)	15.5 (64.8%)	27.4 (34.2%)
End of 200 mg weekly dosing (11th dose of 200 mg)	124 (50.4%)	61.8 (123%)	84.6 (74.6%)

Dosing Period	C_{max} (mg/L)	C_{trough} (mg/L)	C_{avg} (mg/L)
End of 200 mg every 2 weeks dosing (16^{th} dose of 200 mg)	97.9 (52.7%)	30.2 (213%)	51.9 (95.3%)
Steady state[a] with 200 mg every 4 weeks dosing	64.8 (45.1%)	6.3 (362%)	20.5 (84.6%)
[a] Steady state values are approximated at Week 28.			

Cavg = average concentration over the dosing interval; Cmax = maximum concentration within the dosing interval; Ctrough = concentration at the end of the dosing interval; CV = coefficient of variation.
Source: Table 9 in Applicant's response to label comments (seqn 0038)

Pharmacodynamics

Cytokine Concentrations

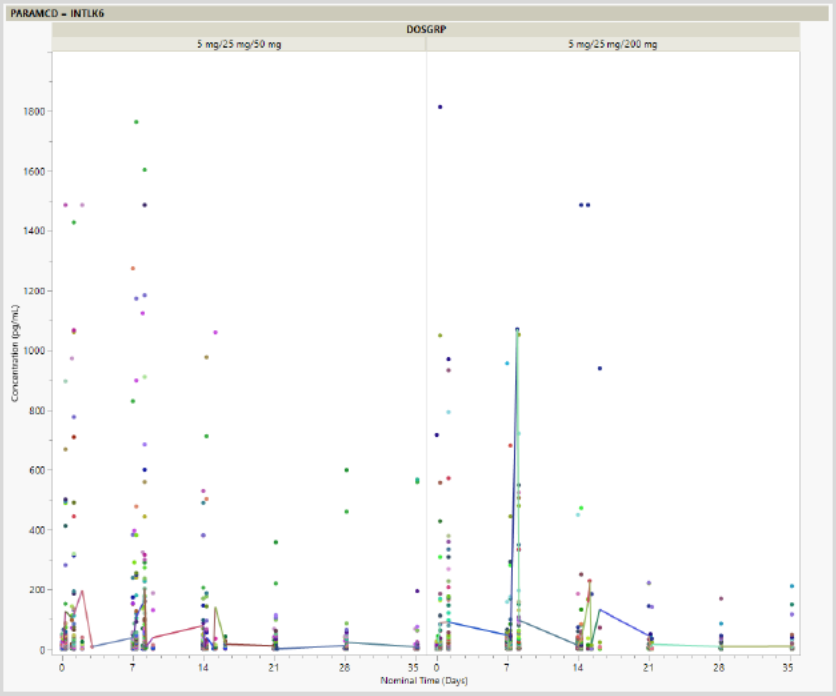
Transient elevation of circulating cytokines including interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 2 (IL-2), interferon gamma (IFN-ɣ), and tumor necrosis factor alpha (TNF-α) was observed at all dose levels starting from 1 mg (0.005 times the recommended dosage) in Study 1826 (**Figure 2).** Following administration of the proposed 5/25/200 mg dosage, transient elevation of cytokines (e.g., IL-6, IL-10, IL-2, IFN-ɣ and TNF-α) 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. A similar trend was observed following administration of a 5/25/50 mg dosage (**Figure 3**). The summary of IL-6 concentrations for the total samples, samples without tocilizumab and samples with tocilizumab following administration of the proposed 5/25/200 mg dosage is summarized in **Table 22**. It is noteworthy that administration of tocilizumab complicates the assessment of the IL-6 release profile as it causes increases in circulating IL-6 concentration through blockage of IL-6R.

Figure 2: FDA - Plasma Cytokine Levels Over Time and Dose Level in Patients with RRMM During Dose Escalation

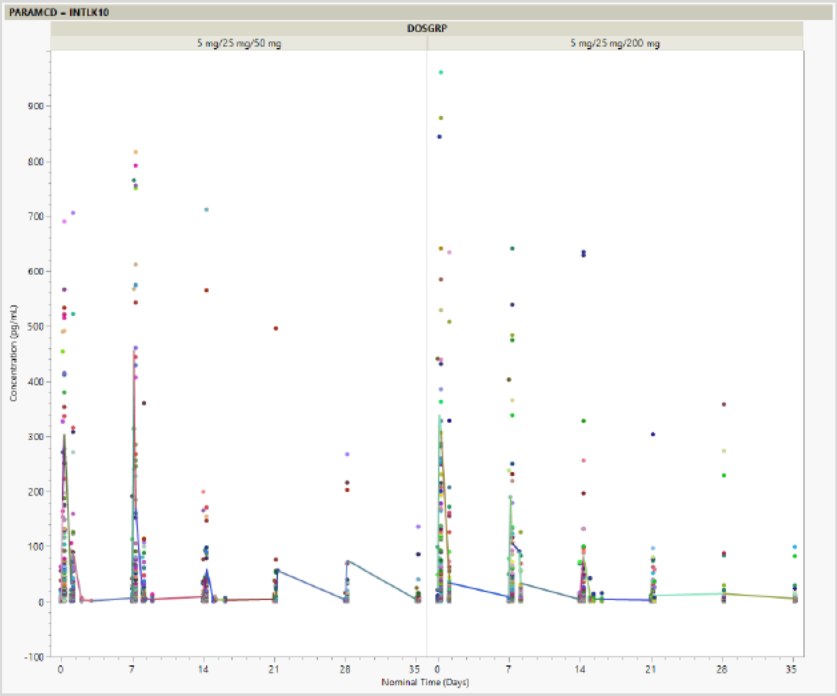
Source: FDA analysis created from Study 1826 ADLB dataset.

Figure 3: FDA - Plasma Cytokine Levels Over Time and Dose Level in Patients with RRMM in Phase 2 Cohort 1 (5/25/50 mg, left panel) and 5/25/200 mg Dosage (right panel)

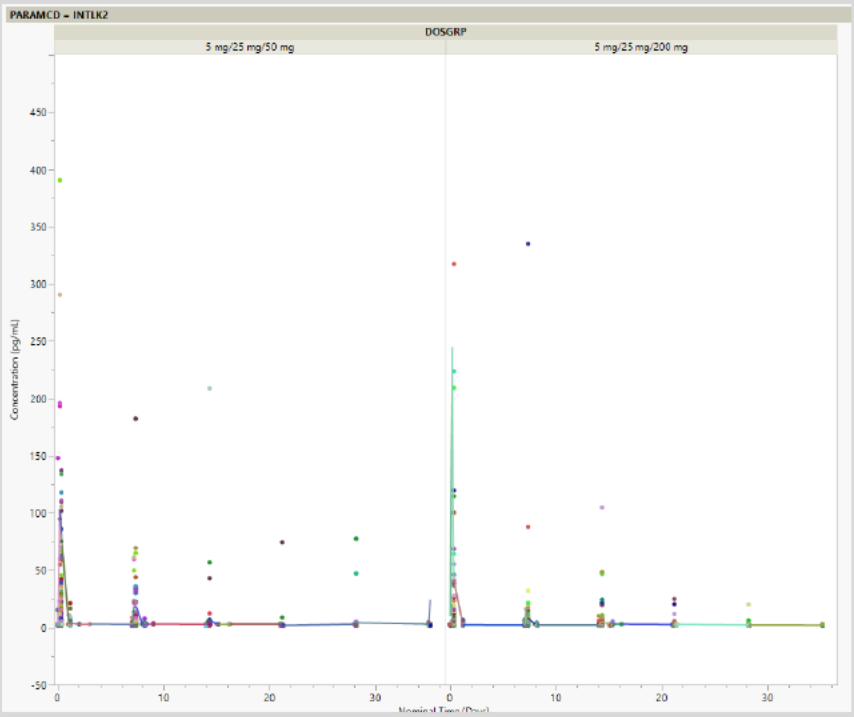
a) IL-6



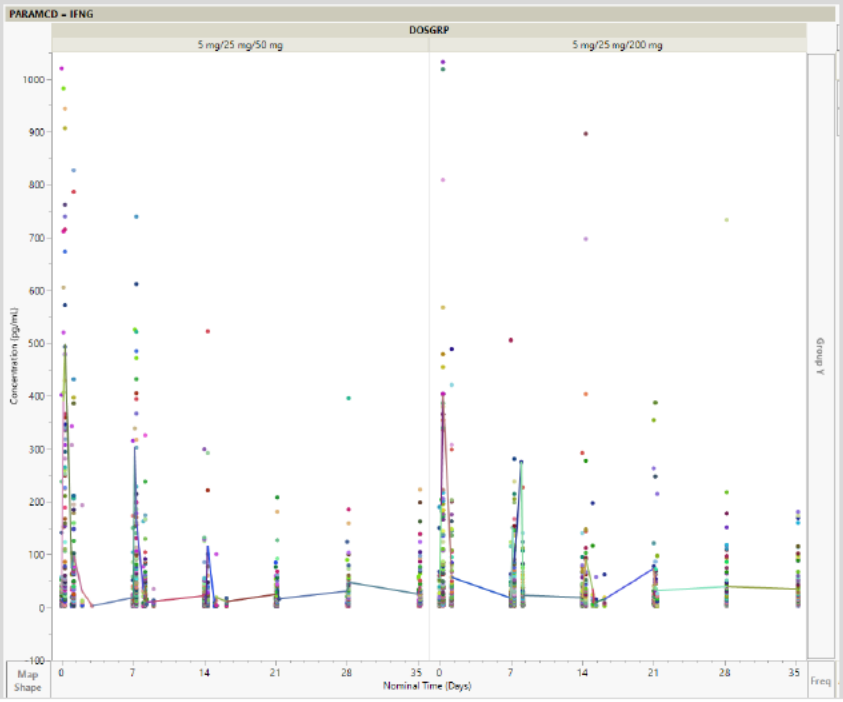
b) IL-10



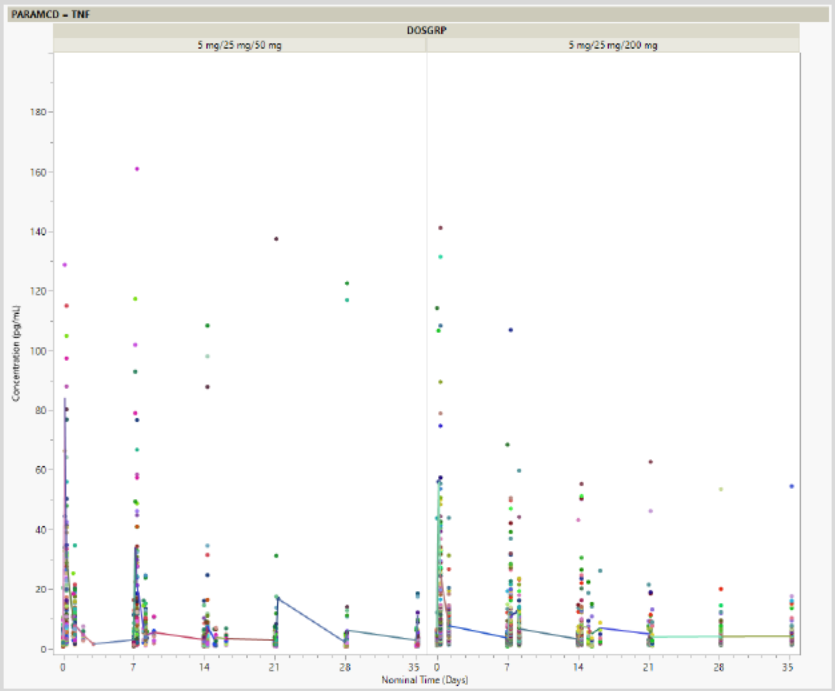
c) IL-2



d) IFN-γ



e) TNF-α



Source: FDA analysis created from ADCTK dataset submitted on 4/11/2024 in response to FDA IR

Table 22: FDA - Summary of Plasma IL-6 Concentration Profiles Following 5/25/200 mg Dosage

	Week	Dose (mg)	Timepoint	N	Mean (SD)	Median	25th, 75th percentile	2.5th, 97.5th percentile	Range
Step-up Doses	W1D1	5 mg	pre-dose	115	42.0 (353)	1.84	1.27, 3.88	1.27, 25.9	1.27, 3726
			pre-dose without toci use	115	42.0 (353)	1.84	1.27, 3.88	1.27, 25.9	1.27, 3726
			pre-dose with toci use	0	0	0	0	0	0
			4 hr. post dose	106	88.1 (415)	4.98	1.62, 13.5	1.27, 1050	1.27, 3712
			4 hr. post dose without toci use	102	65.4 (383)	4.48	1.54, 9.93)	1.27. 428	1.27, 3712
			4 hr. post dose with toci use	4	668 (789)	372	149, 1186	113, 1814	113, 1814
			24 hr. post-dose	107	91.3 (281)	8.53	1.83, 33.9	1.27, 933	1.27, 374
			24 hr. post dose without toci use	98	65.2 (258)	7.26	1.64, 23.7	1.27, 378	1.27, 2374
			24 hr. post dose with toci use	9	376 (372)	309	56.5, 573	14.9, 970	14.9, 970
	W2D1	25 mg	pre-dose	107	47.7 (320)	2.19	1.27, 8.53	1.27, 158	1.27, 3183
			pre-dose without toci use	94	48.2 (341)	1.89	1.27, 4.85	1.27, 36.2	1.27, 3183
			pre-dose with toci use	13	44.4 (39.0)	34.7	17.9, 55.8	11.3, 158	11.3, 158
			4 hr. post dose	108	3550 (36603)	1.86	1.27, 11.7	1.27, 444	1.27, 380416
			4 hr. post dose without toci use	95	17.6 (77.0)	1.62	1.27, 3.56	1.27, 169	1.27, 681
			4 hr. post dose with toci use	13	29363 (105478)	49.6	40.3, 176	8.39, 380416	8.39, 380416
			24 hr. post-dose	103	97.4 (327)	6.51	1.62, 50.9	1.27, 721	1.27, 2940
			24 hr. post dose without toci use	14	551 (745)	342	150, 550	21.2, 2940	21.2, 2940
			24 hr. post dose with toci use	89	26.0 (64.6)	3.20	1.47, 21.5	1.27, 158	1.27, 524
Cycle 1	W3D1	200 mg	pre-dose	107	13.5 (47.5)	2.33	1.32, 8.80	1.27, 74.3	1.27, 450
			pre-dose without toci use	91	4.35 (6.37)	1.94	1.27, 3.90	11.27, 24.6	1.27, 39.6
			pre-dose with toci use	16	65.7 (111)	29.1	16.4, 51.0	10.1, 450	10.1, 450
			4 hr. post dose	98	34.6 (160)	1.62	1.27, 10.9	1.27, 250	1.27, 1486
			4 hr. post dose without toci use	84	13.0 (54.4)	1.27	1.27, 2.54	1.27, 84.9	1.27, 472
			4 hr. post dose with toci use	14	165 (389)	38.2	13.7, 60.6	3.56, 1486	3.56, 1486
			24 hr. post-dose	11	156 (444)	2.41	1.62, 36.8	1.27, 1486	1.27, 1486
			24 hr. post dose without toci use	9	7.20 (11.8)	1.62	1.62, 3.63	1.27, 36.8	1.27, 36.8
			24 hr. post dose with toci use	2	826	NA	NA	NA	167, 1486
	W4D1	200 mg	pre-dose	15	45.5 (79.8)	5.58	3.16, 33.4	1.46, 222	1.46, 222
			pre-dose without toci use	12	8.04 (9.21)	5.27	2.74, 8.64	1.46, 33.4	1.46, 33.4
			pre-dose with toci use	3	195 (44.6)	220	144, 222	144, 222	144, 222
			EOI. post dose	91	6.10 (10.0)	1.42	1.27, 5.11	1.27, 38.4	1.27, 50.7
			EOI. post dose without toci use	77	3.00 (4.30)	1.27	1.27, 1.99	1.27, 18.8	1.27, 25.9
			EOI. post dose with toci use	14	23.2 (14.7)	22.3	9.90, 34.8	5.04, 50.7	5.04, 50.7
	W5D1	200 mg	EOI. post dose	97	9.01 (20.8)	1.62	1.27, 6.93	1.27, 46.2	1.27, 169

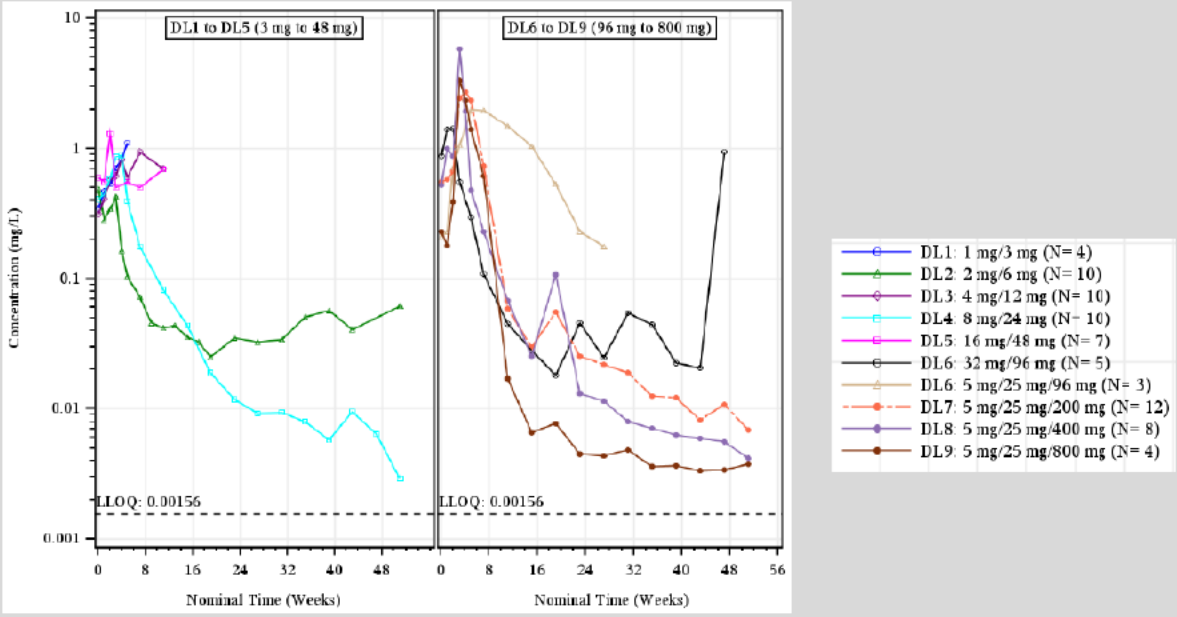
	Week	Dose (mg)	Timepoint	N	Mean (SD)	Median	25th, 75th percentile	2.5th, 97.5th percentile	Range
			EOI. post dose without toci use	80	4.37 (7.03)	1.27	1.27, 4.05	1.27, 24.9	1.27, 41.7
			EOI. post dose with toci use	17	30.8 (41.8)	21.2	6.07, 34.3	1.27, 169	1.27, 169
	W6D1	200 mg	EOI. post dose	92	9.92 (29.7)	1.86	1.27, 4.47	1.27, 117	1.27, 211
			EOI. post dose without toci use	75	2.69 (2.41)	1.62	1.27, 3.25	1.27, 9.24	1.27, 15.6
			EOI. post dose with toci use	17	41.8 (60.4)	19.9	2.65, 39.6	1.27, 211	1.27, 211

EOI = end of infusion; SD = standard deviation; toci = tocilizumab; W1D1 = week 1 day 1.
Source: Reviewer's Analysis based on Table Q4.1 IR response submitted on 04/11/2024

Soluble BCMA

Median predose concentrations of total sBCMA in the first 16 weeks of treatment across the 9 full dose levels (3 to 800 mg QW) during dose escalation are presented in **Figure 4**. After the start of linvoseltamab treatment, concentrations of total sBCMA in serum increased relative to baseline and generally reached maximum predose concentrations around Week 5. Such increases in total sBCMA may be associated with the binding of linvoseltamab to sBCMA in serum and lower clearance of the drug-ligand complex compared to sBCMA. Mean maximum predose concentrations of total sBCMA generally increased with elevation of dose and reached plateau at dose levels 200 mg or higher (i.e., DL7-9). After achieving maximum predose concentrations at around Week 5, concentrations of total sBCMA concentrations declined, and by Week 8 predose concentrations were lower than baseline in some of the dose groups, especially at dose levels 96 mg or higher. The reduction in concentrations may reflect a lower production rate of sBCMA due to reduced tumor burden associated with treatment response.

Figure 4: FDA – Median Predose Concentrations of Total sBCMA in Serum by Nominal Week and Dose Level in Participants with RRMM in Study 1826 Phase 1 Cohorts



Source: R5458-ONC-1826-CP-01V1 Clinical Pharmacology Report, Figure 12.

6.3.2. **Clinical Pharmacology Questions**

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

The proposed dosing regimen for 200 mg for the treatment of RRMM is supported by clinical response data from Study 1826 and the E-R analysis for efficacy.

E-R analyses for efficacy with all treatment doses from phase 1 and phase 2 parts of Study 1826, which included a range from 0.3 to 800 mg full doses of linvoseltamab indicated that the probability of achieving ORR and >CR increased with linvoseltamab exposure in a sigmoidal pattern, and substantial clinical response (71.7%) was predicted at exposures consistent with the median exposure of 200 mg QW dose at week 4 (first full dose), which supports the selection of the 200 mg QW regimen for the treatment of RRMM. Further analysis of the effect of linvoseltamab exposure on PFS by quartiles of exposure for the patients in phase 2 (50 mg and 200 mg dose groups) indicated that there was a statistically significant relationship between linvoseltamab concentration and PFS, supporting the proposed posology of 200 mg regimen.

Clinical efficacy data from Study 1826 indicated that responses were maintained for patients in the phase 2 200 mg group who transitioned from Q2W to Q4W dosing schedule upon achieving a response of ≥VGPR after least 24 weeks of treatment with linvoseltamab. Among patients who transitioned to Q4W dosing, 98.2%, 94.5%, and 84.2% of these patients are expected to maintain their response from the first documented confirmed response (sCR, CR, VGPR, or PR) up to and beyond 6, 9, and 12 months, respectively. In addition, evaluation of total sBCMA and involved FLC, which are strong indicators of disease burden, showed no difference in concentrations when linvoseltamab dosing frequency was changed from Q2W to Q4W. These data are suggestive that a lowering of the disease burden occurring at or before week 24 allows for the maintenance of response at the longer dosing intervals of Q4W.

There is no increase in incidence of relevant safety endpoints with increase in linvoseltamab exposure.

The Applicant's Position:

The totality of the data including the linvoseltamab clinical pharmacology program together with the clinical efficacy results from study 1826 provides sufficient evidence of the effectiveness at the intended registration dose and schedule.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position that clinical pharmacology analyses support the efficacy following the proposed 5/25/200 mg dosage. The efficacy of linvoseltamab was evaluated in patients with RRMM in Study R5458-ONC-1826 (Study 1826). Efficacy was established based on objective response rate (ORR) of 70% (95% CI: 60-78) following the step-up regimen of 5 mg/25 mg and full dose of 200 mg. Refer to Section 8.1.2 for additional information. Supportive evidence of effectiveness from the clinical pharmacology program is summarized below:

The FDA utilized a multivariate dose-response analysis of efficacy to assess the acceptability of the proposed 5/25/200 mg dosage. Dose-response analysis of efficacy generally supports the proposed 200 mg QW full dosage in patients with RRMM. Refer to Section 19.4.2.3 for the detailed dose-response analysis of efficacy.

The Applicant's E-R efficacy conclusions are not adequately supported due to significant limitations, including the use of total drug concentrations rather than free drug concentrations and potential confounding with duration of treatment, dose modifications, and patient response. E-R efficacy associations remain uncertain based on current data. Refer to Section 19.4.2.2 for the detailed FDA assessment of E-R efficacy analyses.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

See Section 6.2.2.2.

The Applicant's Position:

The intended registration dose and schedule for linvoseltamab is appropriate based on effectiveness (see Section 6.2.2.1 and Section 6.3.2.1), step-up dosing to minimize CRS (see Section 6.2.2.1), and E-R for safety (see Section 19.4.2.5), and no dose adjustments are needed for the general population.

The FDA's Assessment:

The FDA agrees with Applicant's position that the proposed dose and schedule of 5/25/200 mg of linvoseltamab is appropriate for the general patient population for which the indication is being sought.

Proposed Dosing Regimen

The FDA assessment of the proposed dosing regimen evaluated the step-up dosing schedule and the treatment dosage separately.

- Step-up dosing regimen

The FDA agrees that the CRS profile for the proposed 5/25/200 mg dosage is acceptable in regards to safety.

Various step-up dosing schedules have been evaluated in the Phase 1 portion of Study 1826, with 31/73 (42.5%) patients experiencing CRS. Most CRS events were grade 1 (27/73 [37.0%] patients), with 4/73 (5.5%) patients experiencing grade ≥2 (**Table 24**). All

grade ≥2 CRS events in Phase 1 occurred in DL5 and DL6 where the week 1 day 1 dose was ≥8 mg (i.e., 16 or 32 mg initial doses split into two separate infusions over 2 days). Implementation of a 5 mg initial dose and a 25 mg intermediate dose appeared to mitigate the CRS risk of the subsequent full doses (e.g., 96 mg or above).

Following administration of the proposed 5/25/200 mg dosage regimen in Phase 2 (**Table 23**, **Figure 5A** and **Figure 6**), CRS mainly occurred following the initial three doses of linvoseltamab with the highest rate (38.5%) observed following the 5 mg initial step-up dose. The incidence of any Grade and Grade ≥2 CRS decreased with each subsequent step-up dose. The Grade ≥2 CRS incidence was 7.7%, 1.8%, and 1.8% following 5 mg, 25 mg, and first 200 mg full dose, respectively. Similarly, the incidence of any Grade and Grade ≥2 CRS also decreased with each subsequent dose of the 5/25/50 mg dosing regimen as shown in **Figure 5B**. The proposed step-up dosing regimen of 5/25/200 mg is acceptable. The 5 mg initial dose and 25 mg intermediate dose can mitigate the CRS risk of the subsequent full doses (i.e., 200 mg).

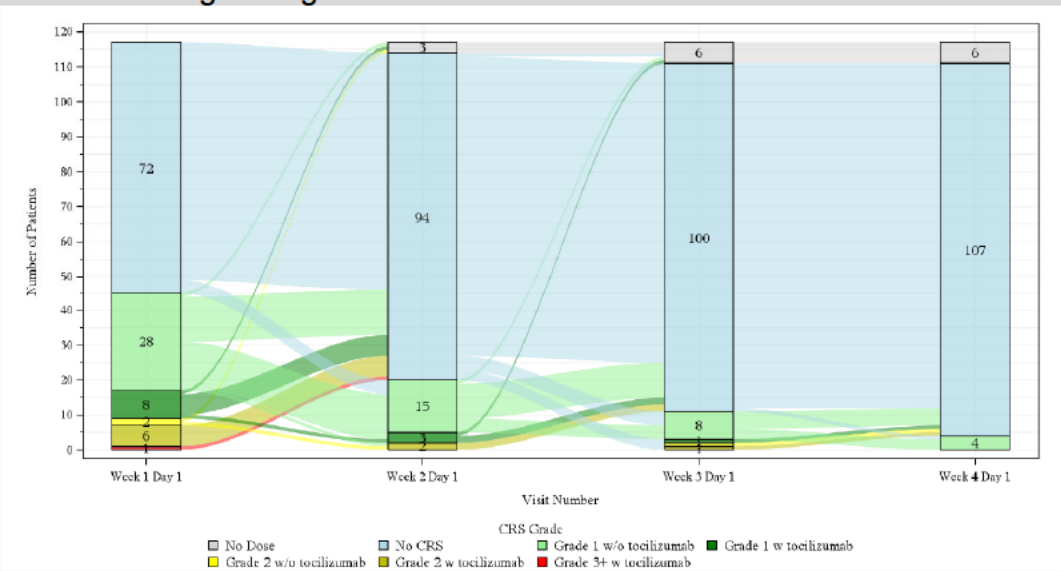
Table 23: FDA – CRS Events by Dose Event Following 5/25/200 mg Dosage Regimen in Study 1826

CRS N (%)	Any Dose N= 117	Initial Dose 5 mg N= 117	Intermediate Dose 25 mg N= 113	First Full Dose 200 mg N= 111	Second Full Dose 200 mg N= 110	Third Full Dose and Beyond 200 mg N= 99
Any Grade	54 (46.2%)	45 (38.5%)	19 (16.8%)	11 (9.9%)	4 (3.6%)	2 (2%)
Max Grade 1	41 (35%)	36 (30.8%)	17 (15%)	9 (8.1%)	4 (3.6%)	1 (1%)
Max Grade 2	12 (10.3%)	8 (6.8%)	2 (1.8%)	2 (1.8%)	0	1 (1%)
Max Grade 3	1 (0.9%)	1 (0.9%)	0	0	0	0
Max Grade ≥4	0	0	0	0	0	0

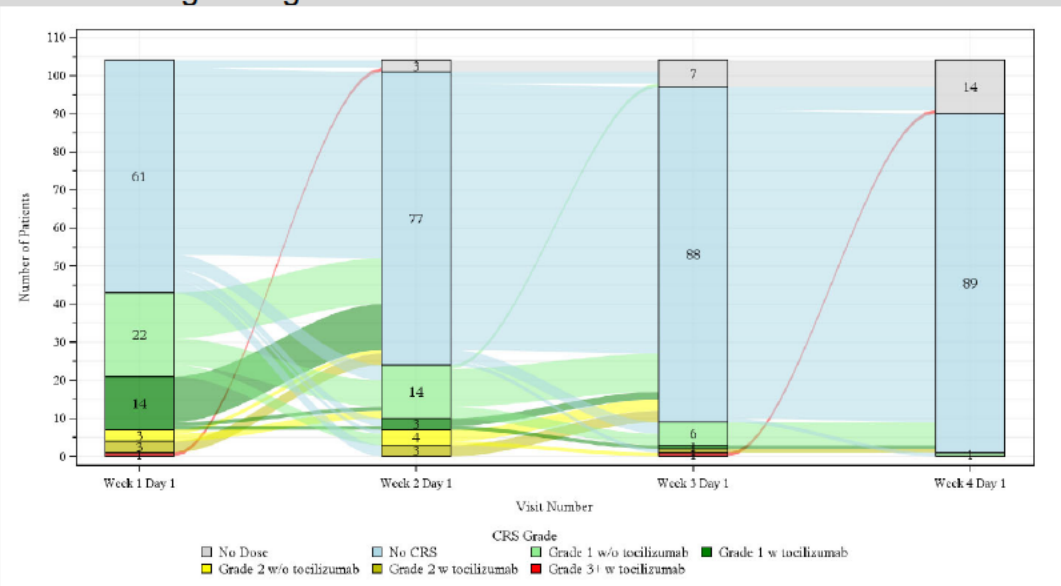
Data displayed for 117 patients in Study R5458-ONC-1826 Phase 1 (n=12) + Phase 2 (n=105) who were scheduled to receive 5/25/200 mg dosage regimen.
Source: Table 20 in Summary of Clinical Safety

Figure 5: FDA – Incidence of CRS by Dose Event with (A) 5/25/200 mg and (B) 5/25/50 mg Dosages

A. 5/25/200 mg Dosage

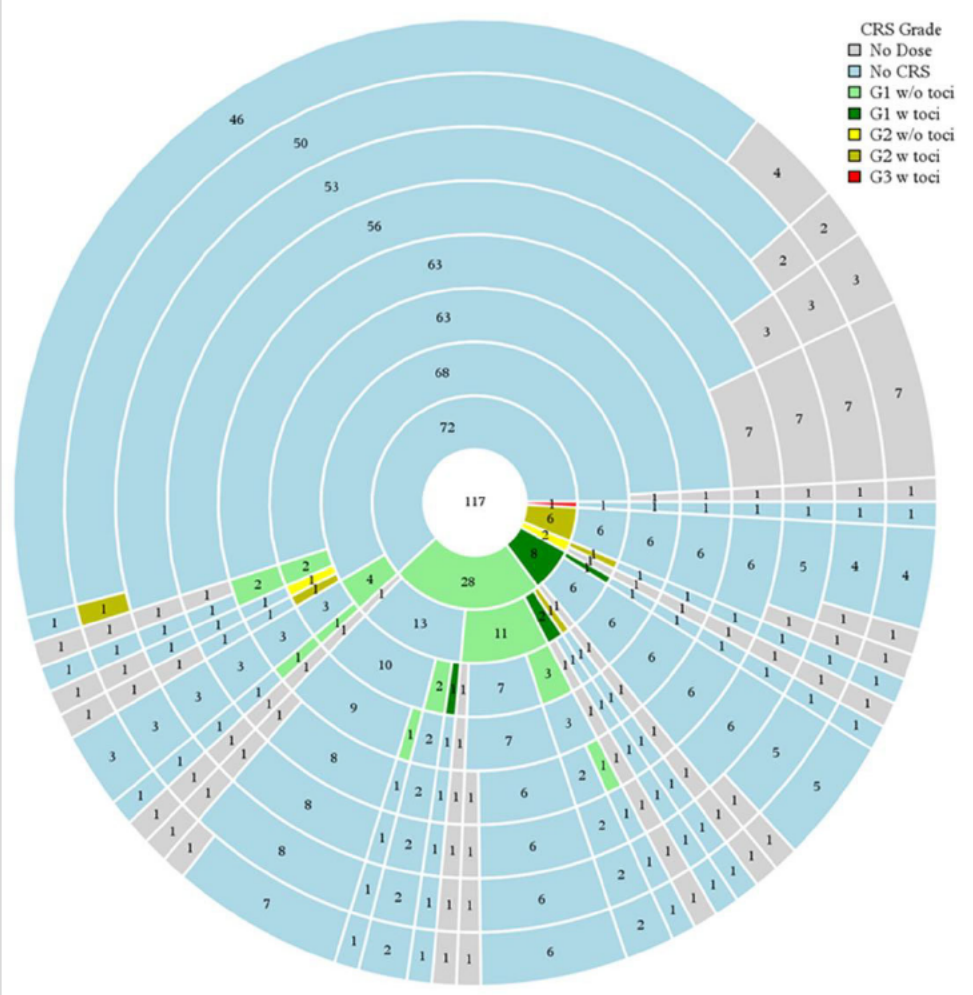


B. 5/25/50 mg Dosage



Data displayed for 117 patients in Study R5458-ONC-1826 Phase 1 (n=12) + Phase 2 (n=105) who were scheduled to receive 5/25/200 mg dosage regimen and for 104 patients in Study R5458-ONC-1826 Phase 1 who were scheduled to receive 5/25/50 mg dosage regimen.
CRS = cytokine release syndrome; w toci = treated with tocilizumab; w/o toci = without tocilizumab.
Source: Figures 1.1a and 1.1b in Applicant's response to 1 March 2024 information request (seqn 00012)

Figure 6: FDA – Incidence of CRS by Worst Toxicity Grade, Dose, and Infusion Week, During the First Eight Doses in All 5/25/200 mg Patients – Sunburst Plot

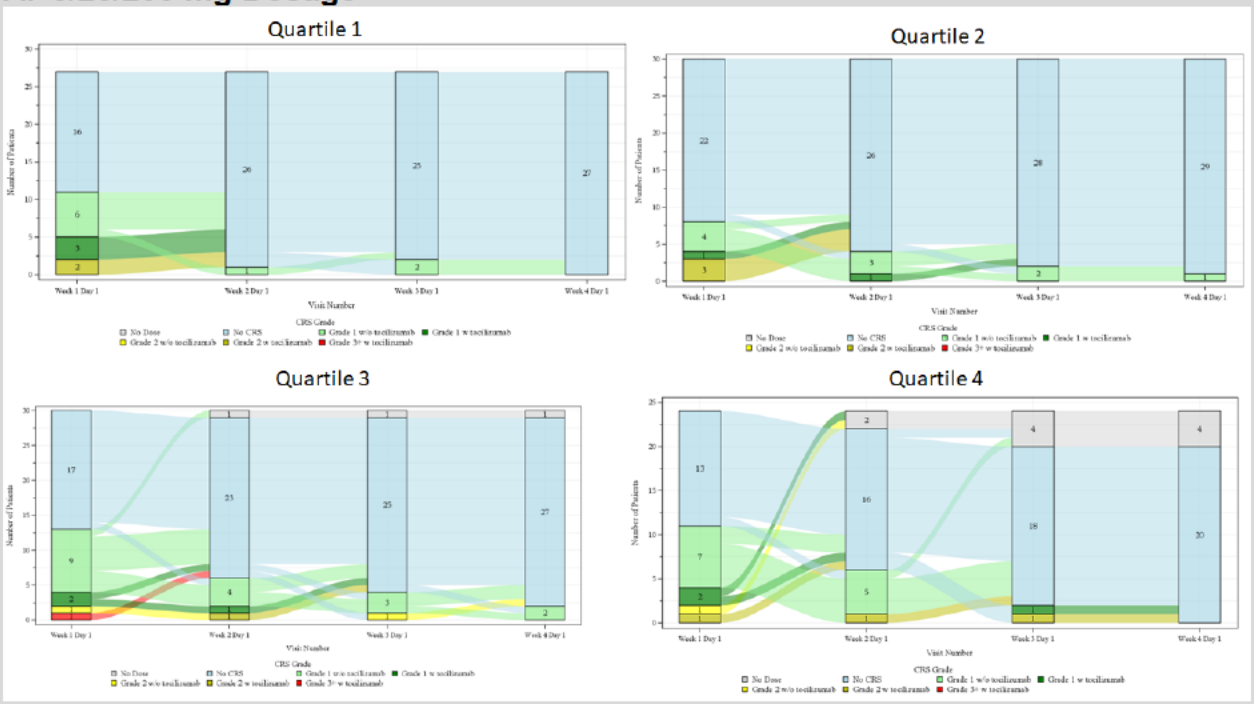


Data displayed for 117 patients in Study R5458-ONC-1826 Phase 1 (n=12) + Phase 2 (n=105) who were scheduled to receive 5/25/200 mg dosage regimen.
CRS = cytokine release syndrome; G = grade; w toci = treated with tocilizumab; w/o toci = without tocilizumab.
Source: Figure 1 in the Summary Clinical Safety Report

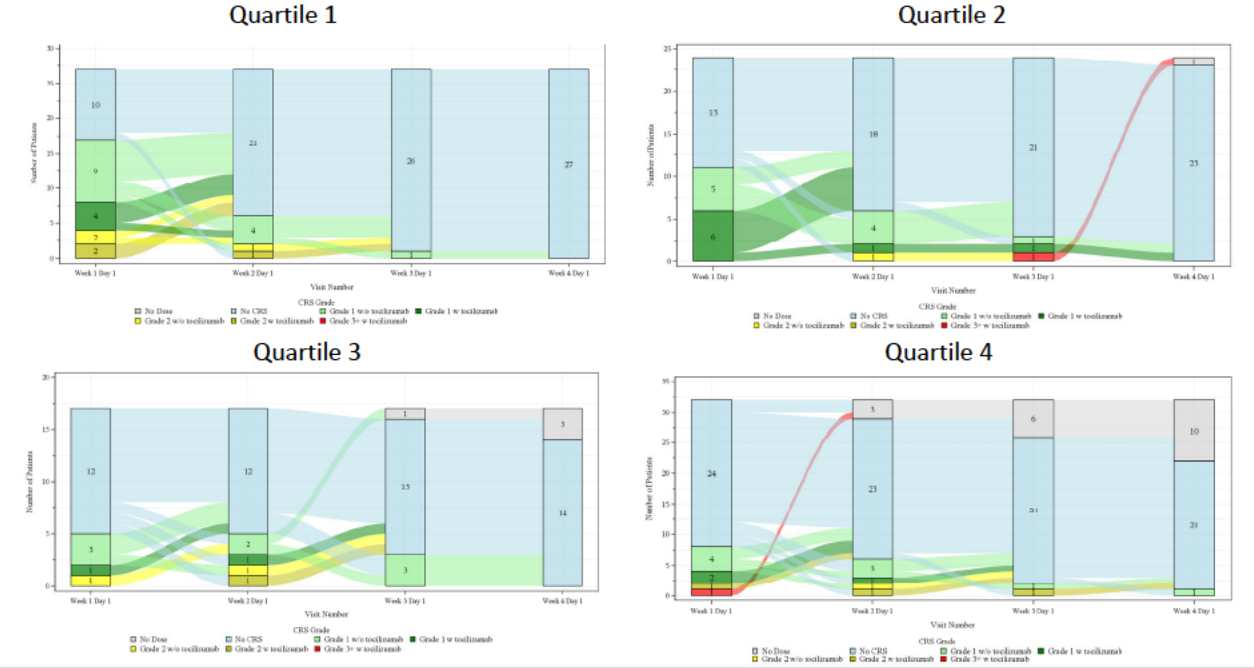
No clear associations were identified between CRS incidence and severity by dose event across baseline sBCMA quartiles following 5/25/200 mg or 5/25/50 mg dosages (**Figure 7**), which provides further supportive evidence that the proposed step-up dosage regimen of 5 mg initial dose and 25 mg intermediate dose can mitigate the CRS risk of the subsequent full dose (i.e., 200 mg) in the general patient population.

Figure 7: FDA – Incidence of CRS by Dose Event Across Baseline Soluble BCMA Quartiles Following (A) 5/25/200 mg and (B) 5/25/50 mg Dosage

A. 5/25/200 mg Dosage



B. 5/25/50 mg Dosage



Quartile 1 = 0 to 25th percentile of sBCMA; Quartile 4 = 75 to 100th percentile of sBCMA.
CRS = cytokine release syndrome; sBCMA = soluble B-cell maturation antigen; w toci = treated with tocilizumab; w/o toci = without tocilizumab.
Source: Figures 1.ba and 1.3a in Applicant's response to 1 March 2024 information request (seqn 00012)

- Treatment dose

The FDA agrees that the proposed treatment dose of 200 mg is acceptable in regards to efficacy and safety from a clinical pharmacology perspective.

Dose finding and dose optimization

Dose finding was conducted in patients with RRMM across full dose levels from 3 to 800 mg (**Table 24**). Antitumor activity was observed even at the lowest dose level evaluated in Phase 1 (DL1: 1mg/ 3 mg). Efficacy estimates appeared to increase with increases of the full dose, but varied widely between DLs, possibly due to the relatively low sample size in each DL. Efficacy appeared to be plateaued at dose levels at 200 mg or higher. Consistently, the PD analysis also reported post-treatment increase in total sBCMA generally increased with elevation of dose and reached plateau at dose levels 200 mg or higher (**Figure 4**), indicating the saturation of linvoseltamab on BCMA+ target cell killing. No maximum tolerated dose (MTD) was identified, and no dose dependent toxicities were observed with linvoseltamab up to 800 mg QW/Q2W, the highest dose tested in Phase 1.

The Phase 2 portion evaluated efficacy of linvoseltamab at 2 different dose levels. The efficacy of linvoseltamab following the recommended 5/25/200 mg dosage appeared to be better than the other evaluated 5/25/50 mg dosage, with better response rates (e.g., ORR, VGPR or better, CR or better) reported (**Table 24**).

Table 24: FDA – Summary of Response Rates (ORR, VGPR or better, CR or better) and CRS Rates Following the Different Linvoseltamab Step-up Regimens in Study 1826 Phase 1 Dose Escalation Portion and Phase 2 Dose Expansion Portion

Dose Level	Dosage (mg)	Number of Patients	Response			CRS			
			ORR[c]	VGPR or better[d]	CR or better[e]	Any Grade	Grade 1	Grade 2	Grade 3
Phase 1 Portion[a]									
DL1	1*/3*/3	4	25%	25%	25%	25%	25%	0	0
DL2	2*6*/6	10	40%	40%	40%	50%	50%	0	0
DL3	4*12/*12	10	10%	10%	10%	30%	30%	0	0
DL4	8*24*/24	10	50%	40%	30%	40%	40%	0	0
DL5	16*/48*/48	7	28.6%	28.6%	14.3%	42.9%	0	42.9%	0
DL6	32*/96*/96 or 5/25/96*/96	8	62.5%	62.5%	12.5%	37.5%	25%	12.5%	0
DL7	5/25/200*/200	12	83.3%	75%	58.3%	41.7%	41.7%	0	0
DL8	5/25/400*/400	8	50%	50%	37.5%	62.5%	62.5%	0	0
DL9	5/25/800*/800	4	75%	50%	50%	50%	50%	0	0
Phase 2 Portion[b]									
Cohort 1	5/25/50	104	48.1%	39.4%	21.2%	54.8%	39.4%	13.5%	1.9%
Cohort 2	5/25/200	105	69.5%	61.9%	44.8%	46.7%	34.3%	11.4%	1.0%

[a]Full doses were administered as QW until Week 15, followed by Q2W started from Week 16.
[b]Full doses were administered as QW until Week 13, followed by Q2W started from Week 14. In Cohort 2, patients who have achieved and maintained VGPR or better at or after Week 24 and received at least 16 doses of 200 mg will be converted to 200 mg Q4W dosing schedule.

[c]ORR is defined as sCR+CR+VGPR+PR
[d]VGRP or better is defined as sCR+CR+VGPR
[e]CR or better is defined as sCR+CR
*The dose was split into 2 separate infusions over 2 days (preferably consecutive, but no more than 3 days apart).
Source: Table 1, Table 21 and Table 53 in Study 1826 CSR; Table 7 in SCE; Table 20 in SCS.

Population PK analysis

The popPK analysis of total linvoseltamab concentrations generally supports the proposed full dosage of 200 mg QW in the general patient population with RRMM. Because of the low occurrence of anti-drug antibodies, there is insufficient information to characterize the effects of anti-drug antibodies on PK, PD, safety, or efficacy. Refer to Section 19.4.1.2 for additional details of the popPK assessment.

Dose-response analysis

Multivariate dose-response analysis supports the proposed 200 mg QW dosage in patients with RRMM. After accounting for other covariates, the higher full dose amount was associated with better ORR, CR rate, and PFS in 221 patients with RRMM who received at least one full dose of 50 mg QW or 200 mg QW in Study R5458-ONC-1826. No association was identified between OS and full dose amount in 265 patients who received at least one full dose ranging from 3 mg to 800 mg. Refer to Section 19.4.2.3 for the detailed dose-response assessment of efficacy.

No safety concerns were identified with the proposed 5/25/200 mg QW dosage from a clinical pharmacology perspective. After accounting for other patient and disease characteristics, the full dose amount was not identified as a significant covariate on the risk of any grade IRR, TEAE leading to dose modification, any grade infection, Grade ≥2 infection, Grade ≥3 neurotoxicity, Grade ≥3 neutropenia, Grade ≥3 anemia, Grade ≥3 thrombocytopenia, or Grade ≥3 leukopenia. However, the E-R safety analysis may be limited by longer duration of follow-up at lower doses (e.g., 50 mg QW) compared to a relatively shorter duration of follow-up at higher doses (e.g., 200 mg QW). Refer to Section 19.4.2.6 for the detailed dose-response assessment of safety.

Exposure-response analysis

The FDA does not agree that the Applicant's conclusions about the E-R for safety and efficacy are adequately supported, given the significant limitations in the E-R analyses including significantly longer treatment duration and follow-up in the 5/25/50 mg cohort compared to the 5/25/200 mg cohort, use of total drug concentrations rather than free drug concentrations, and potential confounding with duration of treatment, dose modifications, and patient response (refer to Sections 19.4.2.2 and 19.4.2.5 for additional details). The E-R efficacy and safety associations remain uncertain based on current data.

Although the E-R efficacy and safety associations remain uncertain based on current data, the proposed 5/25/200 mg dosage is acceptable from a clinical pharmacology perspective based on multivariate dose-response assessments which are described

above in Section 6.3.2.2 and in Appendix 19.4.2.3 and 19.4.2.6.

- Change in dosing interval (200 mg QW for 3 months, followed by Q2W, then Q4W in VGPR or better)

The FDA agrees with the Applicant's proposal on switching dosing frequency from 200 mg QW to 200 mg Q2W at Week 14. The FDA also agrees with the Applicant's proposed decrease in dosing frequency from 200 mg Q2W to 200 mg Q4W dosing for patients who achieved and maintained VGPR or better at or after Week 24. Responses occurred relatively early during treatment in Study 1826, and median time to response was 1.58 months. Among the 70 patients who had switched to Q2W dosing, 95.7% of patients maintained or improved their responses during the Q2W dosing period. Similarly, of the patients who had switched to Q4W dosing, 96.4%, 91.1%, 84.2% of patients maintained or improved their responses, within 0 to 3 months, 3 to 6 months, and 6 to 9 months of Q4W dosing, respectively (**Table 25**).

Table 25: Number of Responders who Maintained or Improved Response During the Assessment Period with Proposed 5/25/200 mg Dosage Regimen

Dosing schedule	Assessment period	Number of patients at the start of window (N)	Number of patients with response at any time during window (N)	Number and percentage (%) of patients maintained or improved response during the assessment period
200 mg QW[1]	Any period	83	80	80 (100.0%)
200 mg Q2W[2]	Any period	70	70	67 (95.7%)
200 mg Q4W	Any period	56	56	47 (83.9%)
	0 – 3 months	56	56	54 (96.4%)
	3 – 6 months	45	45	41 (91.1%)
	6 – 9 months	19	19	16 (84.2%)
	9 – 12 months	4	4	4 (100.0%)

Data cut-off as of 08Sep2023; Data extract as of 16Oct2023.
[1] First Full Dose – Treatment Week 18 for Phase 1 5/25/200 mg Patients and First Full Dose-Treatment Week 16 for Phase 2 5/25/200 mg Patients
[2] Begins at Treatment Week 18 for Phase 1 5/25/200 mg Patients and Treatment Week 16 for Phase 2 5/25/200 mg Patients; the end of Q2W dosing varies by patient.
Number (%) of patients maintained response or maintained or improved response are based on the denominator of patients with response at any time during window.
QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Table 4 in Applicant's IR response submitted on 3/27/2024 (seqn0017)

- Dosage Recommendations for Restarting Therapy after Dose Delay

FDA's Assessment

CRS associated with linvoseltamab treatment occurs primarily within the first three doses of treatment; however, risk of CRS may re-emerge when a patient is off treatment for a prolonged period, i.e., due to dose delay. This is due to re-sensitization of the immune system and potential re-bound of the target cells. The recommendations in the labeling for restarting therapy with linvoseltamab following a dose delay are presented

in **Table 26**.

Table 26: FDA - Recommendations for Restarting Therapy with Linvoseltamab After a Dose Delay

Last Dose Administered	Time since the last dose administered[a]	Action for next dose
5 mg	≤14 days	Administer 25 mg
	>14 days	Restart step-up dosing from 5 mg
25 mg	≤14 days	Administer 200 mg
	>14 days and ≤28 days	Restart step-up dosing from 25 mg
	>28 days	Restart step-up dosing from 5 mg
200 mg	≤49 days	Administer 200 mg
	>49 days	Restart step-up dosing from 5 mg

Administer pre-treatment medications prior to step-up dose 1, step-up dose 2, the first treatment dose, the second treatment dose, and if indicated, subsequent treatment doses.
[a] Consider benefit-risk of restarting linvoseltamab in patients who require a dose delay of more than 30 days.
Source: Table 2 in the proposed labeling.

The FDA assessment on the adequacy of the proposed recommendations for restarting therapy after dose delay, as detailed below, include evaluations of observed CRS data after dose delay and PK simulations following different dosing delay scenarios.

Observed CRS Incidences

Observed incidences of CRS following dose delay in patients who treated the recommend 5/25/200 mg dosage in Study 1826 are summarized in **Table 27**, which indicated that under most scenarios, there was no increase in the risk of CRS following dose delays that were less than the proposed cutoffs for re-priming when compared to overall patients who received the recommended dosage (**Table 23**). However, there was limited clinical data to support the evaluation of a dosing interval of >14 days and ≤28 days after intermediate dose 25 mg. Only 2 cases were reported in the category and neither patient developed CRS after the subsequent treatments. Instead, such dose delay scenario is supported by the PK-based criterion (**Table 28**).

Table 27: FDA - Summary of CRS Events after Dose Delay in Patients Treated with the Recommend 5/25/200 mg Dosage in Study 1826

Last Dose Administered	Time since last dose	Numbers of Patients	CRS Incidence		
			No CRS	Grade 1 CRS	Grade 2 CRS
Step-up Dose 5 mg	**≤14 days**	26	24 (92.3%)	1 (3.8%)	1 (3.8%)
	>14 days	5	4 (80%)	1 (20%)	

Last Dose Administered	Time since last dose	Numbers of Patients	CRS Incidence		
			No CRS	Grade 1 CRS	Grade 2 CRS
Intermediate Dose 25 mg	≤14 days	28	26 (92.9%)	2 (7.1%)	0
	>14 days and ≤28 days	2	2 (100%)	0	0
	>28 days	0	0	0	0
Initial 200 mg QW	≤49 days	24	23 (95.8%)	1 (4.2%)	0
	>49 days	1	1 (100%)	0	0
Second 200 mg QW	≤49 days	18	17 (94.4%)	1 (5.6%)	0
	>49 days	0	0	0	0
Subsequent 200 mg QW	≤49 days	200	199 (99.5%)	0	1 (0.5%)
	>49 days	8	8 (100%)	0	0
200 mg Q2W	≤49 days	192	192 (100%)	0	0
	>49 days	5	5 (100%)	0	0
200 mg Q4W	≤49 days	49	49 (100%)	0	0
	>49 days	9	9 (100%)	0	0

CRS = cytokine release syndrome; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Applicant's response to IR dated 3/12/2024 and 05/03/2024.

PK Simulations

The dosage recommendations for restarting the doses or repeating doses were also assessed based on PK simulation. Linvoseltamab concentration after each dose delay scenario was compared to linvoseltamab concentrations after the recommended dose schedule. In general, the C_{trough} at the maximum allowed dose delay interval should be no more than 20% lower when compared to the C_{trough} of the next lower dose level (e.g., the step-up doses) to adequately mitigate the risk of CRS. Simulated linvoseltamab exposures under the dose restart recommendations are summarized in **Table 28**. The PK-based criterion supported the proposed recommendations for most dose delay scenarios. The scenarios that didn't meet PK-based criterion (i.e., 5 mg and 25 mg with dose delay less than 14 days, the first 200 mg dose with dose delay less than 49 days) were supported by the observed safety data (i.e., Observed CRS Incidences, **Table 27**).

Table 28: FDA - Simulated Linvoseltamab C_{trough} for Dose Delay Scenarios

Last Dose Administered	Duration Since Last Dose	Proposed Action for Next Dose	Simulated Median C_{trough} [a]	Reference C_{trough}
Step-up dose 1 5 mg	≤14 days	25 mg	0.1291 ng/mL	0.2522 ng/mL
	>14 days	Restart step-up dosing from 5 mg		

Last Dose Administered	Duration Since Last Dose	Proposed Action for Next Dose	Simulated Median C_{trough} [a]	Reference C_{trough}
Step-up dose 2 25 mg	≤14 days	200 mg	0.7734 ng/mL	1.467 ng/mL
	>14 days and ≤28 days	25 mg	0.288 ng/mL	0.2522 ng/mL
	>28 days	Restart step-up dosing from 5 mg		
200 QW (first full dose)	≤49 days	200 mg	0.8774 ng/mL	1.467 ng/mL
200 QW (second full dose and onward)	≤49 days	200 mg	3.159 ng/mL	1.467 ng/mL
200 Q2W	≤49 days	200 mg	5.996 ng/mL	1.467 ng/mL
200 Q4W	≤49 days	200 mg	3.567 ng/mL	1.467 ng/mL
200 mg QW, Q2W, or Q4W	>49 days	Restart step-up dosing from 5 mg		

[a] Ctrough is simulated at the maximum duration of each specified dose delay scenario
Ctrough = trough concentration; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Reviewer's summary of Table 38, Table 42, Table 50, Table 58, Table 78, Table 110, Table 144, and Table 164 in Applicant's Population PK Report (seqn0001) and Applicant's response to IR dated 3/29/2024 (seqn0024)

The proposed labeling also stated that, in order to reduce the risk or CRS and IRR, the patients should receive a prophylactic pretreatment regimen including dexamethasone IV before step-up dose 1, step-up dose 2, the first & second full treatment dose of 200 mg, and after a CRS event. The dose of dexamethasone is 40 mg before step-up dose 1, step-up dose 2, the first treatment dose (i.e., 200 mg) and the next dose following occurrence of CRS and/or IRR. The dose of dexamethasone can be reduced to 10 mg once a treatment dose (i.e., 200 mg) of linvoseltamab is tolerated without CRS or IRR with 40 mg dexamethasone pretreatment. Such recommendation of pretreatment medication may further reduce the CRS risk in patients who experience a dose delay, given that patients with dose delay due to CRS will receive at least two doses of dexamethasone when linvoseltamab treatment resumes (i.e., a 40 mg dose prior to the resumed linvoseltamab treatment dose, and if tolerated, a 10 mg dose prior to the subsequent linvoseltamab treatment dose).

Overall, the dose restart after dose delay recommendations are supported by the available PK and safety data as well as the labeling recommendations on premedication treatment.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

See Section 6.2.2.2.

The Applicant's Position:

No alternative dosing regimen or management strategy is required for subpopulations based on intrinsic factors.

The FDA's Assessment:

The FDA agrees with the Applicant that there is no alternative dosing regimen is required for subpopulations based on age, body weight, sex, race, or ethnicity in patients with RRMM.

No clinically significant differences in exposure to linvoseltamab were observed based on age (37 to 91 years), weight (44 to 172 kg), sex, race (White [n=205], Asian [n=18], or Black [n=44]), ethnicity (Hispanic or Latino [n=22], not Hispanic or Latino [n=251]), mild to moderate renal impairment (creatinine clearance [CLcr] by Cockcroft-Gault equation: 30 to 89 mL/min), or mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST).

The effects of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease (CLcr less than 15 mL/min), moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN with any AST) on the PK of linvoseltamab are unknown. No impact of organ impairment on PK is expected given linvoseltamab is a large, targeted protein and bispecific antibody. Refer to Section 19.4.1 for the detailed popPK model and analysis.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Linvoseltamab is not anticipated to interact directly with CYP450 enzymes, other drug metabolizing enzymes, or drug transporters, and therefore, no drug-drug interaction studies have been conducted with linvoseltamab.

The Applicant's Position:

Linvoseltamab is studied as monotherapy via IV administration, and no food-drug or drug-drug interaction is expected.

The FDA's Assessment:

The FDA agrees with the Applicant that there is no potential impact of food on linvoseltamab pharmacokinetics since linvoseltamab is given via IV administration.

The FDA disagrees with the Applicant's position that there is no potential DDI between linvoseltamab with CYP enzymes. Linvoseltamab causes release of cytokines that may suppress activity of CYP enzymes. Following the recommended 5/25/200 mg dosage, serum concentrations of cytokines (IL-6, IL-10, IL-2, IFN-γ and TNF-α) were measured before and after administration of each step-up dose and the first treatment dose and at end-of-infusion after administration of the second, third and fourth treatment doses. Transient increase in concentrations of circulating cytokines (IL-6, IL-10, IL-2, IFN-γ and TNF-α) 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 (**Figure 3** and **Table 22**).

Based on FDA's evaluation of available clinical data in the literature and understanding of postulated mechanism of IL-6 mediated CYP suppression and estimated time of CYP recovery, FDA recommends monitoring for potential drug interactions with CYP 450 substrates starting from initiation of the step-up dosing until 14 days after the first 200 mg dose.

X X

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 29: Applicant - Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Primary Studies to Support Efficacy and Safety								
R5458-ONC-1826	NCT03761108	Phase 1/2 open-label, FIH study of the safety, tolerability, anti-tumor activity, and PK of linvoseltamab (anti-BCMA x anti-CD3 BsAb)	Phase 1 Dose escalation; linvoseltamab full dose from 3 mg (DL1) up to 800 mg (DL9); QW/Q2W Phase 2 Dose optimization: Cohort 1: 5 mg/25 mg/50 mg QW/Q2W Cohort 2: 5 mg/25 mg/200 mg QW/Q2W/QW	Primary: ORR by IRC Secondary: ORR by Investigator, DOR, PFS, MRD negativity, OS, Evaluation of PRO	Treatment until disease progression or another discontinuation criterion was met	**Phase 1** 73 (complete) **Phase 2** Cohort 1 104 (complete) **Phase 2** Cohort 2 105 (complete)	**Phase 1** Patients were required to have a diagnosis of active MM that is response evaluable by IMWG response criteria. Patients must have experienced disease progression on or after at least 3 lines of therapy (including a PI, an IMiD, and an anti-CD38 antibody) OR progression on or after an anti-CD38 antibody and have disease that is double refractory to a PI and an IMiD, or intolerance of therapy. **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 antibody).	29 centers across 6 countries

The FDA's Assessment:

The FDA agrees with the Applicant's description of study R5458-ONC-1826. While the Applicant identified the pooled Phase 1 and Phase 2 population who received the 200 mg dose (n=117) as the primary efficacy population, the FDA's analysis of efficacy was based on the indicated population from Phase 2 only (i.e., patients who received at least 4 lines of therapy, including a PI, IMiD, and an anti-CD38 antibody; n=80).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. R5458-ONC-1826

Trial Design

The Applicant's Description:

Study 1826 is a phase 1/2, open-label, FIH study of the safety, tolerability, anti-tumor activity, and PK of linvoseltamab in patients with RRMM who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 mAb. 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 DLs of linvoseltamab and to determine one or more recommended RP2DRs 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).

The phase 1 portion of the study followed a modified 3+3 (4+3) dose escalation design with a 28-day DLT observation period to assess the safety and PK of linvoseltamab and to select 1 or more RP2DRs of linvoseltamab IV as a monotherapy. There were 9 DLs in the phase 1 portion, with full doses ranging from 3 mg to 800 mg. At the time of data cutoff, 73 patients had been treated in phase 1, and enrollment in phase 1 per Protocol Amendment 8 was complete.

The phase 2 portion evaluated the anti-tumor activity, safety, PK properties, PRO, biomarkers, and immunogenicity (ADA) responses in patients treated with linvoseltamab IV monotherapy. Cohort 1 had a 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 until disease progression or another discontinuation criterion was met. Enrollment in this cohort is complete with 104 patients. Cohort 2 had a 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 and thereafter until disease progression or another discontinuation criterion was met. Patients would transition to Q2W, and finally, to Q4W administration of linvoseltamab if they received linvoseltamab for at least 24 weeks and achieved a response of VGPR or better. Enrollment is complete in this cohort with 105 patients.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the study design of Study 1826, a phase 1/2 open-label study of linvoseltamab monotherapy in patients with RRMM who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 monoclonal antibody.

Phase 1 was the dose escalation portion and phase 2 included two cohorts to evaluate the safety and efficacy of two full dose levels: 50mg and 200mg. There were some differences in the treatment regimens received by patients treated at the 200mg dose in phases 1 and 2 of study: patients in phase 1 received the first 200mg dose split into separate 100mg doses administered over consecutive days, patients in phase 1 switched from weekly to every other week dosing at week 16 (rather than at week 14 in phase 2), and only patients with response of VGPR or better in phase 2 transitioned to every 4 week dosing after week 24 of treatment.

Eligibility Criteria

The Applicant's Description:

Men and women ≥18 years of age with a confirmed diagnosis of active RRMM by IMWG diagnostic criteria (Rajkumar, 2014), and response evaluable according to the 2016 IMWG response criteria were enrolled in Study 1826 (Kumar, 2016).

In phase 1, patients must have experienced disease progression on or after at least 3 lines of therapy (including a PI, an IMiD, and an anti-CD38 antibody) OR progression on or after an anti-CD38 antibody and have disease that is "double refractory" to a PI and an IMiD, or intolerance of therapy. The anti-CD38 antibody may have been administered alone or in combination with another agent such as a PI. Refractory disease was defined as lack of response or relapse within 60 days of last treatment.

In phase 2, patients (through Protocol Amendment 5) were required to be triple-refractory and penta-exposed. Triple-refractory was defined as being refractory to prior treatment with at least 1 anti-CD38 antibody, a PI, and an IMiD. Penta-exposed was defined as having prior exposure to 2 PIs, 2 IMiDs (lenalidomide and pomalidomide), and 1 anti-CD38 mAb. Beginning in Protocol Amendment 6, phase 2 inclusion required patients to have experienced disease progression on or after at least 3 lines of therapy (including a PI, an IMiD, and an anti-CD38 antibody) or disease must have been 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.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the key eligibility criteria. The full eligibility criteria are listed in Appendix 19.5

Study Endpoints

The Applicant's Description:

The benefits of linvoseltamab monotherapy for the treatment of adult patients with RRMM after 3 lines of prior therapy were evaluated based on clinically meaningful endpoints. The efficacy endpoints selected for Study 1826 are consistent with health authority guidance and approved therapies in the same disease setting.

ORR in Phase 2 using IMWG criteria (Kumar, 2016), as determined by an IRC, was the primary efficacy endpoint. ORR was defined as the number of responders divided by the number of patients in the corresponding analysis set. 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.

Efficacy in Phase 1 was analyzed through the secondary endpoints of ORR, DOR by IMWG per investigator, PFS by IMWG per investigator, rate of MRD negativity by IMWG, and OS. Efficacy in Phase 2 was analyzed through the secondary endpoints of BOR by IMWG per investigator, DOR and PFS by IMWG per IRC and investigator, rate of MRD negativity by IMWG, and OS.

The FDA's Assessment:

FDA agrees with the Applicant's description of the primary and secondary endpoints evaluated in Study 1826. The endpoints that FDA used to evaluate efficacy of linvoseltamab monotherapy are ORR by IRC and DOR for the Phase 2 200 mg cohort. All other secondary endpoints are considered exploratory. It should be noted that time-to-event endpoints such as PFS, and OS cannot be accurately interpreted in single-arm studies as it is difficult to determine the extent to which the outcomes can be attributed to the treatment effect versus the underlying disease.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Study 1826 original SAP had 3 amendments. The modifications to the original SAP are not considered to have had impact on the integrity of the trial or the interpretation of the results. The original SAP (v1.0) was finalized on 5 Jan 2021, based on Study 1826 Protocol Amendment 5.

The SAP was amended (v2.0) on 22 Jul 2021. Major changes included removing a formal interim analysis and incorporating administrative data reviews; defining primary and secondary populations and adding a hierarchical testing procedure for the Phase 2 primary endpoint; adding IRC determined ORR, DOR, and PFS to Phase 2; adding evaluation of the 200 mg full dose patients.

The next SAP amendment (v3.0) was finalized on 27 Jul 2022. Major changes included revising the primary population in Phase 2 to include an all-comers population of RRMM; updating the statistical test methods to be used; updating the Phase 2 stopping rule, an option to backfill enrollment in Phase 1, secondary analysis variables, list of AESI, list of variables and groups for subgroup analysis.

The current amendment (v4.0) was finalized on 13 Mar 2023. Major changes included updating demographic and baseline disease variables to be summarized; additional detail to confirm response per IMWG criteria; additional summaries and analyses for treatment exposure and observed time response and progression; additional supportive analyses for primary and secondary efficacy; updates to list of variables and groups for

subgroup analysis; updating the primary safety analysis to cover time period between first dose up to 30 das post last treatment administration; including additional safety summaries for CRS/IRR events, neurologic events, and infections.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the SAP amendments. The FDA also notes the following details regarding the statistical analysis plan, itself.

Sample Size Calculations and Assumptions:

- Sample size calculations for each cohort of the Phase 2 portion of study were based on providing at least 80% power to reject the null hypothesis of an overall response rate (ORR) of ≤31% at a 1-sided significance level of 0.025 if the true ORR is 45%. Based on these calculations, the sample size of each phase 2 cohort was determined to be 104. The FDA notes that inferential procedures used for sample size calculations are not used to evaluate the results from a single-arm trial. Instead, the efficacy decision is based on the lower limit of a 95% confidence interval to exceed a clinically relevant response rate.

- The FDA notes that the justification for the historical reference rate of 31% lacked justification in the BLA submission. In February 2024, the FDA requested the Applicant provide a justification for the historical reference rate. The Applicant responded that the ORR threshold of 31% established was based on the FDA-recommend response rate from other approved agents at the time. These agents, used for similar or more refractory populations of patients with RRMM, had response rates ranging from 25% to 30%.

Analysis of Endpoints:

- While the analysis of the primary efficacy variable was to be based on the phase 2 portion of study, supportive analyses of the primary efficacy variable included the evaluation of ORR in various subpopulations, including the combined 200mg population. The primary analysis planned for this BLA was based on a clinical cut-off of September 08, 2023.

- For continuous variables, descriptive statistics were used. For categorical or ordinal data, frequencies and percentages were provided. For time-to-event data, median and 95% confidence interval (CI) were summarized by Kaplan-Meier method.

Protocol Amendments

The Applicant's Description:

All changes in the conduct of the study were implemented by protocol amendments to the original study protocol, dated 11 Sep 2018, as described in the study protocol. Key changes in study conduct through Protocol Amendment 8 are detailed in Table 30. Although the study protocol was amended twice after the completion of Protocol Amendment 8, no patients were enrolled under Protocol Amendment 9 or Protocol Amendment 9 US-1. Protocol Amendment 9 included a provision allowing IRC review of the 12 patients in Phase 1 that received a full dose of 200 mg, which is the only change to the analysis of Study 1826 compared with Protocol Amendment 8.

Table 30: Applicant - Protocol Amendments for R5458-ONC-1826

Amendment/ Date	Major Changes
Amendment 1 20 Sep 2018	• The definition of DLT was clarified.
Amendment 2 24 Oct 2018	• 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 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	• Modified 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.
Amendment 5 13 Aug 2020	• The phase 2 portion of the study has been amended to include approximately 84 patients with MM without EMP and up to 20 patients with EMP who are triple-refractory and penta-exposed1 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	• 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
Amendment 7 10 Dec 2021	• 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 EMP 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 32 weeks

Amendment/ Date	Major Changes
	• 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
Amendment 8 08 May 2022	• 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 was changed for the initial dose (week 1) from 48 hours to 24 hours from the start of study drug administration.

Source: Study R5458-ONC-1826 CSR Table 2

The FDA's Assessment:

The FDA agrees with the Applicant's description of the protocol amendments and also notes the following notable changes that were implemented in Amendments 5 and 6:

- Amendment 5: Applicant added a safety evaluation to take place after the first 15 patients received 1 cycle of study drug in order to further evaluate the requirement for hospitalization following the initial doses of linvoseltamab.
- Amendment 6:
  - A blinded IRC was added to evaluate the primary ORR endpoint and select secondary endpoints.
  - Hospitalization requirement following the week 1 dose was increased from 24 hours to 48 hours to align with the onset and duration of CRS.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH GCP Guidelines, and other applicable laws and regulations.

The FDA's Assessment:

The FDA agrees with the Applicant's position that Study 1826 was compliant with Good Clinical Practices. No issues were identified that indicate a significant risk to data quality.

Financial Disclosure

The Applicant's Position:

Information on financial disclosures for Study 1826 is provided in Section 1.

The FDA's Assessment:
FDA reviewed the submitted financial disclosure information and agrees with the Applicant's position. As no disclosable financial interests, arrangements, or payments were identified, Form 3455 was not applicable.

Patient Disposition

The Applicant's Position:

A total of 73 patients were enrolled in the Phase 1 (dose escalation) portion of the study and treated with linvoseltamab IV doses of 1 mg up to a maximum of 800 mg. Among the Phase 1 Patients, as of the data cutoff date, core treatment (ie, treatment received prior to re-treatment with linvoseltamab or IPDE to a higher dose of linvoseltamab) was ongoing for 9 (12.3%) patients, with the majority of patients off core treatment. The most common reason for discontinuing the study was progressive disease (34/73 [46.6%]).

As of the data cutoff date, 08 Sep 2023, there were 209 patients who were enrolled in Phase 2 of the study and had been treated with at least 1 dose of linvoseltamab. 104 patients were enrolled in Phase 2 Cohort 1 with the intention to receive the 50 mg full dose ("Phase 2 50 mg Patients") and 105 patients in Phase 2 Cohort 2 with the intention to receive the 200 mg full dose ("Phase 2 200 mg Patients"). At the time of data cutoff, fewer patients in the Phase 2 200 mg cohort (53.3%) had discontinued treatment than patients in the Phase 2 50 mg cohort (88.5%). The most frequently reported reason for discontinuation of treatment in both cohorts was PD, with a higher proportion of patients discontinuing due to PD in Phase 2 50 mg Patients vs Phase 2 200 mg Patients (61.5% vs 29.5%, respectively).

Overall, a combined total of 117 patients (12 from Phase 1 and 105 from Phase 2) were enrolled at the 200 mg dose ("All 200 mg Patients"). Core treatment was ongoing for 53 [45.3%] patients. The most frequently reported reason for discontinuation of treatment for the All 200 mg Patients was also PD (37 [31.6%] patients). There were 56/117 (47.9%) of patients ongoing in the study as of the data cutoff date. The most common reason for discontinuing the study was PD (27/117 [23.1%]). The proportion of patients who discontinued prior to reaching full dose was low (5.1%) and similar to the Phase 2 200 mg Patients.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's description of the disposition of the "All 200 mg" population. While the Agency agrees with the use of the "All 200 mg" population for safety analyses, the primary efficacy population was limited to patients treated in phase 2 of the study and was based on the indicated population, those who received 4 or more prior lines of therapy (n=80). A summary of the disposition of patients in the primary efficacy population is shown in Table 31 below.

Table 31: FDA- Disposition of FDA-Defined Efficacy Population

Participants n (%)	**Efficacy Population (n=80)**
End of Treatment	
Participants Entered:	80 (100)
Discontinued	45 (56)
Progressive Disease	26 (33)
Adverse Event	10 (13)
Physician Decision	6 (8)
Patient Decision	1 (1.3)
Other	2 (2.5)
Ongoing	35 (44)
End of Study	
Discontinued	42 (53)
Ongoing	38 (48)

Source: FDA Reviewer; generated from ADSL dataset

Protocol Violations/Deviations

The Applicant's Position:

Important protocol deviations were reported in a total of 41 patients in the Phase 2 200 mg group, 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. 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).

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of protocol deviations. FDA's analysis of protocol violations and deviations was based on the safety population, those in Phases 1 and 2 who received the 200 mg dose (n=117). In the safety population, 43 important protocol deviations occurred in 28 patients (24%). The majority of protocol deviations (60%) were due to procedure not being performed (e.g., disease assessments, screening bone marrow evaluation). Others were due to receiving the wrong treatment or incorrect dose (16%), visit performed outside of window (12%), and entering study despite not meeting eligibility criteria (12%). Based on the number and

types of protocol deviations reported, the FDA agrees with the Applicant that they were not likely to impact the study's results.

Table of Demographic Characteristics

Data:

Table 32: Applicant – Demographic and Baseline Characteristics of Phase 1 200 mg Patients, Phase 2 and All 200 mg Dose Patients

	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%)

	50 mg (N=104)	200 mg (N=105)	Phase 1 200 mg (N=12)	All 200 mg Patients (N=117)
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%)
U.S.	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

*Initial dose
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023
Source: M2.7.3 Summary of Clinical Efficacy, Table 5

The Applicant's Position:

Demographic and baseline characteristics of Phase 2 50 mg, Phase 2 200 mg, and All 200 mg Patients were comparable. The mean age of patients was similar in the Phase 2 50 mg (65.5 years) and Phase 2 200 mg Patients (67.6 years). However, the median age of Phase 2 200 mg Patients (71.0 years) was higher than Phase 2 50 mg Patients (65.0 years) and the proportion of patients ≥75 years old was higher in the 200 mg cohort (27.6%) compared with the 50 mg cohort (16.3%). In both Phase 2 cohorts, approximately 55% of patients were male and approximately 70% were White. The percentage of patients who were Black or African American was similar (13.5% in Phase 2 50 mg and 16.2% in Phase 2 200 mg). Although only the Phase 2 200 mg cohort enrolled patients in Korea (9.5% Asian patients from any country), Asian patients were also treated in the 50 mg cohort (5.8%). The mean BMI in both cohorts was approximately 28 kg/m^2, and the majority of patients had an ECOG score of 1. Finally, Phase 2 200 mg Patients had slightly worse performance status (ECOG 1 to 2 of 72.4% vs 65.4%) compared with Phase 2 50 mg Patients.

Baseline disease characteristics in the All 200 mg Patients and Phase 2 200 mg patient groups were similar. Compared with Phase 2 200 mg Patients, Phase 1 200 mg Patients were younger (median age 63.5 years, mean age 65.1 years), more likely to be female (75.0%), and more likely to have a lower median BMI (22.05 kg/m^2). Demographic and baseline characteristics between these groups were otherwise comparable, including patients who were Black or African American (25.0% in Phase 1 200 mg) and had ECOG performance score of 1 (66.7%).

In All 200 mg Patients, the distribution of groups by race, ethnicity, age (<65 vs ≥65 years), and sex (male vs female) among the U.S. patients enrolled in Study 1826 appear to be similar to the SEER reported distribution of race/ethnicity among patients with MM in the U.S. In Study 1826, for All 200 mg Patients, the age prevalence of 37.6% <65 years and 62.4% ≥65 years was comparable with SEER prevalence of 31% <65 years and 69% ≥65 years. Additionally, for All 200 mg Patients, Study 1826 enrolled 17.1% of Black patients, comparable to the SEER prevalence of 22%. Hence, the data from Study 1826 is considered to be representative of the U.S. MM population and informative to the overall risk-benefit profile of linvoseltamab.

The FDA's Assessment:

FDA's analysis of demographics was limited to the safety and FDA-defined efficacy populations.

Analysis of efficacy was limited to 105 patients treated at the 200 mg dose in Phase 2 of the study, given the differences in the treatment regimens received by patients in Phases 1 and 2. In this population, 24% received ≤3 prior lines of therapy, while 76% received ≥4 prior lines of therapy. (b) (4)

Thus, the FDA's primary efficacy population was defined as the population of patients who had received 4 or more prior lines of therapy and were treated in the Phase 2 portion of the study with the 200 mg dose (n=80). The FDA notes that there was underrepresentation of patients of Hispanic/Latino ethnicity (2.5%). Using data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program: SEER 22 2017-2021, the age-adjusted incidence of multiple myeloma was 7.9% in Hispanic males and 5.8% in Hispanic females based on 2017-2021 cases (2). The FDA notes that there was adequate representation of African American patients in Study 1826 (17.1% of the safety population), which is comparable to that of SEER data, which report 17.1% in non-Hispanic Black males and 13% in non-Hispanic Black females (2).

There was adequate representation of patients in older age groups in Study 1826; in the safety population, 36% of patients were between 65-75 years of age and 27% were age 75 or older.

Given the low percentage of patients of Hispanic or Latino ethnicity, additional data is needed in the overall development program of linvoseltamab in order to adequately

characterize the clinical benefit and safety of linvoseltamab in patients of Hispanic or Latino ethnicity. A PMC was considered to obtain additional data regarding the safety and efficacy of linvoseltamab in patients of Hispanic or Latino ethnicity.

The baseline demographics of the FDA-defined efficacy population are provided in Table 33.

Table 33: FDA- Demographic Characteristics of FDA-Defined Efficacy Population

Participants n (%)	**Efficacy Population (N=80)**
Age (Years)	
Median (range) years	71 (37-83)
<65	27 (34)
≥65	53 (66)
≥65 - <75	29 (36)
<75	56 (70)
≥75	24 (30)
Gender, n (%)	
Male	51 (64)
Female	29 (36)
Race, n (%)	
White	55 (69)
Black or African American	11 (14)
Asian	10 (13)
Other	1 (1.3)
Not reported	3 (3.8)
Ethnicity, n (%)	
Not Hispanic or Latino	72 (90)
Hispanic or Latino	2 (2.5)
Not Reported	6 (8)

Source: FDA Reviewer; generated from ADSL dataset

Other Baseline Characteristics

Data:

For Phase 2 50 mg Patients, 59.6% of patients had IgG MM at study entry; 33.7% were at ISS stage II and 23.1% were at ISS stage III. High cytogenetic risk was reported for 26.9% of patients. 16.3% patients had EMP at baseline (per IRC). A BMPC of ≥30% to <60% was reported in 16.3% of patients and a BMPC of ≥60% was reported in 26.9% of patients. Median sBCMA was 379.0 (range: 26.1 to 10200.0) ng/mL.

For Phase 2 200 mg Patients, 54.3% of patients had IgG MM at study entry; 35.2% were at ISS stage II and 16.2% were at ISS stage III. More 200 mg patients had high cytogenic risk (38.1%) than 50 mg patients (26.9%). 17.1% of patients had EMP at baseline (per IRC). Fewer patients in the 200 mg cohort had BMPC of ≥60% reported (17.1%) compared with 50 mg patients (26.9%), whereas both cohorts had similar percentages of patients with BMPC of ≥30% to <60% (19.0% in 200 mg and 16.3% in 50 mg). Median sBCMA was 363.5 (range: 18.7 to 4430.0) ng/mL.

Baseline disease characteristics in the All 200 mg patients and phase 2 200 mg patient groups were similar. Compared with Phase 2 200 mg Patients, the 12 Phase 1 200 mg Patients (DL7) included in the All 200 mg patient group were more likely to have high cytogenic risk (50.0%), BMPC of ≥60% (33.3%), a higher median sBCMA 551.5 ng/mL, and less likely to have EMP at baseline (8.3%).

Among phase 2 50 mg patients, the median number of prior lines of therapy received was 6, with patients having received between 3 and 14 prior lines of therapy. 7.7% had ≤3 prior lines of therapy, and 92.3% had >3 prior lines of therapy. All patients were quadra-exposed and 91.3% of patients were penta-exposed. Among Phase 2 200 mg Patients, the median number of prior lines of therapy received was 5, with patients having received between 2 and 13 prior lines of therapy. 97.1% of the All 200 mg patients received at least 3 lines of prior therapy; 23.8% of patients had ≤3 prior lines of therapy, and 76.2% had >3 prior lines of therapy. Almost all patients (96.2%) were quadra-exposed, but slightly fewer patients in the 200 mg Patients cohort were penta-exposed (77.1%) compared to 50 mg Patients. All 200 mg Patients received similar prior myeloma therapy as the Phase 2 200 mg Patients.

The Applicant's Position:

Baseline disease characteristics of Phase 2 50 mg, Phase 2 200 mg, and All 200 mg Patients were comparable.

The FDA's Assessment:

FDA analysis of baseline disease characteristics was based on the FDA-defined efficacy population (n=80) and is displayed in Table 34. In the efficacy population, all patients had received 4 or more prior lines of therapy and the median number of prior lines was 5 (range 4-13). Twenty-nine percent received 4 prior lines, with 71% having received 5 or more prior lines.

Table 34: FDA- Baseline Disease Characteristics of FDA-Defined Efficacy Population

Participants n (%)	**Efficacy Population (n=80)**
Disease Stage (R-ISS)	
I	17 (21)

II	45 (56)
III	13 (16)
Unknown	5 (6)
ECOG Performance Status	
0	20 (25)
1	60 (75)
Baseline bone marrow plasma cells	
<50%	45 (56)
≥50%	17 (21)
Missing	18 (23)
Cytogenetic Risk	
Standard Risk	48 (60)
High-Risk	32 (40)
Extramedullary Disease by BICR	
Yes	25 (31)
No	55 (69)
Number Prior Lines of	
Median (range) prior lines	5 (4, 13)
<3	0 (0)
3	0 (0)
4	23 (29)
≥5	57 (71)
Prior BCMA-targeted therapy	
ADC	10 (13)
CAR-T	52 (65)
ADC and CAR-T	8 (10)
Anti-BCMA Bispecific	0 (0)
Triple-class exposed	80 (100)
Quadra-class exposed	80 (100)
Penta-class exposed	69 (86)
Triple-class refractory	63 (79)
Penta-drug Refractory (refractory to at least 2 PIs, 2 IMiDs and 1 anti-CD38)	26 (33)
Refractory to last line of therapy	66 (83)

Source: FDA reviewer; generated from ADSL and ADBASE datasets

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

In Phase 2, all patients received concomitant medications. Phase 2 50 mg Patients, 200 mg Patients and All 200 mg Patients received similar concomitant medications. All patients received corticosteroids for systemic use including 98.2% of patients receiving dexamethasone which includes premedication per protocol. 98.6% of patients received analgesics with the majority receiving acetaminophen (paracetamol; 94.0%). 91.1% of patients received antihistamines for systemic use, 78.4% received antibacterials for systemic use, and 52.5% of patients received blood substitutes and perfusion solutions.

The FDA's Assessment:
FDA agrees with the Applicant's comments and also notes the following:

- Compliance: Linvoseltamab was administered intravenously to all study participants
- Concomitant Medications: Based on the IR response received by the FDA on May 14, 2024, the percentage of patients in the safety population who received infection prophylaxis ranged from 2.6% to 91%, depending on the type of infection. In the safety population (n=117), 2.6% of patients received CMV prophylaxis, 54% received PJP prophylaxis, and 91% received HSV and VZV prophylaxis. The medications administered as antimicrobial prophylaxis in Study 1826 were consistent with commonly prescribed medications for patients with relapsed or refractory multiple myeloma. The draft USPI states that prophylactic antimicrobials and anti-viral medications should be administered according to current practice guidelines.
- Premedications: In the protocol, guidance was provided to administer dexamethasone 40 mg IV (along with acetaminophen and an antihistamine) as pre-treatment prior to the initial, intermediate, and first full doses of linvoseltamab. If the first full dose was tolerated without CRS and/or IRR, the dexamethasone dose was to be reduced to 10 mg IV for the subsequent dose. If the linvoseltamab dose was tolerated without CRS and/or IRR, premedications could be discontinued. While guidance was provided, investigators were able to use clinical judgment in the determination of when to decrease and discontinue dexamethasone, so a variety of premedication regimens were administered in the clinical trial.

  Based on the IR response received by the FDA on May 3, 2024, 97% of patients in the safety population received dexamethasone following the initial dose. For the three subsequent doses of linvoseltamab, the percentages of patients who received dexamethasone premedication were 97%, 94%, and 81%. Seventy-four percent of patients received 40 mg of dexamethasone prior to the first three linvoseltamab administrations, and at treatment week 4 (which corresponded to the second full dose for the majority of patients), 38% of patients received 10 mg

dexamethasone, 32% received 40 mg dexamethasone, 19% did not receive any dexamethasone, and 12% received 20 mg dexamethasone.

Details regarding the recommended pre-treatment medications that patients should receive prior to linvoseltamab administration are included in Section 2.3 of the draft USPI. As the premedication regimen received most commonly by patients on the clinical trial aligns with the guidance in the protocol, the draft USPI includes the protocol-specified premedication guidance.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Efficacy data is presented for All 200 mg 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.

Despite minor differences between Phase 1 and Phase 2 inclusion criteria in terms of prior treatment, all patients 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. Notably, the Phase 1 and Phase 2 patient populations were comprised of patients with similar baseline disease characteristics and prior therapy exposures and hence it is justified to pool these patient populations to allow estimation of the response rate with greater precision at the full 200mg dose. In addition, inclusion of Phase 1 patients provides additional DOR data that informs the durability of response at a full dose of 200 mg.

Data: Objective Response Rate (ORR)

Table 35: Applicant - Summary of Best Overall Response Rate Based on IMWG Criteria per IRC in Patients with RRMM

	Phase 2		Phase 1	All
	50 mg (N=104)	200 mg (N=105)	200 mg (N=12)	200 mg (N=117)
BOR Per IMWG Criteria, n (%)				
sCR[a]	19 (18.3%)	42 (40.0%)	6 (50.0%)	48 (41.0%)
CR[a]	3 (2.9%)	5 (4.8%)	1 (8.3%)	6 (5.1%)
VGPR[a]	19 (18.3%)	18 (17.1%)	1 (8.3%)	19 (16.2%)
PR[a]	9 (8.7%)	8 (7.6%)	2 (16.7%)	10 (8.5%)
Minimum Response (MR)	1 (1.0%)	1 (1.0%)	0	1 (0.9%)
SD[b]	18 (17.3%)	12 (11.4%)	0	12 (10.3%)
PD [a]	23 (22.1%)	13 (12.4%)	2 (16.7%)	15 (12.8%)
NE[c]	12 (11.5%)	6 (5.7%)	0	6 (5.1%)
Unconfirmed response (≥PR)[d]	3 (2.9%)	1 (1.0%)	0	1 (0.9%)
Response Per IMWG Criteria				
ORR: sCR+CR+VGPR+PR	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%)
Rate of VGPR or Better (sCR+CR+VGPR)	41 (39.4%)	65 (61.9%)	8 (66.7%)	73 (62.4%)
95% CI[e]	(30.0%, 49.5%)	(51.9%, 71.2%)	(34.9%, 90.1%)	(53.0%, 71.2%)
Rate of CR or Better (sCR+CR)	22 (21.2%)	47 (44.8%)	7 (58.3%)	54 (46.2%)
95% CI[e]	(13.8%, 30.3%)	(35.0%, 54.8%)	(27.7%, 84.8%)	(36.9%, 55.6%)

[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 data cut.
[c] NE 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 CI.
Note: Triple-refractory, quad-refractory, and penta-refractory are not mutually exclusive.
Note: Triple-refractory: Refractory to (daratumumab or isatuximab), and (lenalidomide or pomalidomide or thalidomide), and (bortezomib or carfilzomib or ixazomib). Quad-refractory: Refractory to [(daratumumab or isatuximab), and (any 2 of (lenalidomide, pomalidomide, thalidomide)), and (bortezomib or carfilzomib or ixazomib)], or [(daratumumab or isatuximab), and (lenalidomide or pomalidomide or thalidomide), and (any 2 of (bortezomib, carfilzomib, ixazomib))]. Penta-refractory: Refractory to (daratumumab or isatuximab), and (any 2 of (lenalidomide, pomalidomide, thalidomide)), and (any two of (bortezomib, carfilzomib, ixazomib)).
Data cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023
Source: Module 2.5 Clinical Overview, Table 7

The Applicant's Position:

The primary summary measure of efficacy was ORR (rate of BOR per IRC). The ORR in All 200 mg Patients was 70.9% (95% CI: 61.8, 79.0). All 200 mg Patients had a BOR of ≥VGPR of 62.4% (95% CI: 53.0, 71.2). The BOR rate of ≥CR (CR and sCR) in All 200 mg Patients was 46.2% (95% CI: 36.9, 55.6).

High ORR was observed in multiple pre-specified subgroups in All 200 mg Patients that are considered difficult to treat, including ≥65 to <75 years of age and ≥75 years of age, with high cytogenetic risk, with EMP at baseline, with ISS Stage II/III, penta-refractory patients, and Black or African American patients. Response rate was also high whether patients had ≤3 lines (68.0%) or >3 lines (70.0%) of prior therapy.

Taken together, these data demonstrate high response rates across multiple pre-specified subgroups including those with high-risk characteristics and African American patients. Furthermore, in high-risk subgroups and/or patients with high disease burden, higher efficacy and deeper responses was almost always observed with the 200 mg full dose than the 50 mg full dose.

The FDA's Assessment:

The FDA does not agree with basing the primary efficacy analysis on the All 200 mg patients, which includes data from both Phase 1 and Phase portion of the study. According to the SAP, no primary efficacy variables were collected in the Phase 1 portion. Additionally, the Phase 1 portion was designed as a dose-finding study with the primary objective to determine the RP2D and evaluate safety and tolerability. The FDA notes that heterogeneity may be introduced in combining data from the Phase 1 and Phase 2 with different primary objectives.

Therefore, the FDA's efficacy analysis was limited to the 105 patients from the Phase 2 200mg cohort. Of note, the FDA's primary efficacy analysis and the analysis used in proposed labeling was based on the 80 patients from the Phase 2 200 mg cohort who had received 4 or more prior lines of therapy, in order to align with the (b) (4) indication statement. FDA's efficacy results below are presented for both the Phase 2 200 mg population (n=105) and the Phase 2 200 mg population with 4 or more prior lines (n=80).

The FDA agrees with the Applicant's efficacy results for the Phase 2 200 mg cohort (n=105). The primary efficacy results for these patients, as shown in Table 10 above, can be reproduced by the statistical reviewer. ORR by investigator assessment was 67.6% (95% CI: 57.8%, 76.4%), indicating consistent results with those based on IRC assessment.

The summary of BOR for the Phase 2 200 mg patients with 4 or more prior lines is presented in Table 36. The ORR by IRC for these patients was 70.0% (95% CI: 58.7%, 79.7%), with the lower bound of the 95% CI excluding the pre-specified historical reference rate of 31%. Thus, the study met its pre-specified primary objective.

Table 36: Summary of Best Overall Response Based on IMWG Criteria per by IRC for Patients in the Phase 2 200 mg cohort Who Received Four or More Prior Lines of Therapy

	N=80
BOR Per IMWG Criteria, n (%)	
sCR	31 (38.8%)
CR	5 (6.3%)
VGPR	15 (18.8%)
PR	5 (6.3%)
Response Per IMWG Criteria	
ORR: sCR+CR+VGPR+PR	56 (70.0%)
95% CI for ORR	(58.7%, 79.7%)
Rate of VGPR or Better (sCR+CR+VGPR)	51 (63.8%)
95% CI	(52.2%, 74.2%)
Rate of CR or Better (sCR+CR)	36 (45.0%)
95% CI	(33.9%, 30.3%)

Source: FDA reviewer; generated from ADRS dataset

It was noted that 62 out of 105 (59%) patients in the Phase 2 200 mg cohort had at least 24 weeks of study drug exposure. Among these 62 patients, 56 (90%) had VGPR or better response assessed by investigator and switched from the Q2W to Q4W dosing schedule. Among these 56 patients, 53 had a VGPR or better response assessed by IRC, while the IRC determined that 3 patients had PR at the time of switch to Q4W dosing. The reduction in dosing frequency was not planned in the original protocol but instead, was specified in Protocol Amendment 9 dated March 2023. The FDA notes that due to limitations in the study design, any long-term differences in efficacy between Q2W and Q4W dosing cannot be determined. However, the reduction in dosing frequency had no impact on the evaluation of primary endpoint of ORR and had limited impact on the evaluation of DOR.

FDA does not agree with the Applicant's statement about the subgroup analyses on ORR. Given the relatively small number of patients in subgroups, all results are considered exploratory.

Data Quality and Integrity

The Applicant's Position:

The quality/integrity of the submitted datasets is adequate to facilitate a robust review of the BLA.

The FDA's Assessment:

FDA agrees with the Applicant's position. No issues were identified with the data quality or integrity from the study which could affect the efficacy results. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

Efficacy Results – Secondary and other relevant endpoints

Data: Duration of Response (DOR)

For All 200 mg Patients the estimated median DOR by IRC (per IMWG criteria) as of the data cutoff date was not yet reached (95% CI: 14.2, NE) (median duration of follow-up was 11.10 [range: 0.2 to 34.5] months) ; median duration of follow-up for patients with an objective response of ≥PR was 12.71 ([range: 1.5 to 34.5] months. The proportion of responders (≥PR) maintaining their response at 6, 9, and 12 months in All 200 mg patients was 90.1%, 87.4%, and 77.5%, respectively. The proportion of responders (≥CR) who received 200 mg and who maintained their response at 6 and 9 months after a response of CR was achieved was 90.7% at both timepoints.

As a result of initiating Cohort 1 first, Phase 2 50 mg Patients have had a longer opportunity for follow-up than the Phase 2 200 mg patients included in the All 200 mg Patients group. A comparison with the Phase 2 50 mg Patient data suggests that the durability of responses in patients treated with 200 mg will be similar to, or longer than, patients treated with 50 mg. The proportions of responders (≥PR) in the All 200 mg Patients group and maintained their response at 6, 9, and 12 months of DOR were 90.1%, 87.4%, and 77.5%, respectively, which is somewhat longer than responders who received 50 mg (89.3%, 77.9%, and 75.6%, respectively).

Of the 62/105 (59.0%) Phase 2 200 mg Patients who had ≥24 weeks of study drug exposure, 56 patients achieved an investigator-assessed response of ≥VGPR and switched to Q4W therapy. For patients who transitioned to Q4W dosing, the KM estimated median DOR by IRC (per IMWG criteria) was NR (95% CI: 14.0 months, NE); 9/56 [16.1%] patients progressed after transitioning to Q4W dosing at a median time of 4.86 months, and there was no apparent relationship to the transition to Q4W dosing. The probability of maintaining response (≥VGPR) at 6, 9, and 12 months in Phase 2 200 mg Patients was 98.2%, 94.5%, and 84.2%, from first documented confirmed response (sCR, CR, VGPR, or PR).

Time to Response

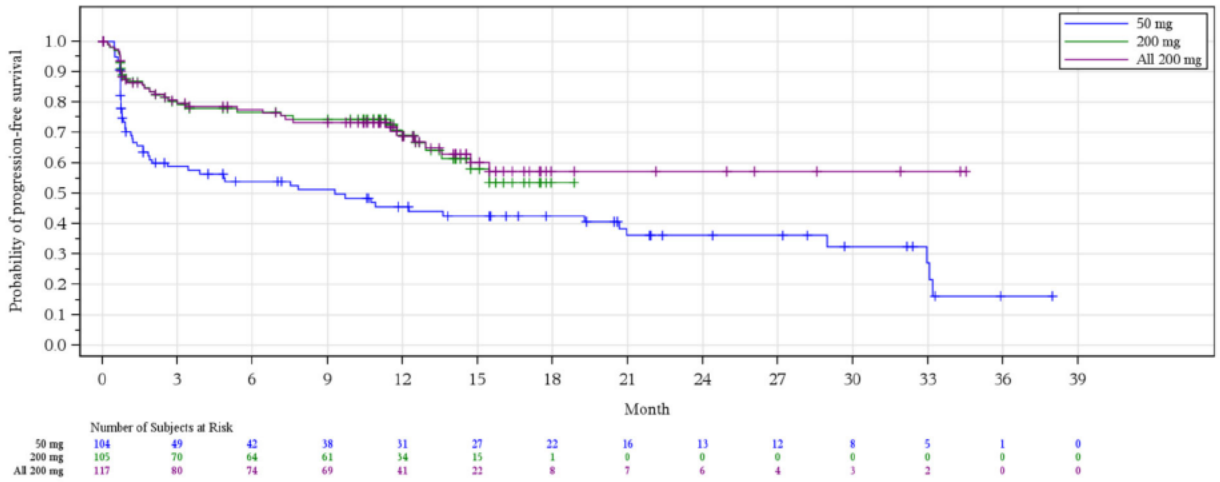
Responses to linvoseltamab occurred early, often by the first efficacy assessment and deepened over time, even as the dose intensity decreased. The median time to ≥PR was 0.95 (range: 0.5 to 6.3) months. The median time to ≥CR was 7.92 (range: 1.9, 13.9) months. Over 95% of responses occurred within 4 months. Overall, 28% of patients achieved CR or better at 9 months and 40% of patients achieved CR or better at 12 months.

PFS and OS

The median PFS in All 200 mg Patients was not reached (range: 14.7 months to NE). The KM estimated probability of PFS at 12 months was 68.8% (95% CI: 58.3, 77.1). In

comparison, PFS was shorter at the lower (50 mg) dose. The KM curve of PFS by IRC is presented in Figure 8. The curves for the 200 mg dose and 50 mg dose diverge early on (approximately within the first month) in treatment, suggesting that the benefit of treatment at 200 mg is seen early.

Figure 8: Applicant - Kaplan-Meier Curve of PFS Per IMWG Criteria (Phase 2 [50 mg and 200 mg] and All 200 mg Patients) per IRC Assessment



Data cutoff as of 08 Sep 2023; data extract as of 16 Oct 2023
Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 4

The median OS in All 200 mg Patients was not reached (range: 21.6 months to NE). The KM estimated probability of survival at 12 months was 74.5% (95% CI: 64.9, 81.8) for All 200 mg Patients (Module 2.7.3 Section 2.2.5). While still early for this endpoint, the trend is in favor of the 200 mg group.

MRD (b) (4)

MRD status was assessed in patients (b) (4)

(b) (4)

The Applicant's Position:

The majority of responders (≥PR) in the Phase 2 200 mg cohort (b) (4) (b) (4) were ongoing at the time of data cutoff date.

The FDA's Assessment:

DOR

The FDA does not agree with the Applicant's statement about (b) (4) (b) (4) which is vague. In a single-arm trial, both the magnitude of the treatment effect and duration of response are critical components of the efficacy evaluation and were used in FDA analyses to establish efficacy.

The median duration of response for the 73 responders in the Phase 2 200 mg cohort was not reached (95% CI: 14.0 months, NE) and the median duration of follow-up was 11.3 months (95% CI: 10.3 to 12.5) using the reverse KM method. The duration of follow-up for the responders met the Agency's recommendation that a minimum of 9-12 months follow-up from the onset of first response (PR or better). The estimated DOR rate was 91.5% at 6 months (95% CI: 82.1, 96.1), 88.5% at 9 months (95% CI: 78.4 94.1), and 76.1% at 12 months (95% CI: 61.1, 85.9).

Additionally, as per the intended indication, the median duration of response for the 56 responders in the Phase 2 200 mg cohort, who received four or more prior lines of therapy and were exposed to a PI, an IMiD and an anti-CD38 mAb, was not reached (95% CI: 12.2 months, NE), and the median duration of follow-up was 11.3 months (95% CI: 10.2 to 12.5) using the reverse KM method. The estimated DOR rate was 92.6% at 6 months (95% CI: 81.6, 97.2), 88.8% at 9 months (95% CI: 76.7, 94.8), and 72.4% at 12 months (95% CI: 54.1, 84.4).

The FDA reviewer noted that the study data lacked detailed reasons for censoring in the DOR analysis, including details regarding censoring for new anti-MM therapy. In April 2024, the FDA requested the Applicant provide detailed censoring reasons for DOR analysis. In response, the Applicant provided updated detailed censoring reasons. Among 57 patients who were censored in the analysis of DOR by IRC, 1 (2%) was due to withdrawal of consent, 4 (7%) were due to other study discontinuation reasons, 2 (4%) were due to new anti-MM therapy, and 50 (87%) were due to data cutoff.

PFS and OS

The time-to-event endpoints, such as PFS, and OS are not interpretable in a single-arm study, and therefore are considered exploratory.

MRD

FDA does not agree with the Applicant's interpretation of the MRD results from Study 1826. As noted by the Applicant, MRD status was assessed in patients (b) (4)

(b) (4)

While the patients with missing results or calibration failure all had (b) (4) MRD results reported, the (b) (4) assay was not appropriately validated. The Division consulted the Center for Devices and Radiological Health (CDRH) for further evaluation of the (b) (4) assay. An IR was sent to the Applicant on April 11, 2024, requesting additional data for (b) (4) assay validation and performance. On May 3, 2024, the Applicant responded and stated that based on FDA feedback, they do not intend to include any data from the (b) (4) assay in the proposed USPI and that they do not intend to perform additional analytical validation (b) (4)

Given the lack of analytical validation demonstrated with the (b) (4) assay, MRD results should not be pooled across the two assays. Further, with the high rates of missing data and calibration failure with the (b) (4) assay, resulting in few patients with available (b) (4) results, MRD results using the (b) (4) assay alone are of limited interpretability. Due to these limitations, MRD data were not considered for inclusion in the draft USPI.

Dose/Dose Response

The Applicant's Position:

Response for 50 mg and 200 mg full doses of linvoseltamab can be found in Table 35. Dose selection rationale can be found in Section 6.2.2.1.

The FDA's Assessment:

Refer to Section 6 and efficacy results provided above for further information about dose selection and response.

Durability of Response

Data:

DOR is presented as a secondary endpoint in Section 8.1.2.

The Applicant's Position:

Responses were durable; among All 200 mg Patients the KM estimated median DOR by IRC (per IMWG criteria) as of the data cutoff date was NR (95% CI: 14.2, NE). In Phase 2 50 mg Patients, the KM estimated median DOR by IRC (per IMWG criteria) was 31.2 months (95% CI: 18.6, NE).
A comparison with the Phase 2 50 mg Patient data suggests that the DOR in patients treated with 200 mg will be similar to, or longer than, patients treated with 50 mg.

The FDA's Assessment:

While the FDA evaluated the durability of response in the Phase 2 200 mg cohort, the primary analysis of DOR was based on the intended indication of patients who received

four or more prior lines of therapy and were exposed to a PI, an IMiD and an anti-CD38 mAb. Refer to FDA's Assessment of above.

Persistence of Effect

The Applicant's Position:

Persistence of efficacy of linvoseltamab was seen in patients with RRMM in Study 1826. Response rates were high, and responses were durable. The durability of efficacy is evident among Phase 2 200 mg and Phase 2 50 mg Patients based on the estimated median DOR by IRC (per IMWG criteria). As of the data cutoff date, the estimated median DOR by IRC was NR (95% CI: 14.0, NE) and 31.2 months (95% CI: 18.6, NE), respectively.

The majority of responders (≥PR) in the Phase 2 200 mg cohort (b) (4) (b) (4) were ongoing at the time of data cutoff date. In addition, responses were maintained in Phase 2 200 mg Patients who achieved a response of ≥VGPR and transitioned from Q2W to Q4W therapy after 24 weeks (N=56). Estimated median DOR by IRC (per IMWG criteria) was NR (95% CI: 14.0 months, NE), and few patients (9/56 [16.1%]) progressed after transitioning to Q4W dosing, at a median time of 4.86 months, and there was no apparent relationship to the transition to Q4W dosing. Among patients who transitioned to Q4W dosing, 98.2%, 94.5%, and 84.2% of these patients were expected to maintain their response after 6, 9, and 12 months, respectively, from first documented confirmed response (sCR, CR, VGPR, or PR).

The FDA's Assessment:

The FDA disagrees with the Applicant's assessment. Persistence of response refers to the assessment of durability after discontinuation of linvoseltamab and is not applicable or evaluable for a treatment that is administered continuously.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Overall (ie, across all weeks) LS mean change from baseline for the GHS/QoL for All 200 mg suggest nominal statistically significant improvements through week 76 and reached the threshold for clinically meaningful improvement by week 44. LS mean change in GHS/QoL did not reach the threshold for clinically meaningful deterioration at any timepoint.

Overall (ie, across all weeks) LS mean change from baseline in fatigue and pain scales for All 200 mg Patients suggest nominal statistically significant improvements in fatigue and pain through week 76; the overall LS mean change for pain exceeded the clinically meaningful threshold of ≤-10. The LS mean changes from baseline first reached the threshold for clinically meaningful improvement for fatigue by week 44 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.

Nominal statistically significant improvements in overall LS mean changes from baseline

were observed for PF, DS, and TSE scales among All 200 mg Patients (Table 53). None of the LS mean changes from baseline in PF, DS, or TSE scores reached the threshold for clinically meaningful deterioration at any timepoint.

The FDA's Assessment:
The FDA does not agree with Applicant's statement about PRO assessments. There was no pre-specified formal hypothesis in the analysis plan. Additionally, the PRO data have limited interpretability in the open label and single-arm trial setting. The treatment effect may be subject to systematic overestimation due to patients' knowledge of treatment assignment. Therefore, these PRO assessments are only considered exploratory and should be interpreted with caution.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Additional analysis were conducted for All 200mg patients included in Clinical Overview (2.5); these included an analysis of 3-month infection incidence by response status (PR or better and CR or better) (section 5.3.5.4 of Clinical Overview) and an analysis of change in median hemoglobin, median lymphocyte count and neutrophil count over time by overall response status (section 5.4. of Clinical Overview).

An analysis of 3-month infection incidence by response status in All 200 mg patients shows a trend for greater decreases in infections and Grade 3/4 infections with deeper responses, further supporting a conclusion that infection risk is driven by MM, and control of MM substantially lowers the risk.

Stratification of responders by best overall response (PR, VGPR, ≥CR) demonstrates that the rise in hemoglobin is most evident in patients with deep responses suggesting that responders, and especially deep responders (VGPR and ≥CR), experience improvements in bone marrow health that are reflected in a rising hemoglobin through 52 weeks on treatment. Trends in lymphocyte and neutrophil counts by responder status through 52 weeks on treatment demonstrate that continued treatment does not have a deleterious effect on these parameters.

The FDA's Assessment:
The FDA does not agree with Applicant's statements about additional analyses conducted on the individual trial. These analyses are considered exploratory and should be interpreted with caution.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
Not applicable.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

Not applicable. BLA761400 is supported by a single pivotal Study (R5458-ONC-1826).

The FDA's Assessment:
Not applicable.

Secondary and Other Endpoints

The Applicant's Position:

Not applicable. BLA761400 is supported by a single pivotal Study (R5458-ONC-1826).

The FDA's Assessment:
Not applicable.

Subpopulations

The Applicant's Position:

Not applicable. BLA761400 is supported by a single pivotal Study (R5458-ONC-1826).

The FDA's Assessment:
Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:
Not applicable.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Linvoseltamab demonstrated clinically meaningful efficacy in patients with RRMM with deep responses. Linvoseltamab monotherapy in All 200 mg patients resulted in high ORR (70.9%; 95% CI: 61.8%, 79.0%) and deep responses (≥CR rate of 46.2%; 95% CI: 36.9%, 55.6%, with MRD negative status at the 10^{-5} threshold achieved for 38.9% (21/54) of patients who achieved ≥CR). In comparison, ORR and depth of response were lower at the lower (50 mg) dose.

The median PFS in All 200 mg Patients was not reached (range: 14.7 months to NE), and the median OS was not reached (range: 21.6 months to NE). The KM estimated probability of PFS at 12 months was 68.8% (95% CI: 58.3, 77.1) and of OS at 12 months was 74.5% (95% CI: 64.9, 81.8). In comparison, PFS was shorter at the lower (50 mg) dose.

Responses to linvoseltamab occurred early, often by the first efficacy assessment and deepened over time, even as the dose intensity decreased. The median time to ≥PR was 0.95 (range: 0.5 to 6.3) months. The median time to ≥CR was 7.92 (range: 1.9, 13.9) months. Over 95% of responses occurred within 4 months. Overall, 28% of patients achieved CR or better at 9 months and 40% of patients achieved CR or better at 12 months. At the lower (50 mg) dose, the ORR rate was 48% and the rate of CR or better was 21%.

Responses were durable; the median DOR for All 200 mg patients was not reached (95% CI: 14.2, NE) (median duration of follow-up was 11.10 [range: 0.2 to 34.5] months; median duration of follow-up for patients with an objective response of ≥PR was 12.71 ([range: 1.5 to 34.5] months. The KM estimated median DOR by IRC (per IMWG criteria) for Phase 2 50 mg Patients was 31.2 months (95% CI: 18.6, NE). A comparison of All 200 mg Patient data with the Phase 2 50 mg Patient data suggests that the durability of responses in patients treated with 200 mg will be similar to, or longer than, patients treated with 50 mg. The proportion of responders (≥PR) maintaining their response at 6, 9, and 12 months in All 200 mg patients was 90.1%, 87.4%, and 77.5%, respectively.

Responses were also durable with Q4W reduced dose frequency in Phase 2 200 mg Patients who completed a minimum of 24 weeks of treatment, had a response ≥VGPR, and transitioned to a reduced dose frequency of Q4W as part of the dosing regimen: the KM estimated median DOR by IRC (per IMWG criteria) was not reached (95% CI: 14.0 months, NE) and the probability of maintaining response (≥PR) at 6, 9, and 12 months was 98.2%, 94.5%, and 84.2% from first documented confirmed response (sCR, CR, VGPR, or PR).

Consistent with the robust efficacy, the estimated mean changes from baseline across PRO endpoints, including GHS/QoL, PF, fatigue, pain, DS, and TSE, suggest nominally significant improvements on average for All 200 mg Patients during the treatment period and overall improvements in pain exceeded the threshold (≤-10 points) for clinically meaningful improvement.

The FDA's Assessment:

The FDA notes that there was no integrated assessment performed, as all efficacy data were from the 200 mg Phase 2 cohort of Study 1826. The efficacy of linvoseltamab is based on evaluation of ORR and DOR, as assessed by an independent review committee in Study 1826, a single-arm trial of linvoseltamab monotherapy in patients with RRMM. Patients received step-up dosing of linvoseltamab (Week 1: 5 mg, Week 2: 25 mg), followed by the treatment dose of 200 mg weekly for 11 doses and Q2W for 5

doses. Patients with response of VGPR or better transitioned to reduced frequency dosing of Q4W, while those with response less than VGPR continued on Q2W dosing.

The FDA determined (b) (4) that an advantage in the context of available therapies was demonstrated for (b) (4) population of patients with 4 prior lines of therapy, (b) (4)
The primary efficacy analysis population was defined according to the (b) (4) indication.

In Study 1826, efficacy was evaluated in 105 patients treated at the 200 mg dose in the Phase 2 portion of study and the primary analysis population was defined as 80 patients who had also received 4 or more prior lines of therapy.

Of the 80 patients in the FDA-defined efficacy population, the median age was 71 years (range: 37-83). Forty percent of patient had high risk disease and 31% had extramedullary disease. The median number of prior lines was 8, with 29% having received 4 prior lines of therapy and 71% having received ≥5 prior lines. All patients were triple-class (PI, IMiD, anti-CD38 mAb) exposed, 79% were triple-class refractory, and 33% were penta-drug (2 PIs, 2 IMiDs, and 1 anti-CD38 mAb) refractory. Eighty-three percent of patients were refractory to the last line of therapy.

The FDA does not agree with the Applicant's position on the following points:

- Durability following reduced dosing frequency: The FDA does not agree with the Applicant's statement regarding the durability of response with switching from Q2W to Q4W dosing frequency in patients who completed a minimum of 24 weeks of treatment and had a response of VGPR or better. Due to the study design limitations, long-term differences between Q2W and Q4W dosing were unable to be evaluated.
- Patient-reported outcomes: The FDA does not agree with Applicant's statement about PRO assessments, given the limitations in assessing PROs in a single-arm trial and given the lack of pre-specified formal hypothesis testing for evaluation of PROs. Refer to FDA's Assessment of above.
- Time-to-event endpoints: Regarding the Applicant's description of time-to-event endpoints (PFS and OS), the FDA notes that these endpoints are considered exploratory and are challenging to interpret in the context of a single-arm trial.

ORR, when supported by durability of response, is considered an acceptable intermediate endpoint that is likely to predict clinical benefit in patients with MM. To support accelerated approval, efficacy data are considered in the context of available therapies. Therapies with regular approval for patients with triple-class exposed RRMM

include selinexor + dexamethasone (ORR 25%, median DOR 3.8 months) and two CAR T-cell therapies: idecabtagene vicleucel (ORR 72%, median DOR 11.0 months) and ciltacabtagene autoleucel (ORR 98%, median DOR 21.8 months). In addition to therapies that are specifically approved for triple-class exposed RRMM, other therapies and combinations of therapies can be effective. CAR-T cell therapies have demonstrated high response rates, along with durability of response, but are not considered to be available to all patients, due to the need for administration at specialized academic centers and due to the complex manufacturing process, which may lead to treatment delays. While not considered to be available therapy for all patients, the majority of patients in the efficacy population from Study 1826 (65%) had received prior CAR-T cell therapy. Thus, in the context of the available therapies for the RRMM triple-class exposed population, linvoseltamab demonstrates clinically meaningful efficacy, based on ORR, and supported by durability.

Based on the totality of data, linvoseltamab demonstrates evidence of effectiveness in patients with RRMM who have received at least 4 lines of prior therapy. As of August 8, 2024, 154 of a planned (b) (4) patients ((b) (4) %) had been enrolled in the proposed confirmatory trial, Study R5458-ONC-2245. The Applicant's projections are that full enrollment will be completed by Q2 2025 and that the readout of the primary PFS endpoint will occur around Q2 2026, and the Division considers the timelines and projections provided by the Applicant to be reasonable.

Due to the manufacturing issues that have been identified at the manufacturing facility of linvoseltamab, the recommended regulatory action for BLA 761400 is a Complete Response. Refer to the OPQ Executive Summary for additional information.

8.2. Review of Safety

The FDA's Assessment:

The safety profile of linvoseltamab was determined based on data from patients treated at the 200 mg dose in Study 1826. There were three differences between the treatment regimens received by Phase 1 vs. Phase 2 patients (as described in 'The Applicant's Position' in Section 8.2.1 below); while these precluded the ability to pool the Phase 1 and 2 populations for efficacy, the differences were not considered to meaningfully affect the safety evaluation. Thus, the FDA safety analysis includes patients treated in Phases 1 and 2 of the study at the 200 mg dose (12 from Phase 1 and 105 from Phase 2, for a total n=117).

The FDA analyses for safety were conducted based on datasets provided by the Applicant for Study 1826, with a data cut-off of September 08, 2023.

8.2.1. Safety Review Approach

The Applicant's Position:

For this application, clinical safety data for linvoseltamab monotherapy are available only from Study 1826, therefore there is no pooling of safety data across studies. 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 SAF. 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").

For the All 200 mg Patients set, it is appropriate to combine Phase 1 and Phase 2 patients treated with a 200 mg dose because differences in per protocol treatment of these patients do 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 vs 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).

Notably, overall the Phase 1 and Phase 2 patients treated at 200 mg dose had comparable demographic and baseline disease characteristics with similar disease severity. There were minor differences between Phase 1 and Phase 2 in terms of prior treatment, but all patients 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). The only baseline disease characteristic difference between Phase 1 200 mg and Phase 2 200 mg Patients was EMP status. Overall, the Phase 1 and Phase 2 200 mg patient populations were comprised of patients with similar baseline disease characteristics and prior therapy exposures.

The FDA's Assessment:

FDA agrees with the Applicant's approach to the safety evaluation, as described in the FDA's assessment above Section 8.2.1, and considers that based on the nature of the differences in the treatment regimens received by Phase 1 and Phase 2 patients, it is acceptable to pool data between phases for the purposes of the safety evaluation.
FDA's review of safety included a review of treatment-emergent AEs, SAEs, deaths, dose modifications, including discontinuations, and adverse events of special interest (AESIs). In addition to the AESIs identified by and analyzed by the Applicant, the FDA also performed an analysis of hepatotoxicity and based on the findings, has included hepatotoxicity in the Warnings and Precautions of the draft USPI. FDA's safety analysis

utilized grouping of related preferred terms; in some cases, FDA's grouping differed from that of the Applicant. The full listing of FDA's grouped preferred terms is provided in Appendix 19.6.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The mean (SD) exposure for Phase 2 200 mg Patients was 36.9 (25.79) weeks. The median duration of exposure was 47.4 (range: 1 to 82) weeks. The majority of Phase 2 200 mg Patients (57/105 [54.3%] patients) had ≥9 months of exposure to linvoseltamab; 36/105 (34.3%) had ≥12 months of exposure, and 16/105 (15.2%) had ≥15 months of exposure to linvoseltamab.

In Phase 2 50 mg Patients, the mean (SD) exposure was 38.8 (43.69) weeks. The median duration of exposure was 13.9 (range: 2 to 146) weeks. The majority of Phase 2 50 mg Patients (53/104 [51.0%] patients) had ≥3 months of exposure to linvoseltamab, 45/104 (43.3%) had ≥6 months of exposure, 37/104 (35.6%) had ≥9 months of exposure to linvoseltamab, and 28/104 (26.9%) had ≥12 months of exposure to linvoseltamab.

The mean (SD) exposure of All 200 mg Patients is 40.9 (32.77) weeks, and the median duration of exposure was 47.4 (range: 1 to 151) weeks. The mean exposure was longer for All 200 mg Patients than for Phase 2 200 mg Patients due to the longer mean exposure of the 12 Phase 1 200 mg Patients (75.7 weeks).

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.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of exposure to treatment, however FDA analysis was limited to the 'All 200' population. The FDA reviewed, but did not independently confirm, the data provided for treatment exposure in the patients who received the 50 mg dose. The FDA analysis of treatment exposure in the 'All 200' population is provided in tabular format and with the parameter in months, rather than weeks, in Table 37.

Table 37: FDA- Summary of Exposure

	Safety Population (n=117)
Treatment Duration (Months)	
Mean (SD)	9.4 (7.5)
Median (Min, Max)	10.9 (0.30, 34.6)
Number of Doses Administered	
Mean (SD)	20.5 (14.7)
Median (Min, Max)	24 (1, 74)

Source: FDA analysis based on ADEXSUM.xpt

Relevant characteristics of the safety population:

The Applicant's Position:

The median age of All 200 mg Patients was 70.0 (95% CI: 37, 91) years with 62.4% of patients being ≥65 years old. 54.7% of All 200 mg Patients were male, 70.9% of patients were White, 17.1% were Black or African American, and 8.5% were Asian. The mean (SD) BMI was 27.7 (5.99) kg/m^2. The majority of patients (71.8%) had an ECOG score of 1.

This was similar to the baseline characteristic profile of Phase 2 50 mg Patients, with a few notable differences. The proportion of patients ≥75 years was higher in the All 200 mg cohort compared to the 50 mg cohort (26.5% vs 16.3%). The proportion of patients from the U.S. was lower in the All 200 mg cohort (82.9% vs 91.3%), due to enrollment in Spain and Korea starting after the Phase 2 50 mg cohort was already enrolled. Correspondingly, the proportion of Hispanic and Latino patients was also lower in the All 200 mg cohort (3.4% vs 11.5%).

The distribution of groups by race, ethnicity, age (<65 vs ≥65 years), and sex (male vs female) among the U.S. patients enrolled in Study 1826 appear to be similar to the SEER reported distribution of race/ethnicity among patients with MM in the U.S. In Study 1826, the sex prevalence of 45.3% female and 54.7% male was comparable with the SEER prevalence of 45% female and 55% male, and the age prevalence of 37.6% <65 years and 62.4% ≥65 years was comparable with SEER prevalence of 31% <65 years and 69% ≥65 years. Additionally, Study 1826 enrolled 15.6% of Black patients, comparable to the SEER prevalence of 22%. Hence, the data from Study 1826 is considered to be representative and informative to the overall U.S. population.

Overall, baseline characteristics were consistent with expectation in heavily pretreated advanced RRMM patients with high disease burden.

The FDA's Assessment:

The FDA disagrees with the Applicant's statement that the data from Study 1826 is considered representative of the overall U.S. population, and notes that only 3.4% of the safety population were of Hispanic/Latino ethnicity. As noted in Section 8.1.2, the incidence of multiple myeloma in Hispanic patients based on SEER data from 2017-2021 was 7.9% in males and 5.8% in females. Additional data regarding the safety and clinical benefit of linvoseltamab in Hispanic or Latino patients may be warranted. Baseline demographic characteristics of patients in the safety population are shown in Table 38.

Table 38: FDA- Demographic Characteristics of Safety Population

Participants n (%)	**Safety Population (n=117)**
Age (Years)	
Median (range) years	70 (37-91)
<65	44 (38)
≥65	73 (62)
≥65 - <75	42 (36)
<75	86 (74)
≥75	31 (26)
Gender, n (%)	
Male	64 (55)
Female	53 (45)
Race, n (%)	
White	83 (71)
Black or African American	20 (17)
Asian	10 (9)
Other	1 (0.9)
Not reported	3 (2.6)
Ethnicity, n (%)	
Not Hispanic or Latino	107 (91)
Hispanic or Latino	4 (3.4)
Not Reported	6 (5)

Source: FDA reviewer; generated from ADSL dataset

In the safety population, 39% had high-risk disease and 31% had extramedullary disease. The median number of prior lines was 5, with 76% having received 4 or more prior lines. The baseline disease characteristics are presented in Table 39.

Table 39: FDA- Baseline Disease Characteristics of Safety Population

	Safety Population (n=117) N (%)
Disease Stage (R-ISS)	
I	28 (24)
II	65 (56)
III	17 (15)
Unknown	7 (6)
ECOG Performance Status	
0	33 (28)
1	84 (72)
Baseline bone marrow plasma cells	
<50%	66 (56)
≥50%	27 (23)
Missing	24 (21)
Cytogenetic Risk	
Standard Risk	71 (61)
High-Risk	46 (39)
Extramedullary Disease by BICR	
Yes	36 (31)
No	81 (69)
Number Prior Lines of	
Median (range) prior lines	5 (2, 16)
<3	4 (3.4)
3	24 (21)
4	24 (21)
≥5	65 (56)
Prior BCMA-targeted therapy	0
ADC	10 (9)
CAR-T	76 (65)
ADC and CAR-T	8 (7)
Anti-BCMA Bispecific	0
Triple-class exposed	117 (100)
Quadra-class exposed	112 (96)
Penta-class exposed	90 (77)

Triple-class refractory	96 (82)
Penta-drug Refractory (refractory to at least 2 PIs, 2 IMiDs and 1 anti-CD38)	33 (28)
Refractory to last line of therapy	100 (85)

Source: FDA reviewer; generated from ADSL and ADBASE datasets

Adequacy of the safety database:

The Applicant's Position:

The Sponsor considers that the primary SAF of 117 patients pooled from Phase 2 (n=105) and Phase 1 dose level 7 (n=12) who were dosed with 200 mg full dose in Study 1826 (see Section 8.2.1 for pooling rationale) and all supportive evidence from all Phase 1 and Phase 2 patients (n=282 including 105 patients at a lower clinically active full dose of 50 mg) in Study 1826 are sufficient to adequately evaluate the safety and support registration of linvoseltamab for the proposed indication.

The FDA's Assessment:

The FDA agrees with the Applicant that the safety database based on the primary safety population of 117 patients pooled from Phases 1 and 2 of the study is sufficient to evaluate the safety of linvoseltamab. In the 'All 200' Population, median duration of study follow up was 11.8 months (range 0.3, 34.5).

FDA performed only a high-level analysis of the safety profile between the two dose levels to capture any notable differential safety findings, which are presented in Table 40. Rates of TEAEs were similar between the two dose levels. There were higher rates of dose interruptions, infections, and ICANS at the 200 mg dose level, as compared to the 50 mg dose level, while rates of other dose modifications and other AESIs were comparable between dose levels. For further FDA comments on dose selection, refer to Section 6.2.

Table 40: FDA- Safety Overview by Dose Level

	5/25/50mg Dose Level (n=104) N (%)	**5/25/200mg Dose Level (n=117) N (%)**
Safety Overview		
Any Grade TEAEs	102 (98)	117 (100)
Grade 3-4 TEAEs	83 (80)	96 (82)
Grade 5 TEAEs	9 (9)	14 (12)
Serious TEAEs	77 (74)	86 (74)
Dose Modifications		
AE leading to dose reduction	19 (18)	16 (14)

AE leading to dose interruption	52 (50)	83 (71)
AE leading to discontinuation	13 (13)	19 (16)
Select AESIs		
CRS	57 (54)	54 (46)
Neurotoxicity	64 (61)	63 (54)
ICANS	5 (5)	9 (8)
Infections	64 (62)	85 (73)

Source: FDA reviewer; generated from ADAE dataset

The FDA also notes that the assessment of the adequacy of the safety database is made in the context of linvoseltamab being used to treat a life-threatening disease. The evaluation of safety is limited by the single-arm trial design, and there is currently no randomized data available comparing linvoseltamab to standard-of-care therapy.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

The safety data integrity and submission quality in Study 1826 are considered adequate for regulatory review.

The FDA's Assessment:

The quality of the safety data submitted was adequate for substantive primary review. The Applicant provided the full datasets for patients enrolled in Study 1826.

Categorization of Adverse Event

The Applicant's Position:

AE analysis was performed on TEAEs during core treatment (defined as the treatment received by a patient prior to re-treatment or IPDE), unless explicitly noted otherwise. TEAEs were defined as those AEs that newly occurred or worsened during the period from first dose up to 30 days post-last study drug administration or the day prior to the start of new treatment for MM, whichever occurred first, and any treatment-related AEs that occurred regardless of timing, except after start of re-treatment or after IPDE.

Laboratory results, vital signs, or ECG abnormalities were recorded as AEs if they were medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation, and/or fulfilling a seriousness criterion. All AEs were coded using MedDRA version 26.0.

The FDA's Assessment:

FDA's evaluation of safety was based on the Applicant's definition of TEAEs, however the FDA notes that the sources used to derive the 'Treatment Emergent Analysis Flag'

in the ADAE dataset were not those that are conventionally used. The FDA noted that in addition to capturing AEs that started between the first dose and the end of period 1 (defined as 30 days post-last study drug administration or day prior to new MM treatment), AEs that started on the same day as the first dose but not prior to the first dose, and AEs that were considered treatment-related and occurred regardless of timing (except for after the start of re-treatment or IPDE), the Applicant also included a derivation based on 'date that AE became Grade 3 or higher between the first dose and period 1 end date, and AE initial severity grade is less than AE most extreme severity grade.'

The FDA sent an Information Request to the Applicant on February 29, 2024, to clarify why only the AEs that became Grade 3 or higher between the first dose and period 1 end date, with initial severity less than most severity, were captured, given that all AEs, including those that have worsened from baseline, should be captured in the ADAE dataset, not just those that worsened to Grade 3 or higher.

The Applicant responded on March 6, 2024, stating that the "Date AE Became Grade 3 or Higher" derivation was included to capture additional worsening events, beyond those captured by the other derivations listed above. The Applicant noted that there were 15 AEs with a maximum severity grade less than 3 or an initial severity grade of 3 or greater that were not captured in the database, and that based on the information in the ADAE dataset, the determination of whether the worsening occurred prior to or following the first dose could not be made. FDA noted that of these 15 events, 6 occurred in patients in the primary safety population. Of those 6 events, 1 was captured as a separate AE in the ADAE dataset. Given that only 5 events remained, for which there was uncertainty about timing before or after to initiation of study treatment, the decision was made to not include these events in the analysis of adverse events.

Other clarifications regarding the derivation of the 'Treatment Emergent Analysis Flag' revealed that in the ADAE dataset (including all patients treated in Study 1826) a total of 29 treatment-related AEs occurred after the 'Period 1 end date' and were included as they were considered treatment-related. While this portion of the definition is also unconventional, given the relatively small number of events included from this derivation, the decision was made to utilize the safety database with the existing 'Treatment Emergent Analysis Flag'.

In order to characterize the duration of safety follow up after completion of study treatment in the safety population, the FDA also queried the Applicant regarding the number of patients whose 'Period 1 end date' was earlier than 30 days after completion of treatment. In the safety population (n=117), 73 patients had a 'Period 1 end date' earlier than 30 days after completion of treatment; most commonly, the reason was that patients remained on therapy at the data cut-off date, while in 18 of these patients, the reason was initiation of new MM therapy.

As noted by the Applicant, AEs were coded using MedDRA Version 26.0. CRS and ICANS events were graded according to ASTCT Criteria (Lee et.al., 2019), while all other AEs were graded according to NCI CTCAE version 5.0.

In addition to the AESIs identified by the Applicant, the FDA also identified hepatotoxicity as an AESI. FDA analysis of TEAEs was based on FDA grouping of related grouped terms, some of which differed from grouping used in the Applicant's analysis. Refer to Appendix 19.6 for the full list of FDA's grouped terms.

Routine Clinical Tests

The Applicant's Position:

All safety procedures were conducted at pre-specified timepoints, per protocol. These assessments included, but were not limited to, body weight, vital signs, physical examination, ECG, and laboratory testing (blood chemistry, hematology, urinalysis, etc)

The endpoints used in this study were standard, validated, and relevant to the objectives set forth in the study protocol.

The FDA's Assessment:

The safety procedures and endpoints were considered adequate in the context of the study.

8.2.4. Safety Results

Deaths

Data:

Table 41: Applicant - On-treatment Deaths up to 30 days from End of Treatment*- Phase 2 and All 200 mg Dose

	Phase 2		All
	50 mg (N=104)	200 mg (N=105)	200 mg** (N=117)
Number of Deaths, n (%)	12 (11.5%)	8 (7.6%)	8 (6.8%)
Primary cause of death			
ADVERSE EVENT	7 (6.7%)	6 (5.7%)	6 (5.1%)
PROGRESSION/RECURRENCE OF DISEASE	4 (3.8%)	2 (1.9%)	2 (1.7%)
OTHER	1 (1.0%)	0	0

* Summary presents deaths occurring from the first dose day 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 for multiple myeloma, whichever comes first.
**All 200 mg (N=117) = Phase 1 200 mg patients (n=12) + Phase 2 200 mg patients (n=105)
Data cut-off as of 08Sep2023; Data extract as of 16Oct2023

Source: Module 2.5 Clinical Overview, Table 14

Table 42: Applicant - Adverse Events Leading to On-treatment Death *– Phase 2 and All 200 mg Dose

	Phase 2		
AE Description, n (%)	**50 mg (N=104)**	**200 mg (N=105)**	**All 200 mg** (N=117)**
Number of patients with any Adverse Event n (%)	7 (6.7%)	6 (7.5%)	6 (5.1%)
Infections			
COVID-19	2 (1.9%)	0	0
COVID-related lung infection	0	1 (1.0%)	1 (0.9%)
COVID-19 infection	1 (1.0%)	0	0
Escherichia sepsis	0	1 (1.0%)	1 (0.9%)
Sepsis (Hemophilus influenzae)	0	1 (1.0%)	1 (0.9%)
Septic shock	1 (1.0%)	1 (1.0%)	1 (0.9%)
Septic shock (Pseudomonas bacteremia)	0	1 (1.0%)	1 (0.9%)
Non—infection adverse events			
Intracranial hemorrhage	1 (1.0%)		
Lung embolism	1 (1.0%)		
Sudden death	1 (1.0%)		
Worsening chronic kidney disease	0	1 (1.0%)	1 (0.9%)

* Deaths occurring from the first dose day 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 for multiple myeloma, whichever comes first.
**All 200 mg (N=117) = Phase 1 200 mg patients (n=12) + Phase 2 200 mg patients (n=105)
Data cut-off as of 08Sep2023; Data extract as of 16Oct2023
Source: Module 2.5 Clinical Overview, Table 15

The Applicant's Position:

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. The most common cause of death was "AE" and occurred in 6/117 (5.1%) patients. In 3/117 (2.6%) patients the AE was assessed as related to linvoseltamab.

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%]).

In All study patients (N=282), the incidence of total deaths up to 30 days from end of treatment, and of those deaths due to AEs, were 8.9% and 5.3%, respectively.

In the All 200 mg Patients, there were 14/117 (12.0%) patients with a TEAE leading to death. The most common SOC was Infections and infestations (11/117 [9.4%] patients), including PTs of COVID-19 pneumonia (3/117 [2.6%] patients), Septic shock (2/117 [1.7%] patients), Escherichia sepsis, Hemophilus sepsis, PJP, Pneumonia influenzal, PML, and Pseudomonal sepsis (1/117 [0.9%] patients each). Most TEAEs of infection leading to death occurred in the first 3 months of treatment. The TEAEs leading to death were assessed as related to linvoseltamab in 3/117 (2.6%) patients and were PJP, PML, and Pseudomonal sepsis.

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; this difference was primarily driven by a lower rate of TEAEs in the SOC of Infections and infestations leading to death (5/104 [4.8%]). The TEAEs leading to death were assessed as related to linvoseltamab in 1/104 (1.0%) patient, specifically an event of PML.

The FDA's Assessment:

The FDA notes that the analysis of deaths should be focused on those that occurred in patients treated at the 200 mg dose, and that the rate of fatal TEAEs, regardless of relatedness to linvoseltamab, should be presented. FDA performed adjudication of all deaths that occurred in patients in the safety population and adjudicated two deaths identified by the Applicant as deaths due to PD instead as deaths due to AE (one event of TLS and one event of encephalopathy). Based on FDA adjudication and analysis, 19 patients (16%) died due to fatal adverse events. Of these 19 events, 9 occurred within 30 days of the last linvoseltamab dose and 10 occurred more than 30 days after the last linvoseltamab dose. FDA's analysis of fatal AEs is presented in Table 43.

Table 43: FDA- Fatal Treatment Emergent Adverse Events

	Safety Population (n=117)
Death due to AE	19 (16)
Infections	14 (12)
Encephalopathy	2 (1.7)
Chronic Kidney Disease	1 (0.9)
Respiratory Failure	1 (0.9)
Tumor Lysis Syndrome	1 (0.9)

Source: FDA Reviewer; generated from ADAE dataset and review of 'Study 1826 Narratives'

The specific types of fatal infections included sepsis (8 patients), COVID-19 pneumonia (3 patients), PJP pneumonia (1 patient), influenza pneumonia (1 patient), and progressive multifocal leukoencephalopathy (PML; 1 patient).

Serious Adverse Events

The Applicant's Position:

In All 200 mg Patients, 86/117 (73.5%) patients experienced an SAE. The most common SAEs by PT (≥5% of total patients) were CRS (32/117 [27.4%]), Pneumonia (15/117 [12.8%]), COVID-19 (8/117 [6.8%]), and Acute kidney injury (6/117 [5.1%]). 50/117 (42.7%) patients had grade 3 or 4 SAEs, and 14/117 (12.0%) had grade 5 SAEs. In 65/117 (55.6%) patients with SAEs, at least 1 SAE was considered treatment-related. The most common treatment-related PTs (≥5% of patients) were CRS (32/117 [27.4%]) followed by Pneumonia (10/117 [8.5%]), which are both anticipated risks for linvoseltamab.

In Phase 2 50 mg Patients, the percentage of patients experiencing an SAE (77/104 [74.0%]) and the percentage experiencing a treatment-related SAE (53/104 [51.0%]) was similar to All 200 mg Patients. The most common SAEs by PT (≥5% of patients) and the most common treatment-related SAEs by PT were also similar to All 200 mg Patients.

The FDA's Assessment:

The FDA notes that the evaluation of AEs, including SAEs, was based on an assessment of all AEs, rather than those considered treatment-related.
FDA agrees with the rate of SAEs that occurred in the safety population (74%), however, based on the FDA approach to grouping of terms, the most common types of SAEs according to FDA analysis differ from those reported by the Applicant. The FDA analysis of SAEs is presented in Table 44. The most common SAEs were cytokine release syndrome (27%), pneumonia (24%), and sepsis (10%).

Table 44: FDA-Serious Adverse Events in ≥4%

	Safety Population (n=117) N (%)
Any SAE	86 (74)
Immune System Disorders	
Cytokine Release Syndrome	32 (27)
Infusion Related Reaction	5 (4.3)
Infections and Infestations	
Pneumonia	28 (24)
Sepsis	12 (10)
COVID-19 Infection	8 (7)
Upper Respiratory Tract Infection	6 (5)

Urinary Tract Infection	5 (4.3)
Nervous System Disorders	
Encephalopathy	9 (8)
Renal and Urinary Disorders	
Acute Kidney Injury	6 (5)
Blood and lymphatic system disorders	
Febrile Neutropenia	5 (4.3)

Source: FDA Reviewer; generated from ADAE dataset

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

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, PJP, 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 Phase 2 50 mg Patients, the incidence of TEAEs that led to study drug discontinuation (13/104 [12.5%]) was similar to All 200 mg Patients.

The FDA's Assessment:

The FDA agrees with the Applicant's statement regarding the percentage of patients in the safety population who experienced TEAEs leading to study drug discontinuation (16%). However, based on FDA grouping and analysis, FDA analysis of the types of AEs leading to study drug discontinuation differ from those presented by the Applicant. Results of the FDA analysis are presented in Table 45. The most common TEAEs leading to treatment discontinuation were infections (pneumonia and sepsis).

Table 45: FDA- TEAEs Leading to Treatment Discontinuation in >1%

	Safety Population (n=117) N (%)
TEAE Leading to Treatment Discontinuation	19 (16)
Pneumonia	5 (4.3)
Sepsis	5 (4.3)
Encephalopathy	2 (1.7)

Source: FDA Reviewer; generated from ADAE dataset

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Overall, 86/117 (73.5%) of All 200 mg Patients had at least 1 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 1 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.

The FDA's Assessment:

The FDA agrees with the percentage of patients who experienced dose modifications (74%), and also performed an analysis of the types of AEs leading to dose modification. In the FDA analysis presented in Table 46, dose modifications include treatment interruptions, treatment delays, and dose reductions due to TEAEs. The most common TEAEs leading to dose modifications were neutrophil count decrease, URI, and pneumonia.

Table 46: FDA- TEAEs Leading to Dose Modifications in ≥5%

	Safety Population (n=117) N (%)
TEAE Leading to Dose Modifications	86 (74)
Neutrophil Count Decrease	34 (29)
Upper Respiratory Tract Infection	21 (18)
Pneumonia	20 (17)
COVID-19 Infection	14 (12)
Cough	9 (8)
Cytokine Release Syndrome	7 (6)
Fever	6 (5)

Source: FDA Reviewer; generated from ADAE dataset

Significant Adverse Events

Data:

See relevant data throughout Section 8.2.4.

The Applicant's Position:

Key AEs observed for linvoseltamab were CRS, infections, and hematologic events. The safety profile is manageable and consistent with the mechanism of action and is similar to other treatments in this class.

The FDA's Assessment:

The FDA agrees with the Applicant that CRS, infections, and hematologic events were key AEs seen with linvoseltamab treatment, and that details regarding these AEs are described throughout Section 8.2.4. The FDA also notes that hepatotoxicity was found to be a key AE; the description of hepatic laboratory findings and the plan to include hepatotoxicity in the Warnings and Precautions of the label are described under the 'Laboratory Findings' section below.

Treatment-Emergent Adverse Events and Adverse Reactions

Data:

Table 47: Applicant – Summary of Most Common TEAEs by Preferred Term (≥20% in either Phase 2 cohort) – Phase 2 and All 200 mg Patients

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%)

**All 200 mg (N=117) = Phase 1 200 mg patients (n=12) + Phase 2 200 mg patients (n=105)
Note: All AEs were coded using MedDRA Version 26.0. NCI grades were coded using CTCAE Version 5.0.
Note: A patient who reported multiple TEAEs with the same PT 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 cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023

Source: Module 2.7.4 Summary of Clinical Safety, Table 10

Table 48: Applicant - Summary of Grade 3 or Higher TEAEs by Preferred Term and NCI Grade (≥5% in either Phase 2 Cohort) - Phase 2 and All 200 mg Patients

	Phase 2				All	
	50 mg (N=104)		200 mg (N=105)		200 mg** (N=117)	
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

**All 200 mg (N=117) = Phase 1 200 mg patients (n=12) + Phase 2 200 mg patients (n=105)
Note: All AEs 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 PT.
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 cutoff as of 08 Sep 2023; Data extract as of 16 Oct 2023.
Source: Module 2.7.4 Summary of Clinical Safety, Table 11

Table 49: Applicant - Adverse Reactions in ≥10% of Patients with Relapsed or Refractory Multiple Myeloma Treated with Linvoseltamab 200 mg in Study 1826

Adverse Reaction	Linvoseltamab (N=117)	
	Any Grade (%)	Grade 3 or 4 (%)
Infections and infestations		
Pneumonia	37 (31.6%)	24 (20.5%)
Upper respiratory tract infection	32 (27.4%)	3 (2.6%)
COVID-19	20 (17.1%)	6 (5.1%)

Adverse Reaction	Linvoseltamab (N=117)	
	Any Grade (%)	Grade 3 or 4 (%)
Urinary tract infection	16 (13.7%)	7 (6.0%)
Immune system disorders		
Cytokine release syndrome	54 (46.2%)	1 (0.9%)
Hypogammaglobulinemia	15 (12.8%)	1 (0.9%)
Metabolism and nutrition disorders		
Decreased appetite	17 (14.5%)	1 (0.9%)
Gastrointestinal disorders		
Diarrhea	42 (35.9%)	2 (1.7%)
Nausea	27 (23.1%)	0
Vomiting	22 (18.8%)	0
Constipation	20 (17.1%)	0
Respiratory, thoracic and mediastinal disorders		
Cough	47 (40.2%)	0
Dyspnoea	26 (22.2%)	1 (0.9%)
Nasal congestion	19 (16.2%)	0
General disorders and administration site reactions		
Fatigue	42 (35.9%)	0
Edema	20 (17.1%)	1 (0.9%)
Pyrexia	20 (17.1%)	0
Chills	12 (10.3%)	0
Investigations		
Hyperuricaemia	12 (10.3%)	2 (1.7%)
Nervous system disorders		
Musculoskeletal pain	59 (50.4%)	3 (2.6%)
Headache	26 (22.2%)	1 (0.9%)
Pain	26 (22.2%)	1 (0.9%)
Motor dysfunction	20 (17.1%)	2 (1.7%)
Encephalopathy (excl. ICANS)	19 (16.2%)	4 (3.4%)
Psychiatric disorders		
Insomnia	15 (12.8%)	0

Adverse Reaction	Linvoseltamab (N=117)	
	Any Grade (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash	19 (16.2%)	3 (2.6%)
Vascular disorders		
Hypertension	12 (10.3%)	5 (4.3%)

All adverse events were coded using MedDRA Version 26.0. NCI grades were coded using CTCAE Version 5.0.
A patient is counted only once for multiple occurrences within a system organ class/grouped term/preferred term.
CRS was graded by adapted criteria from Lee (2019).
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
Source: Module 2.5 Clinical Overview, Table 20

The Applicant's Position:

In All 200 mg Patients, the most common TEAE was CRS (54/117 [46.2%]). The other most common TEAEs (≥20% patients by PT) were events anticipated in an elderly and/or late-line MM population: 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 TEAEs were generally comparable between All 200 mg Patients and Phase 2 50 mg Patients.

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 Phase 2 50 mg Patients, the overall incidence of Grade 3 or 4 TEAEs was similar to All 200 mg Patients. The most common grade 3 or 4 TEAEs (≥5%) by PT were generally similar to All 200 mg Patients, although Neutrophil count decreased was reported more commonly in All 200 mg Patients, WBC count decreased, and Lymphopenia were reported more commonly in the Phase 2 50 mg Patients.

There are a few neurologic or psychiatric events which are considered ADRs but not considered neurotoxicity of linvoseltamab (headache, insomnia, encephalopathy, and motor dysfunction). These events were thoroughly assessed for neurotoxicity and the Sponsor found insufficient evidence in these analyses to establish these as identified risks of linvoseltamab. In fact, alternative etiologies were established or considered more likely for all severe instances of these events for which case narratives were available. Nonetheless, they are considered ADRs based on the identification methodology criterion of TEAE incidence ≥10%, which was met by the number of

patients with grade 1 and 2 events, for which there is insufficient information to properly assess for alternative etiology.

The FDA's Assessment:

The FDA agrees, generally, with the AE profile presented by the Applicant. The FDA's detailed analysis of TEAEs was limited to safety population of patients who received the 200 mg dose of linvoseltamab. The FDA also notes that based on FDA grouping of AEs, which represents a consistent approach used with other products, the grouping for neurologic toxicity includes all terms within the Neurologic Disorders and Psychiatric Disorders System Organ Classes, including terms which were excluded by the Applicant. The FDA's analysis presented below excludes laboratory terms, as laboratory terms were evaluated separately, by lab-shift analysis; these are presented within Section 8.2.4. Finally, slight differences in some AE incidences by the FDA and Applicant are not unexpected due to methodological differences in the grouping of terms.

Table 50 summarizes all-cause treatment-emergent AEs, excluding laboratory terms, in the primary safety population, using a threshold of ≥15%. The most common non-laboratory AEs were musculoskeletal pain, cytokine release syndrome, cough, upper respiratory tract infection, diarrhea, fatigue, and pneumonia.

Other clinically-relevant AEs that occurred in <15% of patients in the safety population included:

- Neurologic Disorders: sensory neuropathy (11%), motor dysfunction (9%), ICANS (8%)
- Infections and Infestations: sepsis (10%), CMV infection (4.3%), progressive multifocal leukoencephalopathy (0.9%)
- Injury, Poisoning and Procedural complications: infusion related reaction (following linvoseltamab administration; 9%)
- Blood and Lymphatic Disorders: febrile neutropenia (8%)

The distinction made by the Applicant in the characterization of events as CRS vs. IRR is described in Section 8.2.5.1. Of note, the rate of IRR reported above, as occurring following linvoseltamab administration, is 9%. There were other IRR events that occurred in the safety population, following administration of other agents (IVIG and pentamidine); the overall rate of IRR in the study population including IRRs that occurred following these other agents is 13%. Given the temporal relationship between certain IRR events following administration of other agents known to cause IRRs, the plan for labeling was to include the 9% rate of IRR related to linvoseltamab administration only.

Table 50: FDA- Most Common Treatment-Emergent Adverse Events (≥15%)

SOC or Main SOC /Grouped PT	Safety Population (n=117)	
	Any grade, %	G 3-4, % [a]
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain	53	3.4
Immune System Disorders		
Cytokine Release Syndrome	46	0.9
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	39	0
Dyspnea	19	0.9
Congestion	16	0
Infection	13	0
Upper Respiratory Tract Infection	36	6
Pneumonia[1]	29	21
COVID-19 Infection	17	5
Urinary Tract Infection	16	8
Gastrointestinal Disorders		
Diarrhea	35	1.7
Nausea	23	0
Vomiting	19	0
Constipation	17	0
General Disorders and Administration Site Conditions		
Fatigue	34	0
Edema	19	0.9
Fever	17	0
Anorexia	15	0.9
Nervous System Disorders		
Headache	22	0.9
Encephalopathy[2]	19	3.4

[1]Includes 5 cases of fatal pneumonia
[2]Includes 1 case of fatal encephalopathy
Source: FDA Reviewer; generated from ADAE dataset

Laboratory Findings

Data:

Table 51: Applicant - Select Laboratory Abnormalities That Were New or Worsened from Baseline to Grade 3 or 4 in ≥5% of Patients with Relapsed or Refractory Multiple Myeloma Treated with Linvoseltamab 200 mg in Study 1826

	Linvoseltamab (N=117)	
Laboratory Abnormality	**All Grades (%)**	**Grades 3 or 4 (%)**
Hematology		
Lymphocyte count decreased	97.2	91.7
Hemoglobin decreased	73.5	42.7
White blood cell count decreased	66.7	31.6
Platelet count decreased	65.0	19.7
Neutrophil count decreased	64.2	47.7
Chemistry		
Aspartate aminotransferase increased	61.5	10.3
Hypophosphatemia	54.7	23.9
Alanine aminotransferase increased	47.0	6.8
Creatinine increased	47.0	6.8

NCI grades were coded using CTCAE Version 5.0.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter; n's less than 117 indicate some patients did not have post-baseline values and were not counted in this analysis.
Post-baseline values include scheduled and unscheduled assessments up to the day prior to the start of a new therapy for multiple myeloma
A patient is counted only once for multiple occurrences for the same parameter.
Data cut-off as of 08 Sep 2023; Data extract as of 16 Oct 2023
Source: Module 2.5 Clinical Overview, Table 21

Hematology

In the All 200 mg patient population, 105/117 (89.7%) patients experienced at least 1 new or worsened red blood cell or platelet hematology laboratory abnormality, of which, 55/117 (47.0%) patients experienced a grade 3 to 4 laboratory abnormality. The most frequent grade 3 or 4 abnormalities were anemia (50/117 [42.7%] patients) and platelet count decreased (23/117 [19.7%] patients).

A total of 114/117 (97.4%) experienced at least 1 new or worsened WBC hematology laboratory abnormality, of which, 106/117 (90.6%) patients experienced a grade 3 to 4

laboratory abnormality. The most frequent grade 3 or 4 abnormalities were lymphocyte count decreased (99/108 [91.7%] patients), neutrophil count decreased (52/109 [47.7] patients), and WBC decreased (37/117 [31.6%] patients).

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

Hepatic Laboratory Tests

In All 200 mg Patients, 96/117 (82.1%) patients experienced at least 1 new or worsened hepatic laboratory abnormality, and 19/117 (16.2%) patients experienced a grade 3 to 4 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). Blood bilirubin increased was experienced in 16/117 (13.7%) including 3/117 (2.6%) with grade 3 or 4 abnormalities. Hepatic laboratory abnormalities were mostly observed during step-up dosing period. These changes were transient and eventually returned to baseline values.

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

Renal Laboratory Tests

In All 200 mg patients, 55/117 (47.0%) experienced at least 1 new or worsened renal function laboratory abnormality, of which, 8/117 (6.8%) patients experienced a grade 3 to 4 renal laboratory abnormality. Creatinine increased (8/117 [6.8%]) was the only grade 3 or 4 renal laboratory abnormality. In Phase 2 50 mg patients and All study patients (N=282), renal laboratory abnormalities were similar to All 200 mg patients.

Electrolytes

In the All 200 mg Patients, 110/117 [94.0%] experienced at least 1 new or worsened electrolyte laboratory abnormality, of which, 38/117 (32.5%) patients experienced a grade 3 to 4 laboratory abnormality. The most frequent grade 3 or 4 abnormality (≥5% of patients) was hypophosphatemia (28/117 [23.9%]). In Phase 2 50 mg Patients, electrolyte laboratory abnormalities were similar to All 200 mg Patients. When evaluating All study patients (N=282), no additional safety findings were identified.

Metabolism

In All 200 mg Patients, 67/117 [57.3%] experienced at least 1 new or worsened metabolism laboratory abnormality, of which, 3/117 (2.6%) patients experienced a grade 3 to 4 laboratory abnormality. There were no grade 3 or 4 abnormalities in ≥5% of patients. In Phase 2 50 mg Patients, metabolism laboratory abnormalities were similar to All 200 mg Patients. When evaluating All study patients (N=282), no additional safety findings were identified.

The Applicant's Position:

Trends in mean laboratory values over time showed on-treatment changes consistent with either acute effects of cytokine release, and/or improving bone marrow function with continued treatment. There were no clinically meaningful trends in mean or median changes from baseline during the study in any renal function, electrolyte, or metabolism parameters. Shifts to grade 3 and 4 laboratory abnormalities were observed in <10% of All 200 mg Patients for most parameters except the following: WBC decreased, Lymphocyte count decreased, Neutrophil count decreased, Anemia, Platelet count decreased, and Hypophosphatemia.

The FDA's Assessment:

The FDA generally agrees with that the majority of laboratory abnormalities were consistent with the mechanism of action of linvoseltamab. For the FDA analysis of laboratory AEs, analysis of lab-shift data was performed. Table 52 summarizes new or worsening laboratory abnormalities in the safety population, with the 'n' for each AE corresponding to the number of patients who had a baseline and at least one post-treatment assessment for that parameter.

Grade 3-4 laboratory abnormalities in ≥10% of patients were lymphopenia, neutropenia, anemia, leukopenia, and thrombocytopenia. Grade 4 laboratory abnormalities in ≥5% of patients were lymphopenia, neutropenia, thrombocytopenia, and lymphopenia.

Table 52: FDA- Common (≥10%) Treatment-Emergent Laboratory Abnormalities

Laboratory Abnormality	**N evaluable from 117[1]**	**Safety Population (N=117)**			
		All Grades (%)		**Grades 3 or 4 (%)**	
Hematology		N	%	N	%
Lymphocyte count decrease	106	103	97	97	92
Hemoglobin decrease	117	84	72	49	42
Platelet count decrease	117	75	64	22	19
White blood cell count decrease	117	74	63	36	31
Neutrophil count decrease	107	66	62	50	47
Lymphocyte count increase	106	14	13	0	0
Chemistry					
Sodium decrease	117	62	53	3	2.6
Creatinine increase	117	55	47	8	7
Potassium decrease	117	50	43	5	4.3
Calcium decrease	117	49	42	0	0
Potassium increase	117	26	22	5	4.3

Laboratory Abnormality	N evaluable from 117[1]	Safety Population (N=117)			
		All Grades (%)		Grades 3 or 4 (%)	
Calcium increase	117	25	21	1	0.9
Glucose decrease	117	14	12	1	0.9
Hepatic					
Aspartate aminotransferase increase	117	71	61	12	10
Albumin decrease	117	59	50	2	1.7
Alkaline phosphatase increase	117	58	50	2	1.7
Alanine aminotransferase increase	117	54	46	7	6
Total bilirubin increase	117	14	13	0	0
Hypophosphatemia	113	69	61	30	27

[1]Denominator used to calculate incidence varies from 106 to 117, based on the number of patients with a baseline and at least one post-treatment value
Source: FDA Reviewer; generated from ADLB dataset

An assessment of laboratory abnormalities warranting additional evaluation is provided below:

a. Hepatic laboratory abnormalities and Hy's law analysis

There were high rates of AST and ALT elevation, 61% and 46%, respectively, in patients in the safety population, the majority of which were Grade 1-2. Grade 3-4 AST elevation occurred in 10% of patients and Grade 3-4 ALT elevation occurred in 6% of patients. Thirteen patients experienced total bilirubin elevation of any grade; no Grade 3 or greater events occurred.

The Applicant also identified five subjects treated at linvoseltamab dose levels ranging from 48 mg to 200 mg who met liver analyte criteria for Hy's law. Case-level assessments were performed for each of the 5 subjects, and in each case, an alternate diagnosis was identified (3 CRS events, 1 event of septic shock, and 1 event of TLS and sepsis). Given the identification of compelling alternate diagnoses, the liver function abnormalities in these 5 patients were found to not meet Hy's law and were determined not to be attributable to drug-induced liver injury (DILI).

While it is known that elevations in hepatic labs can occur concurrently or following events of CRS, the rates of AST and ALT elevation were high in patients treated on the clinical trial. Thus, it is important for prescribers to be aware of the incidence of AST and ALT elevation and that they have guidance about adequate monitoring and management strategies for patients who

experience AST or ALT elevation. For this reason, the decision was made to include hepatotoxicity as a 'Warnings and Precautions' in the draft USPI.

b. Hypophosphatemia

There were high rates of hypophosphatemia (61% All Grade and 27% Grade 3-4) in the safety population. Hypophosphatemia has been described with other bispecific antibodies, though rates with other bispecific antibodies appear lower than the rates seen with linvoseltamab. Additional details regarding the time to onset of hypophosphatemia, time to resolution of hypophosphatemia, association with CRS or other events, and treatments administered, will be required to determine whether additional labeling recommendations are warranted.

Vital Signs

The Applicant's Position:

Small variations in mean and median vital signs were seen over time in All 200 mg Patients, Phase 2 50 mg Patients, Phase 2 200 mg patients, and All study patients, but none indicated a trend towards an overall increase or decrease.

The FDA's Assessment:

FDA did not perform an analysis of vital signs in patients treated with linvoseltamab, and notes that vital sign changes such as pyrexia, hypotension, and hypoxia were captured and noted as symptoms of CRS in the study.

Electrocardiograms (ECGs)

The Applicant's Position:

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.

The FDA's Assessment:

Refer to QT section.

QT

The Applicant's Position:

Not Applicable.

The FDA's Assessment:

In general, monoclonal antibody therapies would not be expected to impact the QTc interval and the risk of QTc prolongation due to linvoseltamab is expected to be low.

Immunogenicity

The Applicant's Position:

Over the course of the study, 2 out of 195 patients (1.0%) developed antibodies to linvoseltamab. In both cases these were low titer and transient.

The FDA's Assessment:
Refer to Section 6.3.1 for FDA's assessment of immunogenicity.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Cytokine Release Syndrome

Data:
Frequency and Severity

Table 53: Applicant - Summary of CRS by Severity - Phase 2 and All 200 mg Patients

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%)

*All 200 mg (N=117) = Phase 1 200 mg Patients (n=12) + Phase 2 200 mg Patients (n=105)
Note: All AEs 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 SOC/PT.
Data cutoff as of 08Sep2023; Data extract as of 16 Oct 2023
Source: Module 2.5 Clinical Overview, Table 16

In All 200 mg patients, 54/117 (46.2%) patients experienced an event of CRS. The worst severity experienced by most patients was grade 1 (41/117 [35.0%]) or grade 2 (12/117 [10.3%]), with 1/117 [0.9%] patients experiencing grade 3 CRS. There were no grade 4 or 5 events. The magnitude of the full dose did not appear to affect frequency or severity. Most CRS events occurred during the step-up period and both All 200 mg Patients and Phase 2 50 mg patients received the same step-up regimen, so the similarity in CRS profile is not unexpected.

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).

Timing and Duration

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 (5.60 – 25.27) 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 1 began within approximately 24 hours of the end of the infusion.

Management

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.

The Applicant's Position:

CRS was very common and mostly mild to moderate. CRS was reported in 46.2% of All 200 mg Patients. Most of these patients had grade 1 CRS (35.0%) or grade 2 CRS (10.3%). A single patient had a grade 3 CRS event and there were no grade 4 or 5 CRS events. CRS occurred primarily during the step-up dosing, within 24 hours of start of infusion, and was effectively managed. CRS events mostly occurred with the first dose. 9 of 117 (7.7%) patients experienced their first CRS with subsequent doses. The CRS profile appeared to be independent of the magnitude of the full dose (50 mg or 200 mg).

Risk minimization measures are proposed to mitigate the risk of CRS: The proposed labeling includes boxed warnings and more detailed warnings for CRS, detailed dosing instructions (including pretreatment medications) and dosing schedule, monitoring requirements, and additionally, the Sponsor will provide a REMS with ETASU A and B for the risk of CRS.

The FDA's Assessment:

The FDA generally agrees with the Applicant's analysis and independently conducted the following analyses to verify the Applicant's data. The FDA notes that clinical symptoms of CRS and IRR can be indistinguishable. The method used by the Applicant to distinguish CRS vs. IRR events, taken from the guidance from the Study 1826 protocol, is summarized below:

Acute IRR: <6 hours from the start of the infusion, or within 2 hours after completion of the infusion (whichever is later); associated with typical signs and symptoms including, but not limited to, flushing, tachycardia, hypotension, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and rashes

CRS: 6 or more hours from the start of infusion or more than 2 hours after completion of infusion (whichever later); characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia

The protocol also stated that investigator judgement should be used to recharacterize IRR events as CRS if an event started prior to 6 hours from the start of infusion, but was associated with clinical or laboratory parameters that suggested that the symptoms were due to CRS.

Despite the cut-off of 6 hours not being a validated parameter to distinguish between CRS and IRR events, the FDA did not object to the Applicant's approach. Given that a consistent method, based on protocol-specified criteria, was used by investigators and given that investigators were able to classify events that occurred within 6 hours but appeared consistent with CRS events as CRS, the approach appeared reasonable.

CRS Incidence and Severity
CRS was frequent in patients in the safety population, occurring in 46% of patients (Grade 1: 35%, Grade 2: 10%, Grade 3: 0.9%). There were no Grade 4 or 5 events. The FDA notes that while the majority of cases were Grade 1-2, even Grade 2 CRS is considered clinically significant, as interventions such as IV fluids, supplemental oxygen, and/or supportive medications may be required for management. FDA's analysis of CRS incidence, severity, rates of recurrent CRS, and rates of treatment modifications due to CRS is presented in Table 54.

Table 54: FDA- CRS Incidence and Severity

	Safety Population N (%)
Patients with CRS	**54 (46)**
Maximum Toxicity Grade	
Grade 1	41 (35)
Grade 2	12 (10)
Grade 3	1 (0.9)
Grade 4 – 5	0
CRS SAE	33 (28)
Patients with >1 CRS Event	23 (20)
Dose Reduction due to CRS	5 (4.3)
Dose Interruption due to CRS	5 (4.3)
Discontinuation due to CRS	0

Source: FDA Reviewer; generated from ADAE dataset

The rate of CRS in the safety population was high, despite consistent use of a premedication regimen in patients treated on Study 1826. The protocol-specified premedication guidance included:

- Acetaminophen 650-1000 mg oral
- Diphenhydramine 25 mg oral or IV
- Dexamethasone 40 mg IV during the SUD and 1st 200 mg dose, then reduce to 10 mg IV, then discontinue

Despite consistent use of premedications, the overall incidence of CRS was high.

FDA notes that the initial of dexamethasone used in Study 1826 was notably higher than doses (16 to 20 mg) recommended in the USPI for the approved bispecific antibodies, and that use of the selected dose of dexamethasone may have impacted the rate and severity of CRS seen with linvoseltamab.

FDA's analysis of onset and timing of CRS events, relative to each linvoseltamab dose administered, is presented in Table 55. Most patients experienced Grade 1-2 CRS following the initial or intermediate dose of linvoseltamab, however 21% (17/82) of CRS events occurred following a full dose of linvoseltamab. In Table 55, each separate CRS event is represented, with some patients having experienced more than one CRS event.

Table 55: FDA- CRS Onset and Timing by Grade

	All 200 Population; N (%) Any Occurrence of CRS				
	Initial Dose N=117	**Intermediate Dose N=113**	**1st Full Dose N=111**	**2nd Full Dose and Beyond N=110**	**Any Period N=117**
Subjects with at least 1 CRS event (%)	45 (38)	19 (17)	11 (9)	6 (5)	**54 (46)**
Grade 1	36 (31)	17 (15)	9 (8)	5 (4.5)	**41 (35)**
Grade 2	8 (7)	2 (1.7)	2 (1.8)	1 (0.9)	**12 (10)**
Grade 3	1 (0.9)	0	0	0	**1 (0.9)**
Grade 4	0	0	0	0	**0**
Grade 5	0	0	0	0	**0**

Source: FDA Reviewer; generated from ADLB dataset

The median time to onset of CRS was 11 (range -1 to 184) hours from the most recent dose and the median duration of CRS was 15 (range 1 to 76) hours. As shown in Figure 9, the majority of CRS events (51%) occurred within 12 hours of linvoseltamab administration. However, an additional 40% of events occurred between 12-36 hours post-linvoseltamab administration, and the remaining 7% occurred after 36 hours post-linvoseltamab administration.

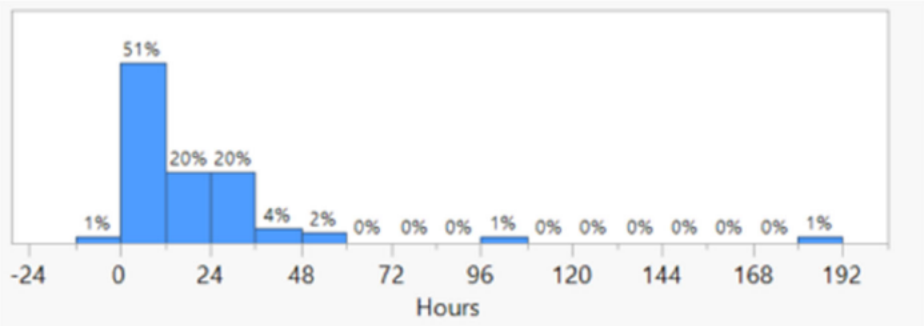


Figure 9: FDA- CRS Onset (hours) from Most Recent Linvoseltamab Dose
Source: FDA reviewer; ADTTSAF dataset

Hospitalization Requirements

Patients were monitored closely on Study 1826. An IR was sent to the Applicant on March 22, 2024, requesting additional details regarding the hospitalization guidelines based on the protocol. The Applicant responded on April 3, 2024, with the following information:

- 38/117 patients were treated under protocol versions requiring 24 hours of hospitalization after the initial and intermediate doses
- 78/117 patients were treated under protocol versions requiring 48 hours of hospitalization after the initial dose and 24 hours after the intermediate dose
- One patient was treated under a protocol version requiring 48 hours of hospitalization after the initial and intermediate doses

Given that patients treated on the clinical trial were all treated on versions of the protocol with mandatory hospitalization, ranging from 24-48 hours after the initial and intermediate doses, and given the safety profile of linvoseltamab, with high rates of CRS despite premedications, the FDA did not agree with the Applicant's proposal to provide guidance in the USPI to monitor patients (b) (4) following the initial and intermediate doses. Based on analysis of timing of CRS relative to each dose and the time to onset of CRS events after the last dose, as described in FDA's assessment of 'CRS Incidence and Severity' above, the FDA concluded that guidance regarding hospitalization for 48 hours following the first dose and 24 hours following the second dose of linvoseltamab should be included in the USPI. Guidance regarding hospitalization following the subsequent linvoseltamab dose, in patients who experience Grade 3 CRS or ICANS, is also provided in the draft USPI.

Management of CRS

The FDA notes that of the patients treated at the recommended dosing schedule of linvoseltamab in Study 1826, 29% received any supportive care (including tocilizumab, corticosteroids, supplemental oxygen, or vasopressors). Nineteen percent of patients received tocilizumab, 11% received corticosteroids, 8% received supplemental oxygen, and 0.9% received vasopressors. Tocilizumab was administered for 26% of Grade 1 CRS events, 83% of Grade 2 events, and 100% of Grade 3 events.

In order to further characterize the impact of tocilizumab usage in the clinical trial, the FDA requested further analyses regarding outcomes following tocilizumab use through an IR sent on April 25, 2024. The Applicant responded on May 3, 2024, with description of the requested analyses. Assessment was limited, as details regarding the rationale for tocilizumab administration in each case of CRS were not captured or provided in Case Report Forms. In the 'All 200 Population', median time to resolution of CRS was 1 day (range 1-4) in those treated with tocilizumab and median time from onset of CRS to next dose of study drug was 8 days (range 6-72 days) in those treated with tocilizumab and 7 days (range 6-18) in those not treated with tocilizumab. For those who received tocilizumab (22 patients of the 'All 200 Population'), tocilizumab was administered at a median of 1 day after onset of CRS (range 1-4) and CRS resolved after a median of 1 day (range -1 to 3) after administration of tocilizumab.

In the study protocol, administration of tocilizumab was per investigator's discretion, and guidelines were provided for administration of tocilizumab for Grade 1 CRS in patients with comorbidities, for Grade 2 CRS with symptoms lasting more than 4 hours, and for all Grade ≥3 CRS.

Based on FDA review of data related to outcomes following tocilizumab administration, the absence of data regarding rationale for tocilizumab administration, and the absence of data on the assessment of safety and efficacy of tocilizumab use, the decision was made to not include the use of tocilizumab or anti-cytokine therapy in the draft USPI. The draft USPI includes recommendations to manage CRS per current practice guidelines.

Guidance for Draft USPI

Overall, there was a high incidence of CRS, including Grade 2-3 events, despite consistent use of premedications, as well as occurrence of recurrent events. Due to these findings, the FDA considers that in addition to the Applicant's proposal to include a boxed warning and 'Warnings and Precautions' for the risk of CRS in the USPI, a REMS with ETASU is also needed to minimize the risk of CRS, and to ensure that the benefits of linvoseltamab outweigh the risks in the post-marketing setting. Given the manufacturing issues precluding approval of linvoseltamab, the USPI and REMS were not finalized.

8.2.5.2. Infusion Related Reactions

Data:

In All 200 mg patients, 11/117 (9.4%) patients experienced an event of IRR. 2/117 (1.7%) patients experienced a grade 3 IRR event. There were no grade 4 or 5 events. The magnitude of the full dose did not appear to affect frequency or severity of IRR. IRR occurrence was highest following the initial dose (6/117 [5.1%]), with fewer patients experiencing IRR following the intermediate dose (3/113 [2.7%]) and first full dose and beyond (4/111 [3.6%]). 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).

The Applicant's Position:

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.

The FDA's Assessment:
The parameters used to guide investigators to classify events as CRS vs. IRR are described in Section 8.2.5.1. Given the consistent protocol-defined approach towards characterization that was used, and given that investigators were able to classify events that occurred within 6 hours but appeared consistent with CRS events as CRS, the FDA did not object to the Applicant's approach.

The FDA agrees with the data presented by the Applicant and also notes the following details. A total of 12 IRR events occurred in 10 patients (9%); breakdown of incidence by maximum grade was Grade 1: 2.6%, Grade 2: 4.3%, and Grade 3: 1.7%. Six IRR events occurred during linvoseltamab infusion, 3 events occurred within 1 hour of the end of infusion, 2 events occurred between 1-2 hours after the end of infusion, and 1 event occurred 2 hours after the end of infusion. Symptoms of IRR included pyrexia, dyspnea, hypotension, jaw pain, chills, and hypotension.

While events of CRS and IRR were characterized based on protocol-defined criteria, signs and symptoms of each type of event may overlap. Given the 9% incidence of IRR events, including Grade 3 events, the FDA agreed with the Applicant's proposal to include information about IRR events within the 'Warnings and Precautions' for CRS within the USPI.

8.2.5.3. Neurotoxicity (including ICANS)

Data:

In the SAP for Study 1826, 3 methods to analyze neurotoxicity (including ICANS) were pre-defined: Methods 1 and 2 each consisted of a search strategy of neurologic and psychiatric terms requested by a Health Authority, and Method 3 was a method developed by the Sponsor to identify ICANS cases through adjudication. Only Method 3 identified neurologic toxicity of linvoseltamab that could not be readily explained by alternative etiologies and all of these were cases consistent with ICANS (adjudicated ICANS). After the SAP was finalized, the Sponsor received requests from Health Authorities for 3 additional analyses of neurologic events, according to 3 group terms for encephalopathy, motor dysfunction, and sensory neuropathy. Sponsor analysis by these group terms, as well as an analysis of all other terms reported in the Neurologic disorders and Psychiatric disorders SOCs, did not reveal any neurologic toxicity of linvoseltamab other than that already characterized by Method 3 (adjudicated ICANS).

Adjudicated ICANS

Table 56: Applicant - Adjudicated ICANS by Sequential Dose - All 200 mg Patients

	Initial Dose	Intermediate Dose	First Full Dose	Second Full Dose	Third Full Dose and Beyond	Any Period
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

*One patient received a split dose (100 mg, 100 mg) for the first planned dose of 200 mg.
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 08 Sep 2023; Data extract as of 16 Oct 2023
Source: Module 2.5 Clinical Overview, Table 17

In the All 200 mg patients, 1/117 (0.9%) patient discontinued treatment due to ICANS. When evaluating ICANS leading to dose delays/interruptions, 2/117 (1.7%) patients had dose delays/interruptions due to ICANS. 1/117 (0.9%) patient had dose reduction due to ICANS. The dose reduction affected the step-up dosing, but did not affect the full dose.

The Applicant's Position:

The Sponsor assessed reports of neurologic and psychiatric events and found ICANS to be the single important neurotoxicity established for linvoseltamab. Adjudicated ICANS was reported in 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 all concurrent with CRS or IRR and primarily occurred during the first day after dosing. The majority of patients recovered from ICANS and went on to receive additional treatment with linvoseltamab. The ICANS profile appeared to be independent of the magnitude of the full dose (50 mg or 200 mg).

The FDA's Assessment:

The FDA agrees with the Applicant's approach for identifying ICANS events and with the identified incidence of ICANS. However, the FDA does not agree with the methods that were used to capture events of neurologic toxicity. The Applicant's approaches excluded terms that are conventionally included in FDA's assessment of neurologic toxicity. The FDA analysis of neurologic toxicity, instead, included all TEAEs within the Nervous System Disorders and Psychiatric Disorders SOCs.

The results of the FDA's analysis of the incidence and severity of ICANS events were consistent with the analysis presented by the Applicant in Table 57. The median time to

onset of ICANS was 3 days (range 1-59 days) and median duration was 2 days (range 1-11 days). Two patients required treatment interruptions due to ICANS, one required a dose reduction, and one required treatment discontinuation.

Using the above methodology, FDA analysis of neurologic toxicity showed that neurologic TEAEs occurred in 46% of patients in the safety population, with Grade 3-4 events occurring in 8%.

Table 57: FDA-Analysis of Neurologic Toxicity

	Safety Population N (%)	
	All Grades	**Grade 3-4**
Any TEAE in Nervous System or Psychiatric Disorder SOC	**54 (46)**	**9 (8)**
Nervous System Disorders SOC	**51 (44)**	**8 (7)**
Psychiatric Disorder SOC	**27 (23)**	**2 (1.7)**
AEs Categorized as Neurologic TEAEs		
Headache (GT)	26 (22)	1 (0.9)
Encephalopathy (GT)	20 (17)	4 (3.4)
Insomnia	14 (12)	0
Sensory Neuropathy (GT)	13 (11)	0
Dizziness	10 (9)	0
ICANS	9 (8)	3 (2.6)

Source: FDA analysis based on ADAE.xpt

Guidance for USPI

The Applicant proposed to include a boxed warning for the risk of ICANS and proposed to issue a REMS for the risk of ICANS. Given the results of FDA's neurologic toxicity analysis, with high rates of neurologic toxicity, including 8% of patients with Grade 3-4 events, the FDA determined that the boxed warning and REMS should be expanded to include the risks of "neurologic toxicity, including ICANS."

8.2.5.4. Infections

Data:

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%]). 40/117 (34.2%) patients had grade 3 or 4 infections and 11/117 (9.4%) had grade 5 infections. Of the patients with Grade 5 infections, 5 were considered on-treatment deaths. The overall rate and severity of infection was generally comparable between Phase 2 50 mg and All 200 mg patients, with the exception of fatal infections.

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%], and COVID-19 pneumonia and Pneumocystis jirovecii pneumonia (each 5/117 [4.3%]).

5/117 (4.3%) patients experienced an infection TEAE that resulted in on-treatment death (ie, up to 30 days after their last dose of linvoseltamab or the day prior to the start of new RRMM therapy, whichever came first). 4 out of 5 of these infection deaths occurred during the patient's first 3 months of therapy, and 4 out 5 occurred in non-responders.

In All 200 mg patients, 11/117 (9.4%) patients experienced an infection TEAE that resulted in death at any time. These 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 Pneumonia influenzal (1/117 [0.9%] patient).

Opportunistic Infections

In All 200 mg patients, 12/117 (10.3%) patients experienced opportunistic infections. By high level term, 6/117 (5.1%) patients experienced CMV infections, 5/117 (4.3%) patients experienced Pneumocystis infections, and 1/117 (0.9%) patient experienced Polyomavirus infection; 1 patient with CMV also experienced Candida infections (Oesophageal candidiasis) and Herpes viral infections (Ophthalmic herpes simplex).

Overall, 7/117 (6.0%) patients experienced serious opportunistic infection. 7/117 (6.0%) had grade 3 or 4 opportunistic infections and 2/117 (1.7%) patients also had 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 in the first 3 months.

The Applicant's Position:

The infection profile was anticipated in this patient population with late-line MM that has been immunocompromised by both their underlying disease and multiple therapies. The profile included serious infections and opportunistic infections frequently seen in this population, which were managed according to standard clinical practice. Infections were reported in 72.6% of All 200 mg Patients. The most common infections by PT, were COVID-19, Pneumonia, and Upper respiratory tract infection. 34.2% of patients had grade 3 or 4 infections and 9.4% had grade 5 infections. Serious infections were reported in 41.9% of All 200 mg Patients. The overall rate of infections was slightly higher in All 200 mg Patients than in Phase 2 50 mg Patients (72.6% vs 61.5%).

Overall, the data are most consistent with the hypothesis that the well-known infection risk of MM accounts for a substantial component of the overall infection risk observed in the first 6 months of treatment. As MM is more well controlled with continued treatment at the higher dose of linvoseltamab, the associated MM-component of infection risk is also more well controlled, resulting in decreases in infection incidence only at the higher dose.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's assessment of the incidence of infections in the safety population and the description of most common infections. While FDA agrees that the overall rate of infections was slightly higher in patients treated at the 200 mg dosage as compared to the 50 mg dosage, the FDA did not analyze the rates of infections occurring within the 6 months of treatment or after the initial 6 months of treatment at each dosage, and thus cannot verify the statement made by the Applicant that a decrease in infection incidence after 6 months was seen only at the higher dosage.

There were minor differences in the rates of each type of infection and in the rate of opportunistic infections described between the Applicant and FDA, due to grouping methodology used by the FDA. Based on FDA adjudication of deaths, the incidence of death due to infections was 12%, higher than the 9.4% incidence reported by the Applicant. FDA's analyses of infections, including fatal infections and opportunistic infections, are described below.

In the safety population, 73% of patients experienced any grade infection and 38% experienced a Grade 3-4 infection. FDA's summary of infections that occurred in >5% of patients in the safety population is shown in Table 58.

Table 58: FDA- Infections Occurring in >5% of Patients

	Total N = 117 n(%)	
	All Grades	**Grade 3-4**
Infections and Infestations SOC	**85 (73)**	**44 (38)**
Upper Respiratory Tract Infections (GT)	41 (35)	6 (5)
Pneumonia (GT)	34 (29)	24 (21)
COVID-19 Infection (excluding PNA)	20 (17)	6 (5)
Urinary Tract Infection (GT)	19 (16)	9 (8)
Sepsis	12 (10)	7 (6)
Thrush	6 (5)	0

Source: FDA analysis based on ADAE.xpt

Based on FDA adjudication of deaths, fatal infections occurred in 12% of patients in the safety population. Types of fatal infections and the number of patients in which they occurred were: sepsis (8), COVID-19 pneumonia (3), PJP pneumonia (1), influenza pneumonia (1), and PML (1).

Opportunistic infections included occurred in 11% of patients in the safety population and included CMV, PJP, HSV, fungal pneumonia, herpes zoster, and PML.

Guidance for USPI
The draft USPI includes a Warning and Precaution to communicate the risk of infection with linvoseltamab. This includes guidance to administer prophylactic medications according to current practice guidelines.

8.2.5.5. Neutropenia

Data:

In All 200 mg Patients, grade ≥3 neutropenia by laboratory value was experienced by 53/117 (45.3%) patients. Incidence within successive 3-month windows from first dose was ≥10% in almost all time windows with no clear trend. The overall incidence in Phase 2 50 mg Patients was similar (42/104 [40.4%]) as were the incidences across time windows.

Reports of these abnormalities as TEAEs were also very common. In All 200 mg Patients, 48/117 (41.0%) patients reported 105 events of any grade neutropenia (including PTs of Neutrophil count decreased and 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 a grade 5 event. In 2/117 (1.7%) patients, at least one event was serious. 97 of the 105 events were recovered or were recovering at the time of the data cutoff, and linvoseltamab was not discontinued due to any of them. There was a lower incidence of neutropenia TEAEs in Phase 2 50 mg Patients (30/105 [28.8%]), and lower incidence of maximum grade 4 events (14/104 [13.5%]) than observed in All 200 mg Patients. Other aspects of the profile were the same as observed in All 200 mg Patients: a low incidence of serious events (1/104 [1.0%] patients); almost all events recovered or recovering (80 of 84); and no event leading to permanent discontinuation of linvoseltamab.

Febrile neutropenia was experienced in 9/117 (7.7%) patients treated with 200 mg linvoseltamab experienced 10 events. Maximum severity was grade 3 in 8/117 (6.8%) patients, grade 4 in 1/117 (0.9%) patients, and grade 5 in none. The profile of febrile neutropenia in Phase 2 50 mg Patients was similar: 7/104 (6.7%) patients experienced 7 episodes, severity was grade 3 except in one case of grade 4, most events were serious, all patients recovered, and no event led to permanent discontinuation.

The Applicant's Position:

Based on the frequency of episodes of severe neutropenia and febrile neutropenia, and the context of the untreated MM population not experiencing neutropenia as a

background event, neutropenia was identified as an ADR of linvoseltamab and is included in proposed product labeling. Further, recognizing the general importance of optimal management of febrile neutropenia in oncology patients, neutropenia, including febrile neutropenia, was considered an important identified risk of linvoseltamab and is proposed for communication in the Warnings and Precautions section of the label.

The FDA's Assessment:

The FDA's analysis of neutropenia was based on laboratory-shift analysis and did not include an analysis of neutropenia events reported as TEAEs. Based on FDA's analysis of the safety population, there was a 62% incidence of all grade neutropenia, a 47% incidence of Grade 3-4 neutropenia, and a 25% incidence of Grade 4 neutropenia.

Guidance for USPI
The standard FDA approach towards reporting of laboratory data is to utilize lab-shift data, rather than AE reporting data, given the risk that use of AE data can underreport the true incidence. For this reason, the draft USPI includes the incidence of neutropenia based on the laboratory dataset. Given the high rates of neutropenia, FDA agrees with the Applicant's proposal to include a Warning and Precaution for neutropenia, with general management guidance, in the draft USPI.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

No COA analyses informing safety/tolerability were reported in this application.

The FDA's Assessment:
The FDA agrees that no COA analyses were performed in Study 1826; this section is not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

The effects of age, sex (male or female), ethnicity (Hispanic or Latino: yes, no), and race (White, Black or African American, Asian, or Other) on overall incidence of TEAEs, SAEs, Grade ≥3 TEAEs, and TEAEs leading to treatment discontinuation, dose interruption/delays, dose reduction, or death were examined. Overall, there were no meaningful differences in the incidence of events by subgroup, and results were consistent with the total populations.

The FDA's Assessment:
The FDA agrees, in general that there were no notable differences identified based on race or ethnicity, however interpretation of these analyses are limited, as there are too few patients in certain racial and ethnic groups to draw meaningful conclusions.

The FDA disagrees that there were no meaningful differences in the safety profile of linvoseltamab in patients separated by age category. FDA's analysis of TEAE incidence and severity, as well as dose modifications, by age category, is shown in Table 59. Of note, the ≥65 age group represented in the table also include patients 75 years of age and older. The incidence of Grade 5 TEAEs was higher in the 75 years and older age group, as compared to the under 65 and 65 years and older age groups. Given the significance of Grade 5 TEAEs and the observed trend by age group, the draft USPI includes a statement about the higher rates of Grade 5 TEAEs seen in patients 75 years of age and older.

Table 59: FDA- Overview of Safety by Age

	Safety Population (N=117) N (%)		
	<65 (N=44)	**≥65 (N=73)**	**≥ 75 (N=31)**
Any Grade TEAEs	44 (100)	73 (100)	31 (100)
Grade 3-4 TEAEs	38 (86)	58 (80)	24 (77)
Grade 5 TEAEs	5 (11)	9 (12)	6 (19)
Serious TEAEs	37 (84)	49 (67)	21 (68)
AE leading to dose reduction	6 (14)	10 (14)	5 (16)
AE leading to dose interruption	28 (64)	55 (75)	26 (84)
AE leading to discontinuation	7 (16)	12 (16)	5 (16)

Source: FDA analysis based on ADAE.xpt

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees that this section is not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

In accordance with the ICH guidelines ICH S9 (2009) (ICH, 2009), no carcinogenicity studies have been conducted because linvoseltamab is intended to treat patients with advanced cancer.

The FDA's Assessment:
FDA agrees that no carcinogenicity studies have been conducted.

Human Reproduction and Pregnancy

The Applicant's Position:

In Study 1826, pregnant or breastfeeding women were excluded. As of the safety data cutoff date, there were no reports of use of linvoseltamab during pregnancy or breastfeeding. Women should be advised to use effective contraception and not breastfeed during treatment and for at least 4 months after the last dose of linvoseltamab. This recommendation is based on the median time to reach 3% of C_{max} (11.1 weeks) after cessation of treatment for the linvoseltamab 5/25/200 mg regimen.

The FDA's Assessment:
The FDA agrees with the Applicant's statement that no studies have been performed to evaluate the effects of linvoseltamab on human reproduction and pregnancy. However, the draft USPI includes a Warning and Precaution for embryo-fetal toxicity, consistent with other products in this drug class.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Only adult patients were eligible for inclusion in Study 1826 and all enrolled patients were >= 18 years. No studies were conducted in pediatric patients and the Applicant requested a waiver of pediatric studies, which was agreed to by FDA, as described in Section 10.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

No cases of overdose with linvoseltamab have been reported. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable as linvoseltamab is not yet a marketed product in any region.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Risk minimization measures including a REMS program (as has been the case for other approved BsAbs in this disease space) are proposed to mitigate the risks of linvoseltamab and protect the patient. The proposed labeling measures include boxed warnings for CRS and ICANS; more detailed warnings for CRS, ICANS, Infections, and Neutropenia; detailed dosing instructions (including pretreatment medications) and dosing schedule, monitoring requirements, and instructions for specific treatment situations (eg, with occurrence of AE or after a dosing delay). Additionally, the Sponsor will provide a REMS with ETASU A and B for the risks of CRS and ICANS.

The FDA's Assessment:

FDA agrees with the Applicant that a REMS with ETASU is needed, however notes that the risk of 'ICANS' should be expanded to the risk of 'neurologic toxicity, including ICANS', based on FDA's assessment of neurologic toxicity (Section 8.2.5.2). FDA also notes that the three bispecific antibodies approved for treatment of RRMM (teclistamab, talquetamab, and elranatamab) each have a REMS with ETASU in place for the risks of CRS and neurologic toxicity, including ICANS. The rates of CRS seen with linvoseltamab are comparable to rates seen with these other products, and the rates of neurologic toxicity (particularly Grade 3 events) are either comparable, or higher (e.g., the rate of Grade 3 neurologic toxicity with linvoseltamab is higher than that seen with teclistamab). While other bispecific antibodies are currently approved for the treatment of RRMM with REMS, experience with use of these bispecific antibodies may be limited in certain practice settings, such as community-based practices. Given the manufacturing issues precluding approval of linvoseltamab, the REMS was not finalized.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The safety data in this submission are adequate to characterize the safety profile of linvoseltamab in patients with RRMM. In study 1826 a total of 282 patients were exposed to linvoseltamab, including 117 patients treated at the recommended dose of 5/25/200 mg.

In Phase 1 of Study 1826, a total of 73 patients were treated across 9 dose escalation cohorts, with the last cohort treated at the maximum full dose of 800 mg of linvoseltamab. Linvoseltamab was well tolerated with no maximum tolerated dose reached. In Phase 2, 209 patients were treated across 2 cohorts, with full doses of 50 mg and 200 mg. In both cohorts and in the All 200 mg patient group, linvoseltamab demonstrated an acceptable safety profile in the context of efficacy in a late-line MM population.

The proposed 5/25/200 mg dosing regimen of linvoseltamab has a generally acceptable and manageable safety profile. The important risks of linvoseltamab were established and well-characterized. These risks are similar to those of approved BCMA-targeted therapies in MM populations: CRS, IRR, ICANS, infections (including opportunistic infections), and neutropenia. For the All 200 mg patients:

- CRS was the most reported TEAE (observed in 46.2% of patients). Most of these patients had grade 1 CRS (35.0%) or grade 2 CRS (10.3%). A single patient had a grade 3 CRS event and there were no grade 4 or 5 CRS events. CRS occurred primarily during the step-up dosing, within 24 hours of start of infusion, and was effectively managed. With continued dosing, CRS events decreased both in incidence and severity. The most common signs and symptoms were typical of CRS including Pyrexia, Chills, Hypoxia, and Tachycardia. The median time to onset was 11.04 hours and the median duration was 14.81 hours. Overall, all grade ≥2 CRS events except 1 began within approximately 24 hours of the end of the infusion. There were no CRS events leading to discontinuation and small numbers of patients had dose delays/disruptions (6.0%) and dose reductions (4.3%). Of those with CRS, 42.6% experienced recurrence and all recurrent events were grade 1 or grade 2. Overall, 24.8% of patients received treatment for CRS, most commonly tocilizumab (18.8%) and corticosteroids (11.1%).
- IRR was experienced by 9.4% of patients (grade 3 1.7%, no grade 4 or 5) and occurrence was highest following initial dose (5.1%) with fewer patients experiencing IRR following the intermediate dose (2.7%) and all subsequent doses. The most common signs and symptoms were Pyrexia, Chills, Hypertension and Hypotension.
- ICANS (adjudicated) incidence was 7.7% of patients (grade 1 2.6%; grade 2 2.6%; grade 3 2.6%, no grade 4 or 5). The occurrence was highest after the initial dose and decreased with sequential doses. One patient discontinued treatment due to ICANS. Small numbers of patients had dose delays/interruptions (1.7%) and dose reductions (0.9%). Of those with ICANS, 1 patient experienced recurrence. The median time to onset was 1 day and the median duration was 2 days.
- Infections were reported in 72.6% of patients (grade 3/4 34.2%; grade 5 9.4%) with 41.9% experiencing serious infections. The most common infections were COVID-19, Pneumonia and Upper respiratory tract infections

and the most common serious infections were Pneumonia, COVID-19 and COVID-19 pneumonia, and PJP. Fatal infections were COVID-19 pneumonia, Septic shock, Escherichia sepsis, Haemophilus sepsis, PJP, Pneumonia influenzal, Progressive multifocal leukoencephalopathy, and Pseudomonal sepsis. 9.4% patients discontinued due to an infection, 41.9% had dose delays/interruption (mostly of grade 3/4 infections) and 4.3% had dose reductions due to infections (all grade 3/4 infections). Opportunistic infections were experienced by 10.3% of patients (grade 3/4 6.0%, grade 5 1.7%), including CMV, Pneumocystis, Candida, Fungal, Herpes virus, and Polyomavirus infections. Of these 6.0% were serious and 1.7% were fatal (PJP and PML).

- Infections risk appeared early in the clinical study and improved over time in parallel with improvement in patients' myeloma status. Similarly, anemia, present almost universally at baseline, improved with treatment. Rates of all grade, grade 3/4, and grade 5 infections progressively decreased over time for patients who received 200 mg linvoseltamab but not a lower dose, consistent with the interpretation that at least part of the risk is related to the underlying disease and that risk is improved by treatment with an effective dose linvoseltamab.
- Episodes of grade ≥3 neutropenia by laboratory values were common (45.3% of patients). After an initial temporary increase during the step-up period, mean and median neutrophil counts fluctuated around baseline throughout the study, and episodes of neutropenia were manageable.

Overall, the safety data demonstrate that the safety profile of linvoseltamab is acceptable and manageable. The safety profiles were generally consistent in patients with both 200 mg and 50 mg full doses and any exceptions noted did not appear to be related to linvoseltamab dose. The safety profile of the proposed regimen of linvoseltamab appears consistent with the mechanism of action of linvoseltamab and/or the AEs expected in a pretreated population with RRMM and is similar to other BCMAxCD3 BsAbs, both those approved and in development for RRMM.

The FDA's Assessment:

The FDA agrees that the data in the BLA submission are adequate to evaluate the safety profile of linvoseltamab and that at the proposed dosage, safety profile is generally acceptable and toxicities are manageable. Based on FDA's assessment of the totality of efficacy and safety data, linvoseltamab has a favorable benefit/risk profile for use in patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. Minor differences in rates of AEs were noted between FDA's analysis and the Applicant's analysis, due to methodological differences, including the terms used for grouping of AEs. Refer to Appendix 19.6 for FDA's list of grouped terms.

FDA performed an analysis of the safety profile of linvoseltamab based on 117 patients treated at the 200 mg dose of linvoseltamab in Phases 1 and 2 of Study 1826. In the safety population, the most common AEs (≥20%) were musculoskeletal pain, CRS, cough, upper respiratory tract infection, diarrhea, fatigue, pneumonia, nausea, and headache. SAEs occurred in 74% of patients, most commonly due to CRS, pneumonia, COVID-19, and acute kidney injury. Fatal AEs within 30 days of the last dose occurred in 8% of patients and fatal AEs, including those outside of the 30-day window but FDA-adjudicated as deaths due to AEs, occurred in 16% of patients. Dose modifications, including interruptions, delays, and dose reductions, occurred in 74% of patients. The most common Grade 3-4 laboratory abnormalities (≥10%) were lymphopenia, neutropenia, anemia, leukopenia, and thrombocytopenia. There were high rates of hepatic enzyme elevation (elevated AST: 61% All Grade, 10% Grade 3-4; elevated ALT: 46% All Grade, 6% Grade 3-4).

Of the 117 patients in the safety population, 46% experienced CRS (35% maximum Grade 1, 10% maximum Grade 2, 0.9% maximum Grade 3). There were no Grade 4 or 5 CRS events. Given the high rates of CRS, despite mandatory premedications in the clinical trial, the FDA did not agree with the option for outpatient administration that the Applicant proposed in the USPI, and the FDA revised the draft USPI to include guidance for hospitalization for 48 hours following the first step-up dose and 24 hours following the second step-up dose. Neurologic toxicity occurred in 54% of patients; 8% experienced Grade 3 or greater events. ICANS occurred in 8% of patients, all concurrent with or after resolution of CRS or IRR.

FDA has determined the need for several proposed risk mitigation measures. Based on an evaluation of the safety of linvoseltamab, the FDA has determined that the USPI should include a boxed warning for CRS and neurologic toxicity, including ICANS. Warnings and Precautions for the risks of infections, neutropenia, and hepatotoxicity are also included in the draft USPI. FDA has also determined that a REMS will be required to mitigate the risks of CRS and neurotoxicity including ICANS with linvoseltamab. Given the manufacturing issues identified and outlined in the OPQ Executive Summary, which preclude approval of linvoseltamab, the label and the REMS remains in draft form.

With the above measures, the risks of linvoseltamab appear to be acceptable for patients with RRMM after at least 4 prior lines of therapy, including a PI, IMiD, and anti-CD38 mAb. Due to the manufacturing issues identified at the manufacturing facility of linvoseltamab, the recommended regulatory action is a Complete Response.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues identified in this submission. However, when interpreting the results, it is important to note that the efficacy of linvoseltamab was based on ORR by IRC, which is an intermediate endpoint evaluated in a single arm trial. While the study also assessed other endpoints such as time to response, PFS, OS and PROs, their interpretability is limited in a single-arm trial setting, and hence, they are considered exploratory and were not considered for inclusion in the USPI. Furthermore, the subgroup analyses, conducted with a limited sample size, were regarded as sensitivity analyses for the primary endpoint. As a result, these analyses should be considered exploratory, and results should be interpreted with caution. To verify the clinical benefit of linvoseltamab, a randomized confirmatory clinical trial is ongoing.

The FDA evaluated efficacy of linvoseltamab monotherapy based on the ORR by IRC, supported by DOR, for the Phase 2 200 mg cohort. The evaluation excluded patients from Phase 1 since the primary hypothesis for efficacy was based on the Phase 2 200 mg cohort alone. Additionally, the endpoint for the Phase I portion was safety-related, with efficacy of ORR as a secondary endpoint. Therefore, the efficacy results should be based on 105 patients from the Phase 2 200 mg cohort.

In order to align with the intended indication, the FDA's primary efficacy analyses were based on the 80 patients from the Phase 2 200 mg cohort, who had received four or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on IRC-assessed ORR and supported by durability of response from Study 1826, linvoseltamab has demonstrated substantial evidence of effectiveness in patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. The available data indicate that linvoseltamab demonstrates a clinical meaningful advantage in the context of available therapies for the patient population. The safety profile of linvoseltamab includes toxicities that are consistent with those seen with other bispecific antibodies, currently under accelerated approval, for the treatment of RRMM; these include CRS, neurologic toxicity, infections, neutropenia, and hepatotoxicity. In the context of the (b) (4) indicated patient population and with a REMS program, the risks are acceptable and the overall benefit/risk is favorable.

The Applicant has provided updates regarding the status of accrual to the proposed confirmatory trial, R5458-ONC-2245, during the BLA review process; as of the most recent update on August 8, 2024, 154 of a planned (b) (4) patients had been enrolled,

which represents an increase in enrollment since submission of the BLA. The accrual projections and timelines provided by the Applicant appear reasonable.

Due to the manufacturing issues identified at the linvoseltamab manufacturing facility, outlined in the OPQ Executive Summary, which preclude approval of linvoseltamab, the recommended regulatory action is a Complete Response.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The application was not presented at an advisory committee meeting and no external consultations were utilized in the review.

10 Pediatrics

The Applicant's Position:

Pediatric studies for linvoseltamab were not performed, given that the molecular target has been identified to be non-relevant to the growth or progression of pediatric cancers and that linvoseltamab has been granted orphan drug designation for the treatment of MM.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

11 Labeling Recommendations

Data:
Review of the labeling will be undertaken when the application is otherwise approvable.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Boxed Warning	Included Boxed Warning for CRS, ICANS, and information about the REMS.	N/A
1 Indications and Usage	Indicated for the treatment of adult patients with RRMM (b) (4)	N/A
2 Dosage and Administration	Includes: • Important administration instructions • A table of recommended dosage • A table of pretreatment medications to reduce the risk of CRS and/or IRR • A table for restarting therapy after a dose delay	N/A

	• Management of adverse reactions (CRS, ICANS, and other AEs) • Instructions for preparation and administration	
3 Dosage Forms and Strengths	Single dose vials for injection, at 2 different strengths.	N/A
4 Contraindications	None.	N/A
5 Warnings and Precautions	Includes Warnings and Precautions for CRS, ICANS, REMS, Infections, and Neutropenia.	N/A
6 Adverse Reactions	Includes: • Summary text for the safety population (n=117) of the clinical trial • Tables for adverse reactions (≥10%) and select laboratory abnormalities (b) (4)	N/A
7 Drug Interactions	Includes a statement (b) (4) to monitor for toxicity or concentrations of drugs that are CYP substrates where minimal changes in concentration may lead to serious adverse reactions.	N/A
8 Use in Specific Populations	Includes recommendations for pregnancy, breastfeeding, contraception, pediatric use, and geriatric use.	N/A
(b) (4)		
11 Description	Includes product description of linvoseltamab.	N/A
12 Clinical Pharmacology	Includes details on the mechanism of action, PD, PK, and immunogenicity of linvoseltamab.	N/A
13 Nonclinical Toxicology	Includes details on nonclinical toxicology.	N/A
14 Clinical Studies	Includes study design for Study 1826, patient population, and efficacy results.	N/A
16 How Supplied/Storage and Handling	Includes storage instructions for linvoseltamab in single dose vials.	N/A
17 Patient Counseling Information	Includes patient counseling information for CRS, ICANS, REMS, Infections, and Neutropenia.	N/A
Medication Guide	A Medication Guide has been submitted.	N/A

The FDA's Assessment:

As the recommended regulatory action is a Complete Response, review of the USPI has not been completed. Thus, the table with a summary of labeling changes is not applicable.

Of note, as described throughout this Assessment Aid, the FDA has determined that the benefit -risk is favorable for (b) (4) indication statement and defined the primary efficacy analysis population accordingly. Rationale for the revised statement, which was updated in the draft label, is provided in this section.

The Applicant's proposed indication was for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) The FDA disagreed with the proposed indication statement for the following reasons:

(b) (4)

(b) (4)

Other relevant changes made by the FDA to the draft USPI included a revision to the population used for reporting of efficacy results in Section 14, in order to align with the (b) (4) indicated population.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Based on the risks of CRS and neurologic toxicity, including ICANS, the review team recommends a REMS with ETASU. Given the regulatory recommendation of a

Complete Response, the REMS materials were not finalized or communicated to the Applicant.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Given that the Applicant is seeking Accelerated Approval, there is the need for a confirmatory trial to verify the clinical benefit of linvoseltamab. As the recommended regulatory action is a Complete Response, PMRs and PMCs were not drafted or communicated to the Applicant during the review cycle.

The potential PMRs/PMCs considered by the review team include:

- An accelerated approval PMR to conduct a randomized controlled trial of linvoseltamab in patients with RRMM to verify its clinical benefit.
- Given the limited representation of patients of Hispanic/Latino ethnicity in Study 1826, a PMC for additional data to characterize safety and efficacy in this ethnic group may be considered.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	_X_ Yes __ No

▫	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:

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Chetty R,Gatter K. CD3: structure, function, and role of immunostaining in clinical practice. J Pathol 1994; 173(4):303-307.

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Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016; 17(8):e328-e346.

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Vaidyanathan A, McKeever K, Anand B, Eppler S, Weinbauer GF,Beyer JC. Developmental immunotoxicology assessment of rituximab in cynomolgus monkeys. Toxicol Sci 2011; 119(1):116-125.

Xu S,Lam KP. B-cell maturation protein, which binds the tumor necrosis factor family members BAFF and APRIL, is dispensable for humoral immune responses. Mol Cell Biol 2001; 21(12):4067-4074.

The FDA's References:

1. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022 Aug;97(8):1086-1107. doi: 10.1002/ajh.26590. Epub 2022 May 23. PMID: 35560063; PMCID: PMC9387011.
2. SEER database. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Myeloma— Cancer Stat Facts. Accessed June 2024.

19.2. Financial Disclosure

The Applicant's Position:

Information on financial disclosures for Study 1826 is provided in the table below.

Covered Clinical Study (Name and/or Number):* R5458-ONC-1826

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 322		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The FDA agrees that based on the information provided, no disclosable financial interests or arrangements were identified.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

N/A. All nonclinical pharmacology and toxicology data are included in Section 5.

The FDA's Assessment:
The FDA agrees.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:
The Applicant's final population PK (popPK) model is adequate for the purpose of predicting total linvoseltamab concentration in patients with RRMM. Following the proposed 5/25/200 mg dosage regimen, no clinically relevant differences in total linvoseltamab exposure were identified according to age, weight, sex, race, mild to moderate renal impairment, or mild hepatic impairment.

19.4.1.2. PopPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PopPK Analysis		• Describe linvoseltamab PK in the RRMM population, accounting for relevant intrinsic and extrinsic covariates of exposure. • Estimate post hoc exposure metrics for the trial participants, to enable comparison between subgroups. • Simulate linvoseltamab exposure in the proposed registrational dose regimen.
Study Included		Study 1826 Phase 1 and Phase 2
Dose(s) Included		1mg/3mg, 2mg/6mg, 4mg/12mg, 8mg/24mg, 16mg/48mg, 32mg/96mg, 5mg/25mg/96mg, 5mg/25mg/400mg, 5mg/25mg/800mg, 5mg/25mg/50mg, 5mg/25mg/200mg
Population Included		Patients with RRMM who had received any amount of linvoseltamab and had at least one non-missing post-baseline concentration of linvoseltamab in serum.
Population Characteristics	General	Age (median 66 yrs, range 37-91 yrs, 56.4% subj >=65 yr, 21.6% subj >=75 yr) Weight (median 77.1 kg, range 44.2-171 kg) 151 (53.5%) male; 131 (46.5%) female 205 (72.7%) White; 44 (15.6%) Black or African American; 18 (6.4%) Asian; 7 (2.5%)Other; 8 (2.8%) Not Reported
	Organ Impairment	Hepatic (NCI-ODWG Criteria): 27 (9.6%) mild; 255(90.4%) normal

		Renal (estimated Glomerular Filtration Rate was calculated using the CKD-EP equation) n = 78 (27.7%) normal; 116 (41.1%) mild; 76 (27.0%) moderate;11 (3.9%) severe;1(0.4%) failure
	Pediatrics (if any)	Not Applicable
No. of Patients, PK Samples, and BLQ		Total number of patients: 281 (282 total dosed) There was a total of 6995 concentration records in the analysis set. Postdose concentration records that were BLQ represented 0.0066% (n=46) and were excluded from the analysis.
Sampling Schedule	Rich Sampling	Predose, EOI, 4 h of each split dose at W1-W3 and 24 h, 48h in W1-W3; predose, EOI, 4h in W4; predose and EOI at W5, W6, W8, W10, W12, W14, W16, W18, W20, W22 to W40 or last dose, W44 or 30 days post-last dose, follow-up visits W48, W52, W56, W60 and W64, or W8 and W12 post-last dose
	In ITT Population	Not Applicable
Covariates Evaluated	Static	AGE = baseline age; CARFILZ = Prior Carfilzomib Treatment; CL = clearance; CRCLBL = Creatinine clearance at baseline; CRPBL = C-reactive protein at baseline; ECOGBL = ECOG performance score at baseline; ETHNICN = Ethnicity; HEPCATN = Hepatic Impairment Status; LENALD = Prior Lenalidomide Treatment; MMISTYPN = Multiple Myeloma Type; NPRSYTHP = Number of prior lines of therapy; Q = intercompartmental clearance; RACEN = Race; RENALCN = Renal Impairment Status; SBMCABL = Serum B-cell maturation antigen at baseline; SEXN = Sex; SMPRBL = Serum M-protein at baseline; TOTFRBL = Total Free Light Chain at baseline; VC = Volume of Distribution in Central Compartment; VMAX = maximum nonlinear clearance rate; VP = Peripheral Volume of distribution; WGTBL = body weight at baseline
	Time-varying	IgG, ALB, and FLC

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM® (version 7.5.0) R (4.2.2) and Rstudio	The Applicant's popPK model adequately characterized total linvoseltamab concentration in patients with RRMM, as demonstrated by the goodness-of-fit plots on a semilog scale (Figure 10) and on a linear scale (Figure 11). The Applicant's final popPK model is adequate for the purpose of predicting total linvoseltamab concentration in patients with RRMM.
Model Structure	2-compartment distribution model with parallel linear and nonlinear (Michaelis-Menten type) clearance processes.	
Model Parameter Estimates	Table 61: Parameter Estimates and RSE from Final PopPK Model	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	The parameters were estimated with sufficient precision (most with <30% RSE) and random effects shrinkage was acceptable (<30%). Random effects were normally distributed and unbiased. Model fit, evaluated with CWRES, was unbiased over time and predicted	

	concentration, and across all but the lowest DL.	
BLQ for Parameter Accuracy	Postdose concentration records that were BLQ represented 0.0066% (n=46) and were excluded from the analysis.	
GOF, VPC	Figure 10 GOF Plot	
Significant Covariates and Clinical Relevance	Time-varying IgG, time-varying ALB, and baseline WGT were determined to be statistically significant covariates of CL. IgG and ALB have opposing effects on CL, with higher IgG increasing CL and higher ALB decreasing CL. CL was found to increase with increasing baseline WGT.	The final popPK model identified statistically significant associations between: • Lower time-varying serum albumin concentration and faster linear clearance. • Higher time-varying IgG concentration and faster linear clearance • Higher body weight and faster linear clearance • Higher time-varying free light chain concentration and faster maximum velocity (Vmax) of concentration-dependent clearance • Higher body weight and faster intercompartmental clearance (Q) • Female sex (versus male sex) and 14.8% lower central volume of distribution
Analysis Based on Simulation (optional)		Total linvoseltamab concentration over time is displayed in Figure 12. Following the proposed 5/25/200 mg dosage regimen, no clinically relevant differences in total linvoseltamab exposure were identified according to age (37 to 91 years), weight (44 to 172 kg), sex, race (White, Asian, or Black), ethnicity, mild to moderate renal impairment, or mild hepatic impairment.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	(b) (4)	Linvoseltamab Ctrough increased more than proportionally over a dose range of 96 mg to 800 mg (0.48 to 4 times the recommended full dose). Geometric mean (CV%) linvoseltamab maximum

	(b) (4)	concentration of 127 mg/L (51%) is achieved after the first dose of the Q2W dosing regimen (i.e., the 12th dose of 200 mg). Linvoseltamab clearance is 0.68 L/day (52.2%) at baseline and 0.43 L/day (83.8%) at steady state. Linvoseltamab is expected to be metabolized into small peptides by catabolic pathways.

Table 60: Applicant - Geometric Mean (CV%) of Model-Based Exposure Parameters of Recommended Dosage for Linvoseltamab

	C_{max} (mg/L)	C_{trough} (mg/L)	AUCt[a] (mg*day/L)
200 mg weekly (Week 14)	124 (50.4)	61.8 (123)	592 (74.6)
200 mg every other week (Week 24)	97.9 (52.7)	30.2 (213)	727 (95.3)
200 mg Q4W (Week 48)	64.8 (45.1)	6.3 (362)	574 (84.6)

[a] AUCt for the specified dosing interval, ending at the indicated week.

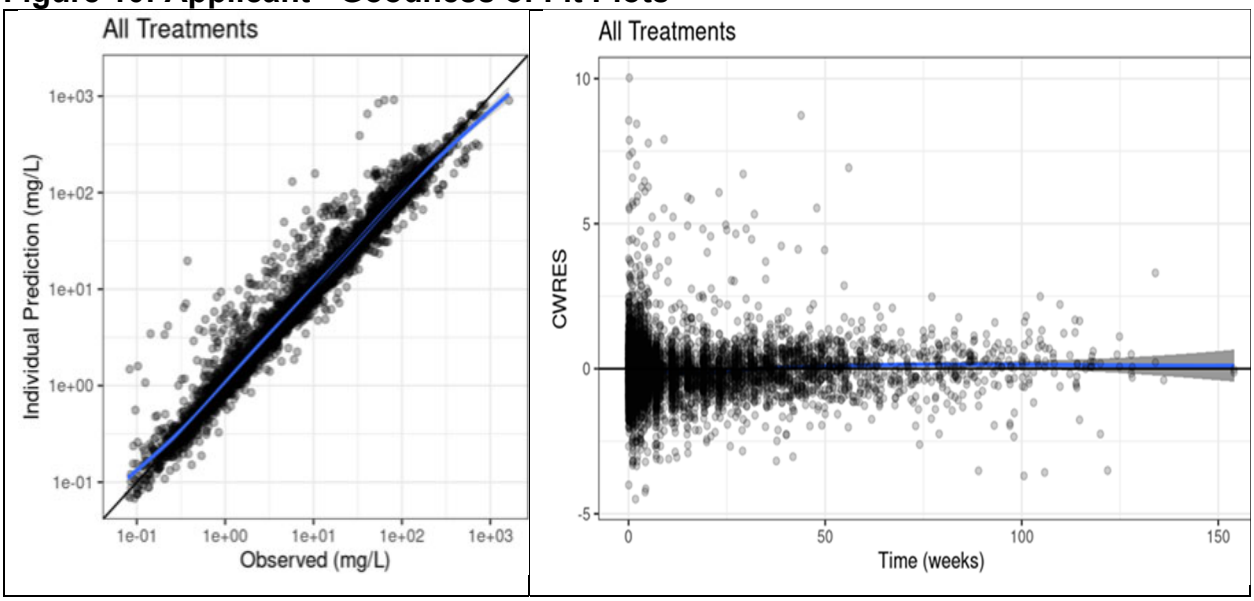
Table 61: Applicant - Parameter Estimates and RSE from Final Population PK Model

Parameter Label	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
V_{max} [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

Parameter Label	Parameter Estimate (95% CI)	RSE (%) [shrinkage (%)]
CL_IGG1 [-]	0.8354 (0.7631 — 0.9077)	4.418
CUT_IFF [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]

Source: Module 5.3.3.5 R5458 PopPK Report Table 1

Figure 10: Applicant - Goodness of Fit Plots



Source: Module 5.3.3.5 R5458 PopPK Report Figure 33, Figure 36

The FDA's Assessment:

The Applicant's final popPK model was developed using data from 281 patients with RRMM in Study 1826. All patients received dosage regimens which included one or two step-up doses before the first full dose, and full dose ranged from 3 mg to 800 mg IV once weekly (QW). The number of patients in each dosage cohort is described in **Table**

62, and patient covariates in the popPK dataset are described in **Table 63** and **Table 64.**

Table 62: FDA - Number of Patients with Population PK Data Per Dose Level

Dose Cohort	Dose Escalation Phase [n]	Dose Expansion Phase [n]	Overall [n (%)]
1 mg/3 mg	4	0	4 (1.4%)
2 mg/6 mg	10	0	10 (3.6%)
4 mg/12 mg	10	0	10 (3.6%)
8 mg/24 mg	10	0	10 (3.6%)
16 mg/48 mg	7	0	7 (2.5%)
32 mg/96 mg	5	0	5 (1.8%)
5 mg/25 mg/50 mg	0	104	104 (37%)
5 mg/25 mg/96 mg	3	0	3 (1.1%)
5 mg/25 mg/200 mg	12	104	116 (41.3%)
5 mg/25 mg/400 mg	8	0	8 (2.8%)
5 mg/25 mg/800 mg	4	0	4 (1.4%)

All patients with popPK data were from Study R5458-ONC-1826.
Source: Reviewer's analysis of Applicant's popPK dataset

Table 63: FDA - Continuous Patient Characteristics in the Population PK Dataset

Covariate	Statistic	5/25/50 mg (n=104)	5/25/200 mg (n=116)	All Other Dose Levels (n=61)	Overall (n=281)
Baseline Age (years)	Mean (SD)	65.5 (9.1)	67.3 (10.2)	65 (9.6)	66.1 (9.7)
	Median	65	69	64	66
	Min - Max	45 - 90	37 - 91	41 - 81	37 - 91
Baseline Weight (kg)	Mean (SD)	78.1 (17.1)	78.5 (20.4)	79.2 (20.3)	78.5 (19.1)
	Median	76.3	76.4	79.8	77.1
	Min - Max	45.7 - 124.4	45 - 171.4	44.2 - 129.1	44.2 - 171.4
Baseline Creatinine Clearance (mL/min)	Mean (SD)	70.5 (23.6)	72.2 (22.5)	75.3 (25.8)	72.3 (23.6)
	Median	69	73.1	80.9	73.2
	Min - Max	23.5 - 114.9	12.4 - 121.2	25.6 - 113.5	12.4 - 121.2
Baseline Albumin (g/L)	Mean (SD)	37.1 (5.9)	37.1 (5.9)	36.6 (5.6)	37 (5.8)
	Median	38	38	38	38
	Min - Max	15 - 48	15 - 48	23 - 48	15 - 48
Baseline Total Bilirubin (umol/L)	Mean (SD)	7.5 (3.7)	8.4 (4.1)	7.9 (3.7)	8 (3.9)
	Median	6.8	7	6.8	6.8
	Min - Max	1.7 - 25.6	2.7 - 23.9	3.4 - 22.7	1.7 - 25.6
Baseline Soluble BCMA (mg/L)	Mean (SD)	0.9 (1.3)	0.6 (0.7)	0.7 (0.8)	0.7 (1)
	Median	0.4	0.4	0.4	0.385
	Min - Max	0 - 10.2	0 - 4.4	0 - 4	0 - 10.2
Baseline Immunoglobulin G (g/L)	Mean (SD)	16.7 (17.2)	14.1 (15)	14.4 (17)	15.1 (16.2)
	Median	8	6.4	4.6	6.1
	Min - Max	0.6 - 64.5	0.4 - 58.6	0.3 - 50	0.3 - 64.5
Baseline Total Free Light Chain (mg/L)	Mean (SD)	1674 (4367)	798 (1179)	1929 (5056)	1367 (3647)
	Median	656	334.6	602.7	544.9
	Min - Max	16.8 - 40082	6.5 - 6588	12.4 - 37738	6.5 - 40082

All patients with population PK data were from Study R5458-ONC-1826. SD = standard deviation.
Source: Reviewer's analysis of Applicant's popPK dataset

Table 64: FDA - Categorical Patient Characteristics in the Population PK Dataset

Covariate	Subgroup	5/25/50 mg (n=104)	5/25/200 mg (n=116)	All Other Dose Levels (n=61)	Overall (n=281)
		n (%)	n (%)	n (%)	n (%)
Sex	Female	48 (46.2%)	52 (44.8%)	30 (49.2%)	130 (46.3%)
	Male	56 (53.8%)	64 (55.2%)	31 (50.8%)	151 (53.7%)
Race	Asian	6 (5.8%)	10 (8.6%)	2 (3.3%)	18 (6.4%)
	Black or African American	14 (13.5%)	20 (17.2%)	10 (16.4%)	44 (15.7%)
	White	75 (72.1%)	82 (70.7%)	47 (77%)	204 (72.6%)
	Other	5 (4.8%)	1 (0.9%)	1 (1.6%)	7 (2.5%)
	Not reported	4 (3.8%)	3 (2.6%)	1 (1.6%)	8 (2.8%)
Ethnicity	Hispanic or Latino	12 (11.5%)	4 (3.4%)	6 (9.8%)	22 (7.8%)
	Not Hispanic or Latino	91 (87.5%)	106 (91.4%)	54 (88.5%)	251 (89.3%)
	Not reported	1 (1%)	6 (5.2%)	1 (1.6%)	8 (2.8%)
Baseline Renal Function (Creatinine Clearance)	Normal (≥90 mL/min)	26 (25%)	28 (24.1%)	24 (39.3%)	78 (27.8%)
	Mild impairment (60 to <90 mL/min)	41 (39.4%)	56 (48.3%)	18 (29.5%)	115 (40.9%)
	Moderate impairment (30 to <60 mL/min)	31 (29.8%)	28 (24.1%)	17 (27.9%)	76 (27%)
	Severe impairment or end stage renal disease (<30 mL/min)	6 (5.8%)	4 (3.4%)	2 (3.3%)	12 (4.3%)
Baseline Hepatic Function	Normal hepatic function	91 (87.5%)	106 (91.4%)	57 (93.4%)	254 (90.4%)
	Mild hepatic impairment	13 (12.5%)	10 (8.6%)	4 (6.6%)	27 (9.6%)
Baseline ECOG Score	0	37 (35.6%)	32 (27.6%)	17 (27.9%)	86 (30.6%)
	1	66 (63.5%)	84 (72.4%)	43 (70.5%)	193 (68.7%)
	2	1 (1%)	0	1 (1.6%)	2 (0.7%)
MM Immune Subtype	Immunoglobulin A	20 (19.2%)	25 (21.6%)	12 (19.7%)	57 (20.3%)
	Immunoglobulin G	62 (59.6%)	64 (55.2%)	28 (45.9%)	154 (54.8%)
	Light Chain	19 (18.3%)	24 (20.7%)	21 (34.4%)	64 (22.8%)
	Other Heavy Chain	3 (2.9%)	3 (2.6%)	0	6 (2.1%)
Number of Prior Lines	2-3 prior lines	9 (8.7%)	28 (24.1%)	8 (13.1%)	45 (16%)
	4-5 prior lines	35 (33.7%)	47 (40.5%)	22 (36.1%)	104 (37%)
	6 or more prior lines	60 (57.7%)	41 (35.3%)	31 (50.8%)	132 (47%)
Received IVIG Therapy	Yes	44 (42.3%)	63 (54.3%)	20 (32.8%)	127 (45.2%)
	No	60 (57.7%)	53 (45.7%)	41 (67.2%)	154 (54.8%)
Anti-drug Antibody Status	Positive	1 (1%)	1 (0.9%)	0	2 (0.7%)
	Negative	65 (62.5%)	81 (69.8%)	44 (72.1%)	190 (67.6%)
	Missing	38 (36.5%)	34 (29.3%)	17 (27.9%)	89 (31.7%)

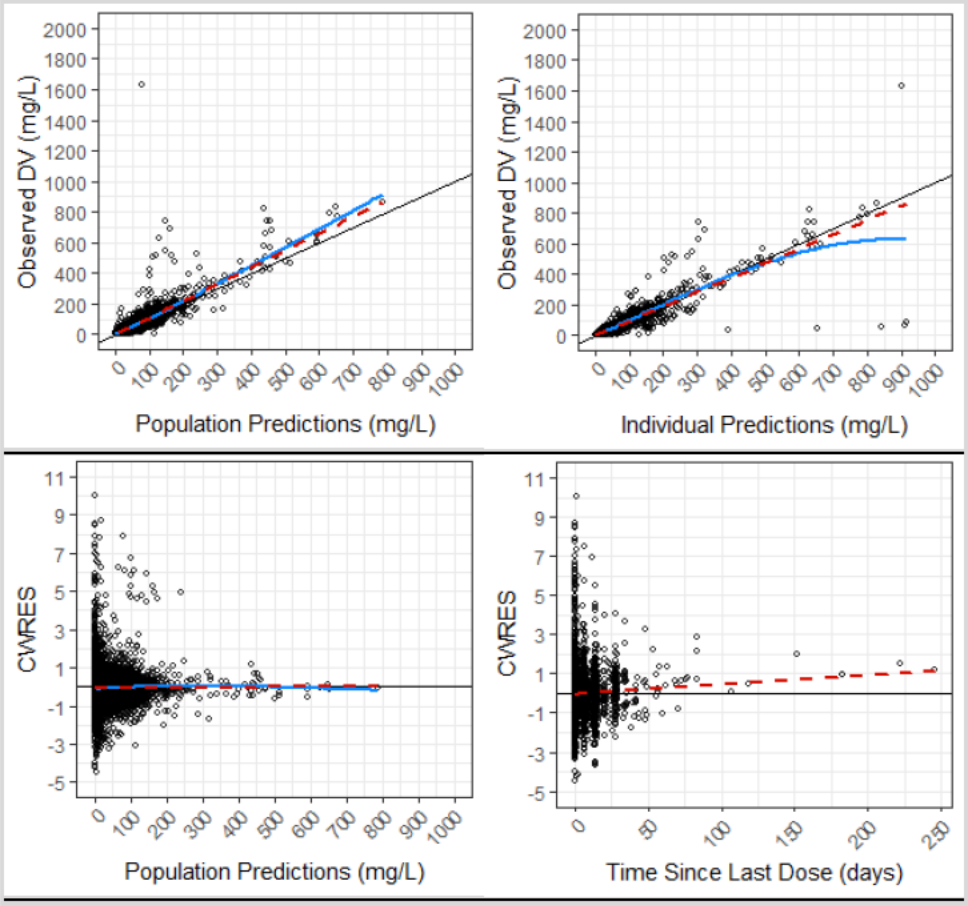
All patients with population PK data were from Study R5458-ONC-1826.
Source: Reviewer's analysis of Applicant's popPK dataset

The Applicant characterized PK of total linvoseltamab concentration in serum using a 2-compartment popPK model with parallel linear clearance and concentration-dependent clearance. The final model parameters are described in **Table 61** above.

Based on goodness-of-fit plots in **Figure 10** and **Figure 11**, the Applicant's popPK model adequately characterized total linvoseltamab concentration in patients with RRMM. The model fit did not differ significantly between patients who received the

5/25/50 mg regimen and patients who received the 5/25/200 mg regimen.

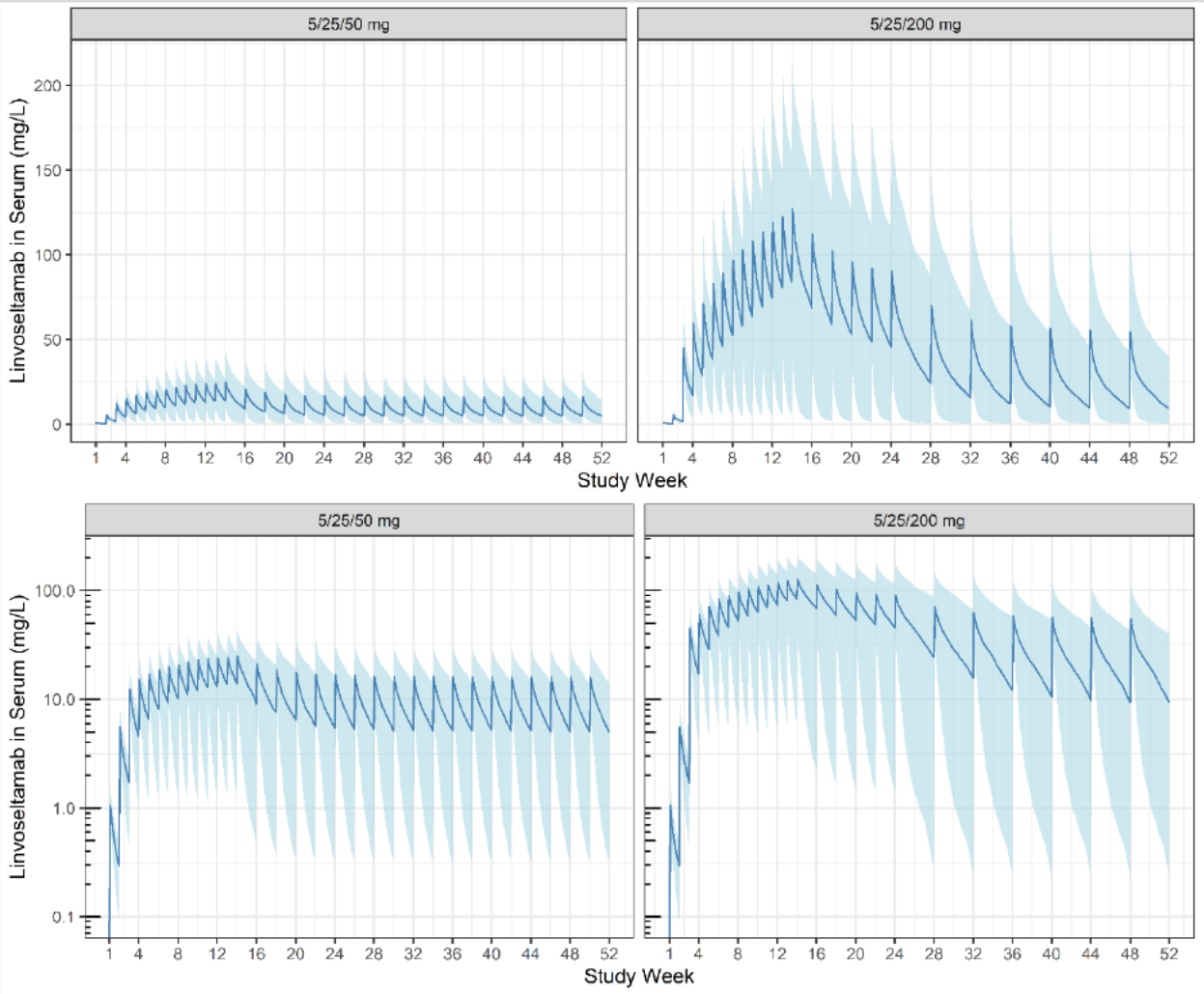
Figure 11: FDA - Total Linvoseltamab Population PK Model Goodness-of-fit Plots on Linear Scale



Loess in solid blue; Linear regression in dashed red. The lower limit of quantification was 0.078 mg/L.
CWRES = conditional weighted residual; DV = observed concentration.
Source: Reviewer's analysis

Figure 12 displays the model-predicted total linvoseltamab PK profile for the 5/25/50 mg and 5/25/200 mg dosage regimens. **Table 65** summarizes the PK parameters for the 5/25/50 mg and 5/25/200 mg dosage regimens, while **Table 66** summarizes total linvoseltamab exposure following the 5/25/200 mg dosage.

Figure 12: FDA - Model-Predicted Total Linvoseltamab Concentration over Time for 5/25/50 mg and 5/25/200 mg Dosages: Linear (top) and Semilog (bottom) Scales



Solid line = median. Shaded region = 5th to 95th percentile.
Total linvoseltamab concentration was simulated in 282 patients in Study R5458-ONC-1826 with RRMM following the 5/25/50 mg dosage regimen (left) and the 5/25/200 mg dosage regimen (right).
For the simulation of the 5/25/50 mg dosage regimen, subjects received 5 mg on the first day of Week 1, then 25 mg on the first day of Week 2, then 50 mg on the first day of Week 3 and once weekly thereafter for a total of 12 doses, then 50 mg every 2 weeks thereafter.
For the simulation of the 5/25/200 mg dosage regimen, subjects received 5 mg on the first day of Week 1, then 25 mg on the first day of Week 2, then 200 mg on the first day of Week 3 and once weekly thereafter for a total of 12 doses, then 200 mg every 2 weeks thereafter for a total of 5 doses, then 200 mg every 4 weeks thereafter.
Source: Reviewer's analysis of Applicant's response to 8Feb2024 IR and Applicant's linvo_exposure_sims-run5200_rmd.txt (seqn0008)

Table 65: Descriptive Statistics for Total Linvoseltamab PK in PopPK Patient Population Using the Final PopPK Model

Parameter	5/25/50 mg	5/25/200 mg
Total clearance after the first dose (L/day)	0.676 (52.2)	0.676 (52.2)
Half-life at first dose (day)	9.37 (49.3)	9.37 (49.3)
Change in total clearance at last QW dose (Week 14) (%)[a]	-32.3 (0.85)	-49.6 (0.594)
Total clearance at last QW dose (L/day)	0.426 (76.5)	0.297 (90.7)
Half-life at last QW dose (day)	11.1 (56.3)	13.6 (63.8)
Change in total clearance at steady state (Week 48) (%)[a]	-22.8 (1.22)	-30 (1.03)
Total clearance at steady-state (L/day)	0.489 (71.6)	0.429 (83.8)
Half-life at steady state (day)	10.9 (56)	11.3 (59.4)
Volume of distribution (L)	7.05 (33.6)	7.05 (33.6)

[a]Statistics shown are arithmetic mean (CV%)
Statistics shown are geometric mean (CV%), except as noted. All study patients were simulated at the indicated dose.
Total linvoseltamab concentration was simulated in 282 patients in Study R5458-ONC-1826 with RRMM following the 5/25/50 mg and 5/25/200 mg dosage regimens.
For the simulation of the 5/25/50 mg dosage regimen, subjects received 5 mg on the first day of Week 1, then 25 mg on the first day of Week 2, then 50 mg on the first day of Week 3 and once weekly thereafter for a total of 12 doses, then 50 mg every 2 weeks thereafter.
For the simulation of the 5/25/200 mg dosage regimen, subjects received 5 mg on the first day of Week 1, then 25 mg on the first day of Week 2, then 200 mg on the first day of Week 3 and once weekly thereafter for a total of 12 doses, then 200 mg every 2 weeks thereafter for a total of 5 doses, then 200 mg every 4 weeks thereafter.
CV = coefficient of variation; QW = every week.
Source: Table 13 in Applicant's Population PK Report

Table 66: FDA - Model-Predicted Total Linvoseltamab Exposure following Proposed 5/25/200 mg Dosage Regimen

PARAM	STATISTIC	Step Up Dose 1 (Week 1)	Step Up Dose 2 (Week 2)	First Full QW Dose (Week 3)	Last Full QW Dose (Week 13)	Last Q2W Dose (Week 22)	Steady State During Q4W Dosing
AUC (mg*day/L)	Geo Mean (CV%)	3.9 (32.8%)	21.1 (35.5%)	181.7 (34.5%)	548.6 (78.3%)	691.8 (99.4%)	580.4 (94.7%)
	Median	4	22	188.7	649.7	837.7	633.2
	5th to 95th percentile	2.2 - 6	11.1 - 32.2	95.3 - 281.3	121 - 1182.5	119.4 - 1848.4	118.1 - 1823.5
Cavg (mg/L)	Geo Mean (CV%)	0.6 (32.8%)	3 (35.5%)	26 (34.5%)	78.4 (78.3%)	49.4 (99.4%)	20.7 (94.7%)
	Median	0.6	3.1	27	92.8	59.8	22.6
	5th to 95th percentile	0.3 - 0.9	1.6 - 4.6	13.6 - 40.2	17.3 - 168.9	8.5 - 132	4.2 - 65.1
Cmax (mg/L)	Geo Mean (CV%)	1.2 (35.6%)	6.4 (36.1%)	49.1 (33.9%)	113.8 (54%)	88.1 (54%)	58.5 (43.3%)
	Median	1.2	6.1	47.9	125	92.2	56.9
	5th to 95th percentile	0.8 - 2.2	4.2 - 11.2	32.7 - 83.9	40.2 - 213.3	36 - 178.1	32.5 - 119.6
Ctrough (mg/L)	Geo Mean (CV%)	0.3 (59.3%)	1.6 (62.3%)	16.1 (60.6%)	63.4 (118.3%)	30.9 (205.4%)	6.9 (378.6%)
	Median	0.3	1.8	17.8	85.3	45.9	10
	5th to 95th percentile	0.1 - 0.5	0.5 - 3.1	4.8 - 29.1	6.7 - 162	1.7 - 113.5	0.2 - 46.5

[a] Steady state values are approximated by reporting exposure following Week 40 dose.
Total linvoseltamab concentration was simulated in 282 patients in Study R5458-ONC-1826 with RRMM following the 5/25/200 mg dosage regimen.
For the simulation of the 5/25/200 mg dosage regimen, subjects received 5 mg on the first day of Week 1, then 25 mg on the first day of Week 2, then 200 mg on the first day of Week 3 and once weekly thereafter for a total of 12 doses, then 200 mg every 2 weeks thereafter for a total of 5 doses, then 200 mg every 4 weeks thereafter.
Cavg = average concentration over the dosing interval; Cmax = maximum concentration; Ctrough = trough concentration; CV = coefficient of variation; geo mean = geometric mean; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Reviewer's analysis of Applicant's final population PK model

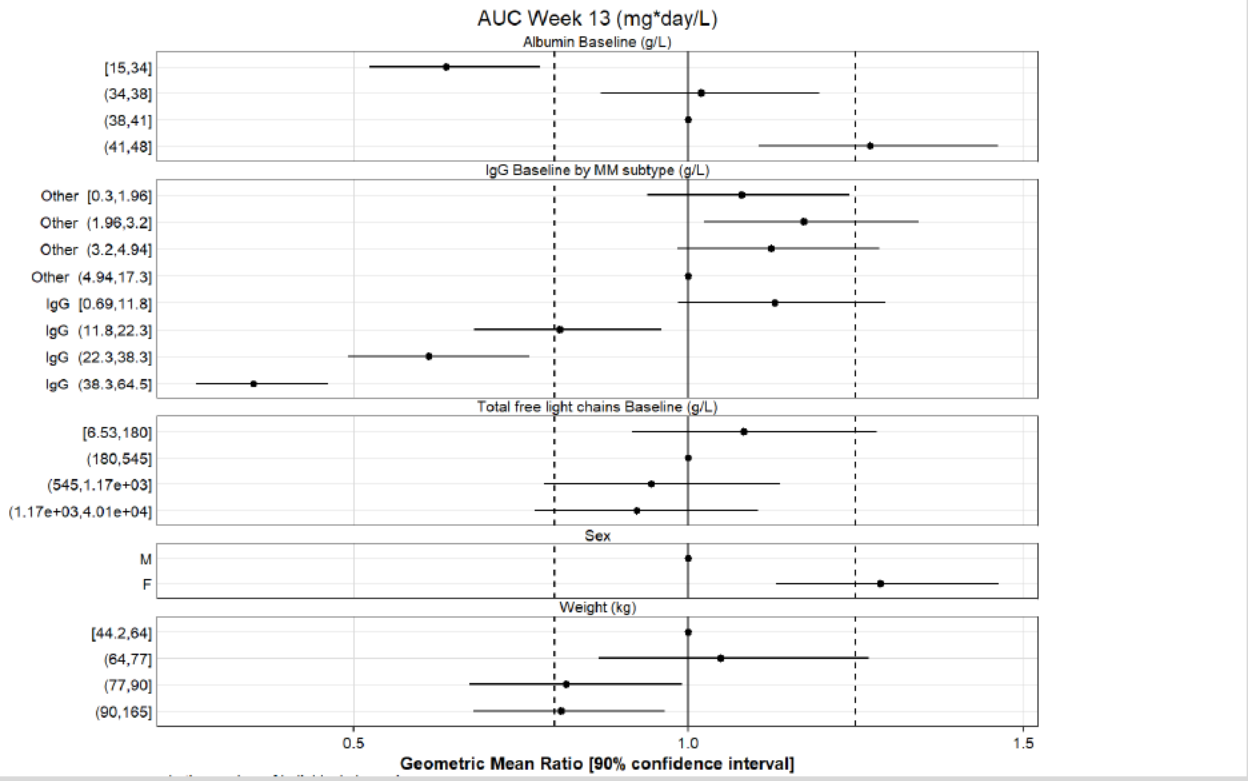
As described in **Table 61**, the final popPK model identified the following statistically significant associations between patient covariates and PK parameters of total linvoseltamab:

- Lower serum albumin concentration (time-varying) is associated with faster linear clearance.
- Higher IgG concentration (time-varying) is associated with faster linear clearance.
- Higher baseline body weight is associated with faster linear clearance.
- Higher total free light chain concentration (time-varying) is associated with faster maximum velocity (Vmax) of concentration-dependent clearance.
- Higher baseline body weight is associated with faster intercompartmental clearance (Q).
- Female sex (versus male sex) is associated with 14.8% lower central volume of distribution.

Figure 13 displays the predicted differences in total linvoseltamab Week 13 AUC following the proposed 5/25/200 mg dosage regimen according to sex and baseline quartiles of albumin, IgG, total free light chain, and body weight. The predicted differences in Week 13 Cmax and Ctrough did not differ significantly from those displayed for AUC in **Figure 13**. Lower total linvoseltamab exposure was associated with lower baseline albumin and higher IgG concentration, which may be associated with worse disease severity. Baseline total free light chain concentration did not yield a statistically significant difference in total linvoseltamab exposure.

Compared to patients with average body weight at baseline (55 to <100 kg), the geometric mean Week 13 AUC is expected to be 17% higher in patients weighing <55 kg and 20% lower in patients weighing 100 kg and above, as summarized in **Table 67**. Body weight (range = 45 to 171.4 kg) had no statistically significant associations with ORR, CR rate, OS, or PFS (refer to Section 19.4.2.3). The difference in exposure according to body weight was not associated with any difference in the risk of investigated safety events (refer to Section 19.4.2.6). In Study 1826 patients who received 5/25/50 mg or 5/25/200 mg, no clear differences in CRS profile were observed across body weight quartiles. The difference in exposure across body weight is not expected to result in a clinically relevant difference in efficacy or safety outcomes. No alternative dosage is recommended according to body weight in adult patients with RRMM.

Figure 13: Geometric Mean Ratio of Week 13 Total Linvoseltamab AUC Across Patient Covariates Following Proposed 5/25/200 mg Dosage Regimen



Note: continuous covariates are displayed as quartiles. Simulated exposure displayed for 282 patients with RRMM in Study R5458-ONC-1826 with population PK data.
AUC = area under the concentration-versus-time curve; F=female; M=male; RRMM = relapsed or refractory multiple myeloma.
Source: Reviewer's analysis of Applicant's response to 8Feb2024 IR and Applicant's linvo_exposure_sims-run5200_rmd.txt (seqn0008)

Table 67: FDA - Simulated Geometric Mean Week 13 Total Linvoseltamab Exposure by Body Weight Subgroup in Study R5458-ONC-1826 Following Proposed 5/25/200 mg Dosage Regimen

Week 13 Exposure Metric	44.2 to <55 kg (n=25)	55 to <100 kg (n=227)	100 kg and above (n=30)	% Geometric Mean Difference	
				44.2 to <55 kg versus 55 to <100 kg	100 kg and above versus 55 to <100 kg
Ctrough (mg/L)	97.4	83.5	66.4	16.6% higher	20.5% lower
Cmax (mg/L)	150	137	145	9.5% higher	5.8% higher
AUC (mg*day/L)	828	710	566	16.6% higher	20.3% lower

AUC = area under the concentration-versus-time curve; Cmax= maximum concentration; Ctrough = trough concentration.
Source: Reviewer's analysis of Applicant's response to 8Feb2024 IR and Applicant's linvo_exposure_sims-run5200_rmd.txt (seqn0008)

The model predicted 28% higher geometric mean Week 13 total linvoseltamab AUC in female patients compared to male patients (**Table 68**). Rates of multiple TEAEs, including dose interruption or delay due to TEAE, infection, CRS, and neutropenia, were ≥10% higher in female patients compared to male patients in the E-R safety dataset (**Table 69**). The FDA's multivariate dose-response analysis of efficacy also identified a potential association between female sex and better OS and PFS after accounting for other patient covariates (refer to Section 19.4.2.3 for detailed analysis). The somewhat higher Week 13 total linvoseltamab AUC in female patients may contribute to the observed differences in safety and efficacy by sex, but sex may also be associated with differences in other patient and disease factors and/or RRMM outcomes. Based on current clinical data, uncertainty regarding covariate impacts on free drug concentrations, and PK variability in the general patient population, the proposed 5/25/200 mg dosage regimen is acceptable in patients of all sexes with RRMM.

Table 68: FDA - Simulated Geometric Mean Week 13 Total Linvoseltamab Exposure in Study R5458-ONC-1826 Female and Male Subjects Following Proposed 5/25/200 mg Dosage Regimen

	Statistic	Female (n=131)	Male (n=151)	% Geometric Mean Difference Female versus Male
Baseline Body Weight	Mean (CV%)	70.5 (23.2 %)	85.4 (21.9 %)	n/a
Week 13 Ctrough (mg/L)	Geo mean (CV%)	94.3 (53.9 %)	73 (63.9 %)	29% higher
Week 13 Cmax (mg/L)	Geo mean (CV%)	151 (39.5 %)	128 (72.7 %)	18% higher
Week 13 AUC (mg*day/L)	Geo mean (CV%)	798 (46.2 %)	625 (57.6 %)	28% higher

AUC = area under the concentration-versus-time curve; Cmax= maximum concentration; Ctrough = trough concentration; CV = coefficient of variation; geo mean = geometric mean; n/a = not applicable.
Source: Reviewer's analysis of Applicant's response to 8Feb2024 IR and Applicant's linvo_exposure_sims-run5200_rmd.txt (seqn0008)

Table 69: FDA - Incidence of TEAEs by Dose and Sex in Study R5458-ONC-1826 Phase 2

	5 mg/25 mg/50 mg		5 mg/25 mg/200 mg	
Treatment Emergent Adverse Event (TEAE)	**Female (n=48)**	**Male (n=56)**	**Female (n=44)**	**Male (n=61)**
Dose Adjustment Due to TEAE	12/48 (25%)	7/56 (12.5%)	5/44 (11.4%)	8/61 (13.1%)
Dose Delay, Interruption, Adjustment or Drug Withdrawn Due to TEAE	28/48 (58.3%)	26/56 (46.4%)	32/44 (72.7%)	37/61 (60.7%)
Dose Interruption or Delay Due to TEAE	26/48 (54.2%)	22/56 (39.3%)	31/44 (70.5%)	32/61 (52.5%)
Drug Withdrawn Due to TEAE	2/48 (4.2%)	7/56 (12.5%)	3/44 (6.8%)	9/61 (14.8%)
Serious Treatment Emergent AE	39/48 (81.2%)	37/56 (66.1%)	27/44 (61.4%)	47/61 (77%)
Anemia	35/48 (72.9%)	40/56 (71.4%)	35/44 (79.5%)	39/61 (63.9%)
Anemia (Grade ≥3)	21/48 (43.8%)	26/56 (46.4%)	16/44 (36.4%)	25/61 (41%)
Cytokine Release Syndrome	37/48 (77.1%)	20/56 (35.7%)	24/44 (54.5%)	25/61 (41%)
Cytokine Release Syndrome (Grade ≥2)	13/48 (27.1%)	3/56 (5.4%)	4/44 (9.1%)	8/61 (13.1%)
Cytokine Release Syndrome (Grade ≥3)	2/48 (4.2%)	0	1/44 (2.3%)	0
Infections	32/48 (66.7%)	31/56 (55.4%)	33/44 (75%)	38/61 (62.3%)

	5 mg/25 mg/50 mg		5 mg/25 mg/200 mg	
Treatment Emergent Adverse Event (TEAE)	**Female (n=48)**	**Male (n=56)**	**Female (n=44)**	**Male (n=61)**
Infections (Grade ≥2)	32/48 (66.7%)	30/56 (53.6%)	31/44 (70.5%)	35/61 (57.4%)
Serious Infections	17/48 (35.4%)	19/56 (33.9%)	13/44 (29.5%)	25/61 (41%)
Infusion Related Reaction	3/48 (6.2%)	7/56 (12.5%)	6/44 (13.6%)	9/61 (14.8%)
Infusion Related Reaction (Grade ≥2)	2/48 (4.2%)	6/56 (10.7%)	2/44 (4.5%)	9/61 (14.8%)
Leukopenia	37/48 (77.1%)	38/56 (67.9%)	30/44 (68.2%)	35/61 (57.4%)
Leukopenia (Grade ≥3)	19/48 (39.6%)	16/56 (28.6%)	17/44 (38.6%)	14/61 (23%)
Lymphopenia	45/48 (93.8%)	53/56 (94.6%)	39/44 (88.6%)	52/61 (85.2%)
Lymphopenia (Grade ≥3)	45/48 (93.8%)	52/56 (92.9%)	36/44 (81.8%)	49/61 (80.3%)
Neurotoxicity (Method 2)	36/48 (75%)	24/56 (42.9%)	22/44 (50%)	27/61 (44.3%)
Neurotoxicity (Grade ≥3, Method 2)	6/48 (12.5%)	3/56 (5.4%)	3/44 (6.8%)	6/61 (9.8%)
Neutropenia	29/48 (60.4%)	26/56 (46.4%)	31/44 (70.5%)	27/61 (44.3%)
Neutropenia (Grade ≥3)	19/48 (39.6%)	22/56 (39.3%)	27/44 (61.4%)	15/61 (24.6%)
Opportunistic Infections	2/48 (4.2%)	3/56 (5.4%)	5/44 (11.4%)	3/61 (4.9%)
Opportunistic Infections (Grade ≥3)	2/48 (4.2%)	2/56 (3.6%)	4/44 (9.1%)	3/61 (4.9%)
Pneumonia	10/48 (20.8%)	10/56 (17.9%)	8/44 (18.2%)	19/61 (31.1%)
Pneumonia (Grade ≥3)	9/48 (18.8%)	8/56 (14.3%)	5/44 (11.4%)	18/61 (29.5%)
Thrombocytopenia	27/48 (56.2%)	34/56 (60.7%)	28/44 (63.6%)	36/61 (59%)
Thrombocytopenia (Grade ≥3)	7/48 (14.6%)	15/56 (26.8%)	8/44 (18.2%)	12/61 (19.7%)

Anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia event data derived from laboratory dataset. All other TEAEs derived from adverse event dataset.
Source: Reviewer's analysis of Applicant's exposure-response safety dataset

Overall, no clinically meaningful differences in the pharmacokinetics of linvoseltamab were observed based on age (37 to 91 years), weight (44 to 172 kg), sex, race (White [n=205], Asian [n=18], or Black [n=44]), ethnicity (Hispanic or Latino [n=22], not Hispanic or Latino [n=251]), mild to moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min by Cockcroft-Gault equation), or mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin >1 to ≤1.5 times ULN, with any AST).

The effect of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease (CLcr less than 15 mL/min) and moderate to severe hepatic impairment (total bilirubin >1.5 times ULN, with any AST) and severe (total bilirubin >3 to 10 times ULN, any AST) hepatic impairment on the PK of linvoseltamab is unknown.

Free versus Total Linvoseltamab Concentrations

The popPK model-predicted exposure represents total drug concentration in serum (i.e., the sum of free drug and drug bound to sBCMA). However, the activity of linvoseltamab is expected to be driven by free drug concentration in serum. The FDA identified relative uncertainties with regard to potential differences between free and total linvoseltamab concentrations, especially during the first three months of treatment. It is unclear how changes in total linvoseltamab concentration according to patient covariates compare to

free linvoseltamab concentration. Differences in free drug concentration according to patient covariates have not been characterized.

For T cell engagers (TCE) with 1:1 platform (i.e., one binding arm to T cell target [e.g., CD3], one binding arm to tumor target [e.g., membrane BCMA]), engagement between the tumor target binding arm and soluble target (e.g., sBCMA) may significantly prevent TCE from engaging to tumor target (e.g., membrane BCMA) and subsequently impact pharmacological activities (e.g., T cell activation, tumor cell killing, cytokine release).

Using the following Equations 1, 2 and 3, the Applicant estimated free drug concentrations from observed total drug concentration, observed total sBCMA concentration, and the dissociation constant (Kd = 0.437 nM; *source: Nonclinical Study Report R5458-PH-18025-SR-01V1, seqn0001*) for each sample with both a total drug and total sBCMA measurement. Out of 6995 total drug concentration PK samples in the popPK dataset, 2482 (35%) samples also had a total sBCMA measurement. The FDA conducted an independent analysis and confirmed the Applicant's estimation with a quasi-equilibrium target-mediated drug disposition (TMDD) model (Equation 4).

$$L_T = L + LB \quad (1)$$

$$B_T = B + LB \quad (2)$$

$$LB = \frac{1}{2} \cdot (L_T + B_T + K_d) - \sqrt{(L_T + B_T + K_d)^2 - 4 \cdot L_T \cdot B_T} \quad (3)$$

$$L = \frac{1}{2} \cdot (L_T - B_T - K_d) - \sqrt{(L_T - B_T - K_d)^2 + 4 \cdot L_T \cdot K_d} \quad (4)$$

L_T: Total linvoseltamab concentration; L: Free linvoseltamab concentration; B_T: Total sBCMA concentration; B: Free sBCMA concentration; LB: Linvoseltamab-sBCMA complex concentration; Kd: Dissociation constant. Source: Equations 1-3: Applicant's response to 1March2023 information request #5 (seqn0012). Equation 4: Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharm Res. 2005 Oct;22(10):1589-96. PMID: 16180117.

Following individual doses of 1 mg to 800 mg QW, free drug concentrations were estimated to be generally lower than total drug concentrations. As shown in **Figure 14,** the ratio of free: total drug concentration profiles following 5/25/50 mg and 5/25/200 mg dosages were less than 0.1 during the first 4 weeks of treatment, indicating a significant effect of sBCMA on free linvoseltamab concentration. The ratio of free: total drug concentration increases over time as sBCMA levels decline. Free drug concentration is estimated to be lower than total drug concentration approximately twenty months after the first 50 mg dose and up to approximately four months after the first 200 mg dose in patients who received the 5/25/50 mg and 5/25/200 mg dosages.

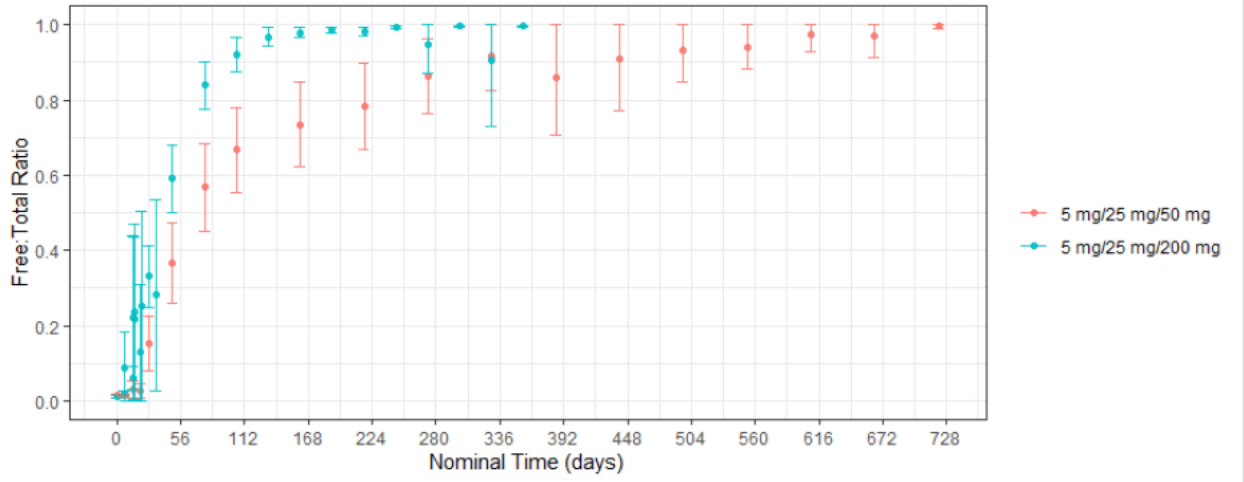
A higher free: total drug concentration ratio closer to 1 indicates low sBCMA levels, which may reflect a lower disease burden since sBCMA is shed from target cells including multiple

myeloma cells. Therefore, the exploratory free:total drug concentration analysis generally suggests that 200 mg QW may yield better efficacy than 50 mg QW. The discrepancies between free and total linvoseltamab concentration and the differences in free:total linvoseltamab ratio over time mean that total linvoseltamab concentrations may not accurately reflect linvoseltamab activity, especially in the first few months of treatment and with lower weekly doses.

On the other hand, CRS profile data following the 5/25/50 mg and 5/25/200 mg dosages (**Figure 7**) did not show any clear differences in CRS profile according to baseline sBCMA levels. Patients at lower baseline sBCMA quartiles did not show substantially different CRS incidence or severity compared to patients at higher sBCMA quartiles during the step-up dosing and initial full dose treatments (i.e., first 4 weeks of treatment), suggesting that at the proposed dose level, the difference in free and total drug concentrations and the impact of sBCMA on cytokine release may not be clinically meaningful.

The current assessment of free:total drug concentration may not be adequate, and a more comprehensive assessment (e.g., full TMDD modeling or quantitative systems pharmacology modeling) may provide better characterization of free linvoseltamab exposure during the treatment. The E-R efficacy and safety analyses in Section 19.4.2.2 and 19.4.2.5 are therefore exploratory because they utilize total linvoseltamab exposure instead of free linvoseltamab exposure.

Figure 14: FDA - Mean Ratio of Free:Total Drug over Time Following 5/25/50 mg and 5/25/200 mg Dosage Regimens



Data shown as mean (95% confidence interval) for all total linvoseltamab concentration samples up to 365 days after first dose with a corresponding total sBCMA measurement in 220 patients who received full doses of 50 mg or 200 mg once weekly in Study 1826. Free linvoseltamab concentrations were estimated using dissociation constant of 0.437 nM.
Source: Reviewer's analysis of Applicant's response to 1March2023 information request #5 (seqn0012)

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The E-R efficacy analysis was limited by the use of total drug concentrations rather than free drug concentrations and potential confounding with selected exposure metrics. Additionally, the E-R efficacy analysis did not accurately characterize ORR or OS in patients with RRMM.

FDA conducted multivariate dose-response analysis to evaluate efficacy, and the dose-response analysis generally supports the proposed full dosage of 200 mg QW in patients with RRMM. Higher full dose was associated with better ORR, CR rate, and PFS after accounting for other patient and disease characteristics in Study R5458-ONC-1826 patients.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Characterize the E-R relationship in RRMM patients treated with REGN5458 in Study R5458-ONC-1826 for selected efficacy variables.
Study Included		Study 1826 Phase 1 and Phase 2
Endpoint		ORR, PFS, OS, DOR
No. of Patients (total, and with individual PK)		No. of patients: 282 total patients, and 281 with individual PK
Population Characteristics	General	- Age median (range): 66 (37-91) years - Weight median (range):77.1 (44.2-171) kg - 151 (53.5%) male; 131 (46.5%) female - 205 (72.7%) White; 44 (15.6%) Black or African American; 18 (6.4%) Asian; 7 (2.5%) Other; 8 (2.8%) Not Reported
	Pediatrics (if any)	Not Applicable
Dose(s) Included		1mg/3mg, 2mg/6mg, 4mg/12mg, 8mg/24mg, 16mg/48mg, 32mg/96mg, 5mg/25mg/96mg, 5mg/25mg/50mg, 5mg/25mg/200mg, 5mg/25mg/400mg, 5mg/25mg/800mg
Exposure Metrics Explored (range)		Individual popPK model predicted post-hoc exposure metrics evaluated are C_{max}, C_{min}, and C_{avg} at weeks 1, 2, 3 and 14 and average weekly exposures (C_{max}, C_{min}, C_{avg}) up to final dose week
Covariates Evaluated		Sex, ethnicity, race, Hepatitis B Virus antibody, hepatic function category, renal function category, age, body weight, ALT, urine M Protein, total bilirubin, albumin, C-reactive protein, calcium, LDH, free kappa light chain, free lambda light chain, light chain involvement, erythrocytes, platelets, lymphocytes, basophils, monocytes, neutrophils, IL8, IFN-gamma, TNF, soluble BCMA, CD69 expression (CD4 and CD8), eosinophils, Ig, ECOG, plasmacytoma. Belantamab category, refractory to the last line of therapy, prior lines of therapy

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Logistic regression analysis	The E-R efficacy analysis was limited by the use of total drug concentrations rather than free drug concentrations and potential confounding with selected exposure metrics. The E-R efficacy analysis is considered exploratory and E-R efficacy conclusions remain uncertain. The Applicant's E-R efficacy analysis does not accurately characterize ORR or OS. The Applicant's models predicted higher odds ratios (ORs) for objective response and hazard ratio for OS compared to the observed clinical results. The Applicant's predicted hazard ratio was not significantly different than the observed hazard ratio for PFS in the 5/25/200 mg cohort compared to the 5/25/50 mg cohort. According to the Applicant's analysis, PFS improved with higher CAVGWK14, higher baseline red blood cell count, and older age.
Model Parameter Estimates	Table 70 for ORR	
Model Evaluation	For all sub-cuts of the analysis data (Phase 1 only, Phase 2 only, Phase 2 + Phase 1 200 mg cohort, Phase 1 + Phase 2) the OR for a 200 mg dose of linvoseltamab is predicted to be 3.67 to 5.06 times higher than in patients receiving a 50 mg dose of linvoseltamab when response is grouped by sCR+CR+VGPR+PR, and 1.57 to 3.58 times higher when response is grouped by sCR+CR For the TTE efficacy analyses across the 3 data sub-cuts (phase 2 only, phase 2 + phase 1 200 mg cohort, and phase 1 + phase 2), the data showed a range of approximately 43.7% to 49.5% reduction in risk to progression or death based on the multivariate COXPH analysis of the PFS endpoint when comparing the 200 mg to the 50 mg cohorts (across the CAVGAVG and CAVGWK14 efficacy exposure metrics), and a range of approximately 26.2% to 33.8% lower risk to die at the 200 mg relative to the 50 mg cohort when assessing the OS endpoint. DOR was not associated with any exposure metric however may be related to the health status of the patients in terms of a baseline RBC associated with lower hazard).	
Covariates and Clinical Relevance	For ORR, besides linvoseltamab exposure, other covariates were baseline levels of monocytes, soluble BCMA, and erythrocytes, and whether the patients had plasmacytoma. For PFS, covariates relating to increased disease burden and tissue destruction (plasmacytoma, baseline sBCMA, serum M protein baseline and baseline LDH) were associated with significantly higher hazard ratios, while increased baseline RBC and drug concentration (contrasting the 200 mg vs 50 mg cohorts) showed significantly lower hazard ratios.	

	OS and ORR showed a strong overlap in significant covariates, suggesting that patients at the higher dose (200 mg) or patients which had lower tumor/disease burden and higher red blood cell concentrations (as a marker of overall health), were more likely to respond to therapy and had longer PFS and OS.	
Simulation for Specific Population	N/A	
Visualization of E-R relationships		
Overall Clinical Relevance for E-R	In the pooled phase 1 and phase 2 data, increasing linvoseltamab exposure was significantly associated with an increased ORR, with the proposed registrational dosing regimen (200 mg) showing a 3.67-fold or 1.97-fold higher ORR compared to the 50 mg regimen, when response is grouped by ORR or ≥CR, respectively. Patients receiving a 200 mg dose compared to those receiving a 50 mg dose are predicted to have an approximate mean 49.5% decrease in risk of progression or death at any given point in time based on the PFS endpoint, and similarly on average an approximate mean of 33.8% decrease in OS at any given point in time when assessing the phase 2 data only. Additionally, there was a substantial overlap in the significant covariates found for PFS, OS, and ORR. DOR was not associated with any exposure metric and may be related to the health status of the patients in terms of a lower baseline RBC associated with a lower hazard.	The Applicant's analysis is limited and considered exploratory for E-R efficacy. Therefore, FDA evaluated dose-response associations with efficacy endpoints to assess the proposed dosage's acceptability. After accounting for other patient and disease characteristics, higher full dose amount was associated with better ORR, CR rate, and PFS. See Section 19.4.2.3 for the full dose-response analysis. Although Applicant's E-R efficacy analysis does not adequately characterize ORR or OS and is considered exploratory, note that the Applicant's description in this summary table misinterprets the odds ratio. The Applicant's E-R model predicts that the odds of overall response are 3.67 times higher in patients who receive the proposed 200 mg QW full dose compared to patients who receive 50 mg QW, and not that 200 mg QW has "3.67-fold or 1.97-fold higher ORR compared to the 50 mg regimen" as stated by the Applicant.

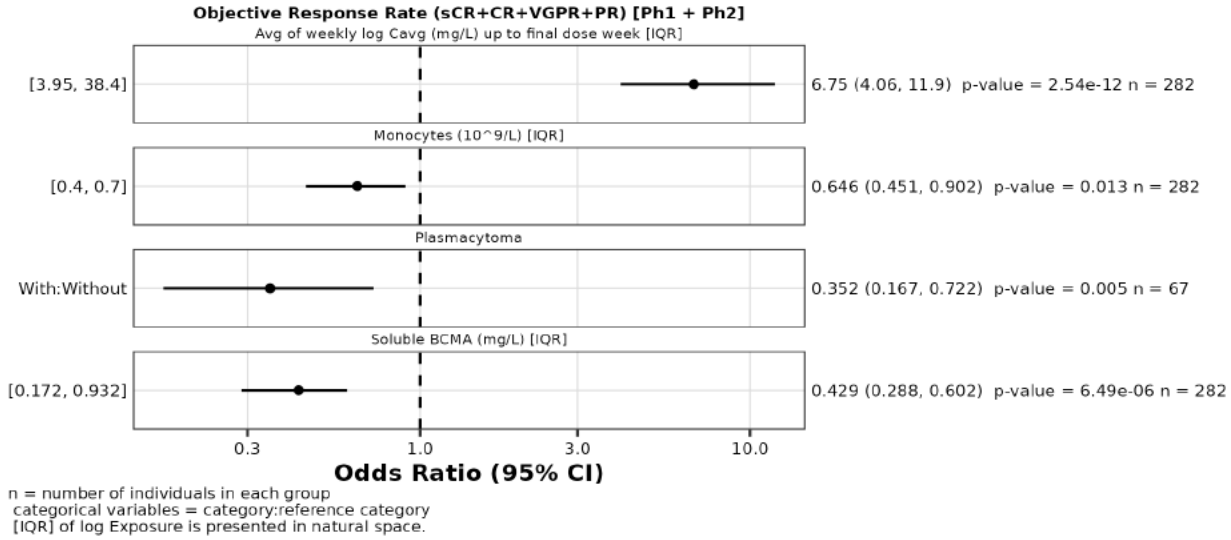
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	N/A	Linvoseltamab exposure-response relationships have not been fully characterized.

Table 70: Applicant - Predicted Response Rates and Odds Ratios 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
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_{avg} (mg/L) up to final dose week	6.28	0.393 (0.161, 0.686)	.
Ph2	209	200 mg	Avg of weekly log C_{avg} (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_{avg} (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_{avg} (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_{avg} (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_{avg} (mg/L) up to final dose week	29.5	0.717 (0.539, 0.846)	3.67 (2.59, 5.39)

Log exposures were transformed to natural space; N = number of patients
Source: Module 5.3.3.5 R5458 E-R Report Table 1

Figure 15: Applicant - Forest Plot of the Final Multivariate Model for Investigator Reported ORR (sCR+CR+VGPR+PR) in Phase 1 + Phase 2 vs Predictors



Source: Module 5.3.3.5 R5458 E-R Report, Figure 3

The FDA's Assessment:

The Applicant's E-R efficacy analysis is considered exploratory and inadequate to support E-R conclusions due to two significant issues which limit confidence in the E-R analysis results:

1. The Applicant's analysis investigated total linvoseltamab exposure rather than free linvoseltamab exposure, which limits the ability to identify true E-R efficacy associations. As described in Section 19.4.1.2, Study 1826 patients potentially may have relatively large differences in total linvoseltamab concentrations versus free linvoseltamab concentrations, especially earlier in treatment and with lower weekly doses. Linvoseltamab is a T cell engaging bispecific antibody and therefore its activity is more closely associated with free rather than total drug concentration, and so the total drug concentration may not adequately reflect efficacy. E-R efficacy associations have not been characterized with free linvoseltamab exposure.

2. The Applicant's analysis investigated time-averaged exposure metrics which may introduce confounding from treatment duration, dose modifications, tolerability, and/or patient response and thereby bias the results towards a positive E-R association. The average minimum concentration up to last dose or time of event (CMINAVG), average concentration up to last dose or time of event (CAVGAVG), and average concentration up to last dose or Week 14 (CAVGWK14) tend to be higher in patients with better response and longer durations of treatment because exposure following each dose increases over time up to Week 14, as illustrated in

Figure 12 in Section 19.4.1.2.

Due to the limitations of the E-R efficacy analysis, clinical evidence and dose-response analysis will be used to assess the appropriateness of the proposed 5/25/200 mg QW dosage regimen. Refer to Section 19.4.2.3 for the dose-response analyses of Study 1826 efficacy.

In addition to the limitations discussed above, the Applicant's E-R efficacy analysis does not accurately characterize ORR or OS in patients with RRMM.

The Applicant's ORR model (**Table 70** and **Figure 15** above) predicts that the odds of objective response are 4.49 (95% CI = 2.66 to 8.08) times higher in the Phase 2 5/25/200 mg cohort compared to the Phase 2 5/25/50 mg cohort. However, the Applicant's predicted odds ratio of 4.49 is higher than the observed odds ratio of 2.26 in Phase 2 patients (*source: reviewer's calculation of odds ratio based on Applicant's E-R report Table 17*). The model over-estimates the difference in ORR between the 5/25/50 mg QW and 5/25/200 mg QW cohorts, which may be related to confounding between the investigated exposure metrics (i.e., CMINAVG, CAVGAVG, and CAVGWK14) and treatment duration, dose modifications, tolerability, and/or patient response.

In regards to OS, the Applicant's final OS model (see summary table above) predicted that 0.662 times (95% CI = 0.441 to 0.993 times) as many patients in the Phase 2 5/25/200 mg cohort would not survive compared to the Phase 2 5/25/50 mg cohort based on median CAVGAVG, baseline lactate dehydrogenase, baseline soluble BCMA, baseline serum M-protein, and plasmacytoma status at baseline. However, the observed hazard ratio of 1.109 (95% CI = 0.637 to 1.932; *source: reviewer's calculation in Phase 2 patients in E-R dataset*) does not show evidence of a survival benefit in the Phase 2 5/25/200 mg cohort compared to the Phase 2 5/25/50 mg cohort.

There was no significant difference in the model-predicted PFS hazard ratio (see summary table above) compared to observed PFS in the Study 1826 Phase 2 dose cohorts. The Applicant's final PFS model predicted that 0.505 times (95% CI = 0.349 to 0.73 times) as many patients in the Phase 2 5/25/200 mg cohort would experience progression or death at any given time compared to the Phase 2 5/25/50 mg cohort based on median CAVGWK14, baseline red blood cell count, and age. The observed hazard ratio for PFS in the 5/25/200 mg QW cohort compared to the 5/25/50 mg cohort was 0.476 (95% CI = 0.299 to 0.757; *source: reviewer's calculation in Phase 2 patients in E-R dataset*).

The FDA notes that time-to-event endpoints, such as PFS and OS, are challenging to interpret in the context of a single-arm trial. Further, randomization was not used to determine enrollment to the two dose expansion cohorts. Thus, the interpretability of comparisons of these time-to-event endpoints between dose expansion cohorts and the phase 2 portion of the trial, as well as comparisons of efficacy and safety between dose levels evaluated in the dose expansion cohorts, is limited.

19.4.2.3. Dose-Response Analysis of Efficacy

The FDA's Assessment

Due to the limitations of the E-R efficacy analysis discussed in Section 19.4.2.2, FDA conducted exploratory multivariate dose-response analysis to evaluate efficacy of the proposed dosage. After accounting for other covariates, higher full dose amount was associated with a statistically significant improvement in ORR, CR rate, and PFS. The dose-response analysis generally supports the proposed 200 mg QW full dosage.

Potential associations between dose and efficacy were investigated using data from patients in Study 1826 who received at least 1 full dose. Independently-assessed ORR, CR, and PFS data were available in 12 patients who received 5/25/200 mg in Phase 1, 105 patients who received 5/25/200 mg in Phase 2, and 104 patients who received 5/25/50 mg in Phase 2 (n=221 total patients). OS data were available in 71 patients in Phase 1, 95 patients in the Phase 2 5/25/50 mg cohort, and 99 patients in the Phase 2 5/25/200 mg cohort (n=265 total patients with full dose ranging from 3 mg to 800 mg QW). Full dose was investigated as a continuous covariate and a categorical covariate. Multivariate logistic regression was utilized for ORR and CR rate while multivariate Cox proportional hazards regression was utilized for PFS and OS.

One notable limitation of the dose-response analysis is that Study 1826 Phase 2 does not provide a truly randomized comparison between the 5/25/50 mg and 5/25/200 mg dosages. The 5/25/50 mg cohort had longer duration of treatment and follow-up compared to the 5/25/200 mg cohort due to the staggered enrollment periods in Phase 2. Additionally, patients in the 5/25/50 mg cohort had a greater median number of prior lines of therapy compared to the 5/25/200 mg cohort (6 prior lines versus 5 prior lines. The proportion of patients with 5 or more prior lines of therapy was 78/104 (75%) patients in the Phase 2 5/25/50 mg cohort versus 57/104 (55%) patients in the Phase 2 5/25/200 mg cohort. There was a slightly higher proportion of female subjects in the 5/25/50 mg cohort compared to the 5/25/200 mg cohort (48/104 [46.2%] versus 43/104 [41.3%]).

After accounting for other covariates, multivariate analysis suggested that higher full dose was associated with a statistically significant improvement in ORR, CR rate, and PFS in patients who received at least one full dose of 50 mg QW or 200 mg QW in Study 1826. No association was identified between OS and full dose amount in patients who received at least one full dose ranging from 3 mg to 800 mg.

Better independently-assessed ORR was associated with higher full dose level, 5 or more prior lines of therapy (versus 2-4 prior lines), older age, lower baseline sBCMA, higher baseline lymphocyte count, and use of IVIG in Study 1826 patients who received 5/25/50 mg QW or 5/25/200 mg QW. The multivariate ORR model is described in **Table 71.**

Better independently-assessed CR rate was associated with higher full dose level, use of IVIG, and absence of plasmacytoma at baseline in Study 1826 patients who received

5/25/50 mg QW or 5/25/200 mg QW. The multivariate model for CR rate is summarized in **Table 72**.

Better independently-assessed PFS was associated with higher full dose level, more lines of prior therapy, lower baseline sBCMA, female sex (versus male), standard cytogenetic risk (versus high cytogenetic risk), use of IVIG, and higher baseline lymphocyte count in Study 1826 patients who received full doses ranging from 3 mg to 800 mg. The multivariate model for PFS is summarized in **Table 73**.

Table 71: FDA - Final Dose-Response Multivariate Model - Independently-Assessed ORR

Covariate	Odds Ratio	Odds Ratio 95% CI	p-value
Full dose level (mg)	1.006	1.001, 1.011	0.015
5 or more prior lines of therapy (versus 2 to 4 prior lines of therapy)	2.984	1.382, 6.741	0.007
Baseline age (years)	1.044	1.009, 1.083	0.016
Baseline soluble BCMA (mg/L)	0.364	0.215, 0.579	<0.001
Baseline lymphocyte count (10^9/L)	1.891	1.113, 3.421	0.026
Use of IVIG (versus no recorded use of IVIG)	9.396	4.382, 21.760	<0.001

CI = confidence interval. Higher odds ratio indicates higher odds of achieving response.
Source: Reviewer's analysis

Table 72: FDA - Final Dose-Response Multivariate Model - Independently-Assessed CR

Covariate	Odds Ratio	Odds Ratio 95% CI	p-value
Full dose level (mg)	1.007	1.003, 1.011	0.002
Use of IVIG (versus no recorded use of IVIG)	3.847	2.047, 7.400	<0.001
Plasmacytoma at baseline (versus no plasmacytoma)	0.279	0.104, 0.660	0.006

CI = confidence interval. Higher odds ratio indicates higher odds of achieving complete response.
Source: Reviewer's analysis

Table 73: FDA - Final Dose-Response Multivariate Model - Independently-Assessed PFS

Covariate	Hazard Ratio	Hazard Ratio 95% CI	p-value
Full dose level (mg)	0.993	0.990, 0.997	<0.001
Number of prior lines of therapy	0.888	0.799, 0.986	0.026
Baseline soluble BCMA (mg/L)	1.373	1.108, 1.701	0.004
Male sex (versus female sex)	2.278	1.358, 3.822	0.002
High cytogenetic risk (versus standard risk)	2.258	1.373, 3.713	0.001
Use of IVIG (versus no recorded use of IVIG)	0.274	0.162, 0.465	<0.001
Baseline lymphocyte count (10^9/L)	0.665	0.456, 0.971	0.03

CI = confidence interval. Higher hazard ratio indicates higher hazard of disease progression or death.
Source: Reviewer's analysis

Full dose amount had no statistically significant associations with OS after accounting for other patient covariates. Better OS was associated with female sex (compared to male),

higher baseline albumin, lower baseline LDH, lower baseline sBCMA, use of IVIG, and higher baseline lymphocyte count in Study 1826 patients who received full doses ranging from 3 mg to 800 mg. The multivariate model for OS is summarized in **Table 74**.

Table 74: FDA - Final Dose-Response Multivariate Model – Overall Survival

Covariate	Hazard Ratio	Hazard Ratio 95% CI	p-value
Male sex (versus female sex)	1.820	1.109, 2.989	0.018
Baseline albumin (g/L)	0.944	0.906, 0.983	0.006
Baseline lactate dehydrogenase (IU/dL)	1.018	1.009, 1.027	<0.001
Baseline soluble BCMA (mg/L)	1.317	1.056, 1.642	0.014
Use of IVIG (versus no recorded use of IVIG)	0.285	0.163, 0.498	<0.001
Baseline lymphocyte count (10^9/L)	0.643	0.424, 0.976	0.038

CI = confidence interval. Higher hazard ratio indicates higher hazard of death.
Source: Reviewer's analysis

Multivariate regression identified a potential association between worse PFS and worse OS with male sex compared to female sex, which is not explained by dose or other patient characteristics. As discussed in Section 19.4.1.2, female patients were predicted to have 28% higher geometric mean Week 13 AUC compared to male patients. However, the difference in exposure by sex does not explain the magnitude of difference in PFS and OS by sex. It is unclear if the efficacy trends according to sex are related to the 28% higher Week 13 total linvoseltamab AUC in female patients compared to male patients, differences in disease pathophysiology by sex, or other factors associated with sex. Overall, the benefit/risk profile supports the proposed 5/25/200 mg dosage in patients with RRMM of all sexes from a clinical pharmacology perspective.

It is unclear why multivariate regression identified a statistical association between more lines of prior therapy and better ORR and PFS. When lines of prior therapy was excluded from the ORR and PFS covariate selection, the resulting models were slightly weaker but still showed statistically significant associations between higher full dose amount and better ORR and PFS.

Overall, the exploratory multivariate dose-response analysis generally supports the proposed full dosage of 200 mg QW in patients with RRMM.

19.4.2.4. ER (safety) Executive Summary

<u>The FDA's Assessment:</u>

The Applicant's E-R safety analysis is inadequate to support any conclusions regarding linvoseltamab E-R safety associations, and the E-R safety analysis is limited by three critical factors:

- shorter duration of treatment and follow up at lower doses compared to doses (e.g.,

5/25/50 mg versus 5/25/200 mg),
- potential confounding from choice of exposure metrics, and
- use of total drug exposure instead of free drug exposure.

Due to the limitations of the E-R analysis, FDA conducted multivariate dose-response analysis to evaluate safety. After accounting for other patient and disease characteristics, full dose amount was not identified as a significant covariate on the risk of any grade IRR, TEAE leading to dose modification, any grade infection, Grade ≥2 infection, Grade ≥3 neurotoxicity, Grade ≥3 neutropenia, Grade ≥3 anemia, Grade ≥3 thrombocytopenia, or Grade ≥3 leukopenia. The dose-response analysis did not identify any concerns with the proposed 200 mg QW full dose in patients with RRMM.

19.4.2.5. ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Characterize the E-R relationship in MM patients treated with REGN5458 in Study R5458-ONC-1826 for safety endpoints of interest.
Study Included		Study 1863 Phase 1 and Phase 2
Population Included		Patients with RRMM who had received any amount of Linvoseltamab
Endpoint		CRS in week 1, infections (any grade, grade ≥2, grade ≥3), anaemia (any grade, grade ≥2, grade ≥3), leukopenia (any grade, grade ≥2, grade ≥3), lymphopenia (any grade, grade ≥2, grade ≥3), neutropenia (any grade, grade ≥2, grade ≥3), thrombocytopenia (any grade, grade ≥2, grade ≥3), opportunistic infections (any grade, grade ≥2, grade ≥3), pneumonia (any grade, grade ≥2, grade ≥3), TEAE (any grade, grade ≥3), any serious TEAE, Neurotoxicity (any grade, grade ≥3), any dose adjustment due to TEAE, drug withdrawal due to TEAE, any dose interruption or delay due to TEAE, and any dose delay, interruption, adjustment or drug withdrawal due to TEAE
No. of Patients (total, and with individual PK)		No. of patients: 282 total patients, and 281 with individual PK
Population Characteristics	General	- Age median (range): 66 (37-91) years - Weight median (range):77.1 (44.2-171) kg - 151 (53.5%) male; 131 (46.5%) female - 205 (72.7%)White; 44 (15.6%) Black or African American; 18 (6.4%) Asian; 7 (2.5%)Other; 8 (2.8%) Not Reported
	Organ impairment	Hepatic (NCI-ODWG Criteria): 27 (9.6%) mild; 255 (90.4%) normal Renal (estimated Glomerular Filtration Rate was calculated using the CKD-EPI equation) n = 78 (27.7%) normal; 116 (41.1%) mild; 76 (27.0%) moderate;11 (3.9%) severe;1(0.4%) failure

	Pediatrics (if any)	-Not Applicable
	Geriatrics (if any)	-Age median (range, 56.4% subj >=65 yr, 21.6% subj >=75 yr) -n (29.4%) male
Dose(s) Included		1mg/3mg, 2mg/6mg, 4mg/12mg, 8mg/24mg, 16mg/48mg, 32mg/96mg, 5mg/25mg/96mg, 5mg/25mg/50mg, 5mg/25mg/200mg, 5mg/25mg/400mg, 5mg/25mg/800mg
Exposure Metrics Explored (range)		Individual model predicted exposure (Cmax, Cavg): exposure at the week of event or final dose week (for censored data); weekly exposures averaged up to and including the week of event, or averaged over the entire treatment (for censored data); exposures at weeks 1, 2, 3, and 14; average of weekly exposures up to final dose week
Covariates Evaluated		Sex, ethnicity, race, hepatitis B Virus antibody, hepatitis C virus antibody, hepatic function category, renal function category, age, body weight, ALT, urine M protein, total bilirubin, albumin, C-reactive protein, calcium, LDH, free kappa light chain, free lambda light chain, free kappa/lambda light chain ratio, erythrocytes, platelets, basophils, lymphocytes, monocytes, neutrophils, IL8, interferon gamma, soluble BCMA, CD69 expression (CD4 and CD8), eosinophils, IgG, ECOG, plasmacytoma. belantamab category (Y/N), refractory to the last line of therapy, light chain involvement, prior lines of therapy

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Constant and Logistic regression model	The Applicant's analysis is limited and considered exploratory for E-R efficacy. FDA evaluated dose-response associations with safety endpoints to assess the proposed dosage's acceptability. The dose-response analysis did not identify any concerns with the proposed 200 mg QW full dose in patients with RRMM. Refer to Section 19.4.2.6 for details regarding the dose-response analysis.
Model Parameter Estimates	Table 75: Summary of most significant exposure metrics and hazard ratios	
Model Evaluation	Table 75: Summary of most significant exposure metrics and hazard ratios	
Covariates and Clinical Relevance	Increases in disease related predictors of baseline sBCMA, baseline LDH, and baseline IgG were found to reduce the time to infection grade ≥3. Increased baseline albumin was also associated with decreased risk of infections of grade ≥3 Previous belantamab treatment and race being Non-White were associated with an increased opportunistic infection risk. Increased baseline platelets and baseline weight were also associate with decreased risk of neutropenia grade ≥3	
Simulation for Specific Population	N/A	
Visualization of E-R relationships	Figure 16:KM plot on probability of not getting an infection of grade ≥3	CRS incidence is impacted by multiple

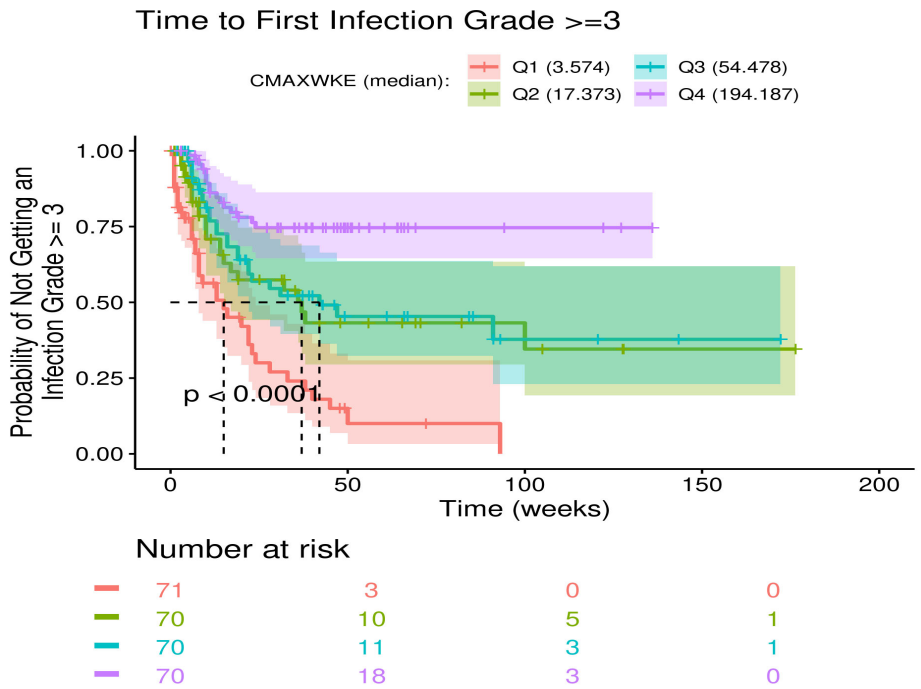
Overall Clinical Relevance for ER	An increase in incidence of CRS in the first week with increase in linvoseltamab exposures (Cmax) at week 1 was observed (doses ranging from 1 to 32 mg) in data from phase 1 and phase 2. E-R relationships for time to first infections grade ≥3 and neutropenia grade ≥3 imply that increasing linvoseltamab exposure decreases the rate and hazard for these safety endpoints while opportunistic infections (of any grade) do not show any trend with increase in exposures.	critical factors such as exposure following an individual dose event, previous step-up doses, time between step-up doses, baseline cytokine concentrations, baseline disease characteristics, and more. It is unclear how Week 1 exposure and Week 1 CRS incidence may be associated with CRS risk with subsequent doses and overall CRS risk. The lower rate of certain safety events with higher time-averaged exposure are most likely explained by the shorter duration of treatment and follow-up in patients with higher dose (i.e., the 5/25/200 mg cohort) as well as confounding between the exposure up to time of event and treatment duration, dose modifications, and tolerability. The current evidence is inadequate to support any conclusions regarding linvoseltamab E-R safety associations.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	N/A	Linvoseltamab exposure-response relationships have not been fully characterized.

Table 75: Applicant - Summary of Most Significant Exposure Metrics and Hazard Ratios Across Safety Endpoints and Data Sub-Cuts Comparing 200 mg to 50 mg Cohorts

Endpoint	Population	N	Exposure Medians (mg/mL) 200 mg : 50 mg cohorts	Exposure Metric	Hazard Ratio (Univariate)	Hazard Ratio (Multivariate)
Infections Any Grade	Phases 1 + 2	282	44.591 : 7.813	CAVGWKE	0.745 (0.653 — 0.849)	0.751 (0.657 — 0.858)
Infections Grade >=2	Phases 1 + 2	282	47.760 : 12.233	CMAXAVG	0.809 (0.709 — 0.923)	0.812 (0.708 — 0.932)
Infections Grade >=3	Phases 1 + 2	282	81.617 : 16.998	CMAXWKE	0.6 (0.479 — 0.75)	0.607 (0.487 — 0.755)
Neutropenia Any Grade	Phases 1 + 2	282	42.152 : 7.772	CAVGWKE	0.597 (0.505 — 0.706)	0.597 (0.505 — 0.706)
Neutropenia Grade >=2	Phases 1 + 2	282	27.050 : 5.167	CAVGAVG	0.686 (0.589 — 0.799)	0.69 (0.593 — 0.804)
Neutropenia Grade >=3	Phases 1 + 2	282	79.132 : 18.036	CMAXWKE	0.632 (0.514 — 0.778)	0.614 (0.499 — 0.755)

The hazard ratio refers to the probability of not having an infection or neutropenia, respectively. Opportunistic infections (at any grade) did not have an exposure associated with it.
Source: Module 5.3.3.5 R5458 E-R Report Table 7

Figure 16: Applicant - Kaplan-Meier Plot Showing Probability of Not Getting an Infection of Grade ≥3 per Quartile of CMAXWKE for Phase 1 + 2 Data



CMAXWKE = C_{max} at the week of the event or until censored (mg/L). Q1, Q2, Q3, Q4 = 0-25%, 25-50%, 50-75% and 75-100% of the data, respectively.
Source: Module 5.3.3.5 R5458 E-R Report Figure 15

The FDA's Assessment:

The Applicant's E-R safety analysis is considered exploratory and inadequate to support E-R conclusions due to three significant issues which limit confidence in the E-R analysis results.

1. The duration of treatment and follow-up were longer in the Phase 2 5/25/50 mg cohort compared to the 5/25/200 mg cohort because enrollment in the 5/25/50 mg cohort began earlier as planned in the study protocol. Refer to Section 8.1.2 for details regarding duration of treatment and follow-up.
2. The Applicant's analysis investigated total linvoseltamab exposure rather than free linvoseltamab exposure, which may limit the ability to identify true E-R safety associations. As described in Section 19.4.1.2, Study 1826 patients potentially may have significant differences in total linvoseltamab concentrations versus free linvoseltamab concentrations, especially earlier in treatment and with lower weekly doses. E-R safety associations have not been characterized with free linvoseltamab exposure.
3. The Applicant's analysis investigated E-R safety associations with time-averaged

exposure metrics which may introduce confounding from treatment duration, dose modifications, tolerability, and/or patient response and thereby bias the E-R results. Patients have lower exposure during the first three months of treatment compared to later weekly doses due to the step-up dosing regimen and accumulation of linvoseltamab exposure, as illustrated in **Figure 12** in Section 19.4.1.2. Patients who tolerated the drug better were more likely to receive a higher number of doses and therefore more likely to experience higher exposure up to time of event or last dose.

The Applicant's analysis found that higher dose (**Table 75**) and higher exposure (**Figure 16**) were associated with lower incidence of infection and neutropenia. These inverse E-R associations are likely explained by the shorter duration of treatment and follow-up in patients with higher dose (i.e., the 5/25/200 mg cohort) as well as confounding between the exposure up to time of event and treatment duration, dose modifications, and tolerability. The current evidence is inadequate to support any conclusions regarding E-R safety associations, or lack thereof, for linvoseltamab.

Clinical evidence and dose-response analysis will be used to determine appropriateness of the proposed 5/25/200 mg QW dosage regimen. Refer to Section 8.2 for the clinical safety analysis. Refer to Section 19.4.2.6 for the dose-response analysis of safety in Study 1826.

19.4.2.6. Dose-Response Analysis of Safety

The FDA's Assessment:

Due to the limitations of the E-R safety analysis discussed in Section 19.4.2.5, FDA conducted exploratory dose-response analysis to evaluate safety of the proposed 5/25/200 mg QW dosage. The dose-response analysis did not identify any concerns with the proposed 200 mg QW full dose in patients with RRMM.

Potential associations between dose and safety events were investigated using data from 265 patients in Study 1826 who received at least one full dose ranging from 3 mg to 800 mg QW, which included 71 patients in Phase 1, 95 patients in the Phase 2 5/25/50 mg cohort, and 99 patients in the Phase 2 5/25/200 mg cohort. Full dose was investigated as a continuous covariate and a categorical covariate. Multivariate Cox proportional hazards regression was utilized to evaluate the time to first safety event and account for differences in treatment follow-up.

After accounting for other patient and disease characteristics, full dose amount was not identified as a statistically significant covariate on the risk of any grade IRR, TEAE leading to dose modification (i.e., any dose delay, interruption, adjustment, or drug withdrawal), any grade infection, Grade ≥2 infection, Grade ≥3 neurotoxicity (method 2), Grade ≥3 neutropenia (laboratory analysis), Grade ≥3 anemia (laboratory analysis), Grade ≥3 thrombocytopenia (laboratory analysis), or Grade ≥3 leukopenia (laboratory analysis).

As described in Section 19.4.1.2, lower body weight and female sex were associated with higher total linvoseltamab exposure. There was a statistically significant association between higher body weight and lower risk of Grade ≥3 anemia as well as Grade ≥3 leukopenia, as summarized in the final multivariate models in **Table 76** and **Table 77**, respectively. Because full dose amount was not included in the final Grade ≥3 anemia or Grade ≥3 leukopenia models, the association between risk and body weight is likely related to factors other than the difference in exposure due to body weight. After accounting for other significant covariates, sex did not appear to be associated with increased risk of Grade ≥3 anemia or Grade ≥3 leukopenia.

Table 76: FDA - Cox Proportional Hazards Model of Grade ≥3 Anemia from Multivariate Dose-Response Analysis

	Hazard Ratio	95% CI	p-value
Baseline Body Weight (kg)	0.987	0.976, 0.998	0.026
Baseline Albumin (g/L)	0.943	0.910, 0.977	0.001
Baseline LDH (IU/dL)	1.007	1.002, 1.012	0.011
Baseline C Reactive Protein (mg/L)	1.006	1.002, 1.011	0.004
Baseline Serum M Protein (g/dL)	1.184	1.036, 1.353	0.013
Baseline Urine M Protein (g/day)	1.248	1.106, 1.409	<0.001

Grade ≥3 anemia confirmed to be derived from laboratory analysis dataset (adlb.xpt) according to Applicant's response to 1Mar2024 IR.
CI = confidence interval.
Source: Reviewer's analysis of Applicant's E-R safety dataset

Table 77: FDA - Cox Proportional Hazards Model of Grade ≥3 Leukopenia from Multivariate Dose-Response Analysis

	Hazard Ratio	95% CI	p-value
Baseline Age (years)	0.974	0.952, 0.997	0.027
Baseline Body Weight (kg)	0.980	0.967, 0.994	0.005
Plasmacytoma at Baseline (versus No Plasmacytoma)	0.484	0.255, 0.920	0.027
Baseline Lymphocytes (10^9/L)	0.650	0.439, 0.962	0.031
Baseline Neutrophils (10^9/L)	0.729	0.598, 0.888	0.002

Grade ≥3 leukopenia confirmed to be derived from laboratory analysis dataset (adlb.xpt) according to Applicant's response to 1Mar2024 IR.
CI = confidence interval.
Source: Reviewer's analysis of Applicant's E-R safety dataset

The dose-response safety analysis contains less uncertainty than the E-R safety analysis, but both the dose-response and E-R safety analyses may be impacted by confounding between the rate of safety events by dose and longer follow-up at lower doses (e.g., 50 mg QW) compared to relatively higher doses (e.g., 200 mg QW). However, no safety concerns were identified for the proposed 200 mg QW full dosage from a clinical pharmacology perspective.

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

E-R analyses for efficacy with all treatment doses from phase 1 and phase 2 parts of Study 1826, which included a range from 1 to 800 mg doses of linvoseltamab indicated that the probability of achieving ORR and CR increased with linvoseltamab exposure in a sigmoidal pattern, and substantial clinical response (71.7%) was predicted at exposures consistent with the median exposure ($C_{average}$) of 200 mg dose, which supports the selection of the 200 mg dosing regimen for the treatment of RRMM. Further time-to-event analyses of PFS and OS using exposures of linvoseltamab for the patients in phase 2 (50 mg and 200 mg dose groups) indicated that, overall, the relationships between drug concentration and PFS or OS were described by monotonically increasing functions. The relationships between linvoseltamab exposures and both PFS and OS, were statistically significant with predicted decrease in risk of progression and death for patients receiving a 200 mg dose compared to those receiving a 50 mg dose.

An increase in incidence of CRS in the first week with increase in linvoseltamab exposures (C_{max}) at week 1 was observed (doses ranging from 1 to 32 mg) in data from phase 1 and phase 2. There was no exposure related trend observed for the incidence of opportunistic infections of any grade possibly due to low number of events overall. Exposure-response relationships for time to first infections grade ≥3 and neutropenia grade ≥3 indicate that increasing linvoseltamab exposure decreases the rate and hazard for these safety endpoints. However, the analyses may be influenced by the many first events occurring during the first few weeks of treatment. Notably, this exposure-response relationship for infections may be indirect and mediated through the patient's baseline characteristics and improving disease status, ie, decreasing myeloma activity over time in patients achieving CR, which occur more readily with the higher exposures associated with the 200 mg dose compared to the 50 mg dose.

The FDA's Assessment:

The E-R safety and efficacy analyses are limited by the differences in treatment duration and follow-up in the 5/25/50 mg cohort compared to the 5/25/200 mg cohort, the use of total drug concentrations rather than free drug concentrations, and potential confounding with time-averaged exposure metrics. Due to these significant limitations, FDA utilized multivariate dose-response analyses to assess the acceptability of the proposed 5/25/200 mg dosage (refer to Section 19.4.2.3 and 19.4.2.6).

Overall, the dose-response analysis of efficacy generally supports the proposed 200 mg QW full dosage in patients with RRMM. No safety concerns were identified with the proposed 5/25/200 mg QW dosage from a clinical pharmacology perspective. No dosage adjustments according to patient characteristics are recommended for the proposed dosage of 5/25/200 mg QW.

19.4.3. Summary of the Bioanalytical Method

Bioanalytical Method Validation Report Name	Bioanalytical Validation Report R5458-AV-19107-VA-01V1 - Validation of a Bioanalytical Method for the Quantitative Measurement of Total REGN5458 in Human Serum
Method Description	The bioanalytical method is an ELISA to determine the concentration of total REGN5458 in human serum. This procedure employs a microtiter plate coated with a mouse monoclonal antibody specific to the anti-CD3 arm of REGN5458 (REGN5766) and utilizes REGN5458 as a standard. The assay includes an acid pre-treatment of serum samples to dissociate soluble target: drug (BCMA:REGN5458) complexes present in the samples and improve detection of drug while soluble target is still present in the serum. Standards, controls and samples are diluted in acetic acid and then neutralized with a Tris-base solution containing an anti-BCMA monoclonal antibody that competes with REGN5458 (to prevent BCMA re-association with REGN5458). Neutralized standards, controls and samples are then added to the plate and REGN5458 captured on the plate is detected using a different biotinylated mouse monoclonal antibody specific to the anti-BCMA arm of REGN5458 (Biotin-REGN7301), followed by NeutrAvidin conjugated with horseradish peroxidase (NeutrAvidin-HRP). A luminol-based substrate specific for peroxidase is then added to achieve a signal intensity of which is proportional to the concentration of total REGN5458.
Materials used for Calibration Curve & Concentration	REGN5458 Labeled Drug Product, Lot# 9031500001, 9.5 mg/mL
Validated Assay Range	Assay Range in Neat (100%) Human Serum = 5-0.078 µg/mL Assay Range in 2% Human Serum (MRD = 1:50) = 100-1.56 ng/mL
Material used for QCs & Concentration	REGN5458 Labeled Drug Product, Lot # 9031500001, 9.5 mg/mL
Minimum required dilution (MRD)	1:50
Source & lot of reagents	- REGN5458 Labeled Drug Product, Lot # 9031500001 (Source: Regeneron) - REGN5766 (mouse anti-REGN5458 monoclonal antibody; specific for the anti-CD3 arm of REGN5458), Lot # RSCH19115 (Source: Regeneron) - Biotin-REGN7301 (biotinylated mouse anti-REGN5458 monoclonal antibody, specific for the anti-BCMA arm of REGN5458), Lot # RSCH19099 (Source: Regeneron)

Regression model & weighting	Weighted 4-parameter logistic, with variable weight: y = (A-D) / (1+(x/C)B) + D Weight = 1/RLU2	
Validation parameters	**Method validation summary**	**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of Standard calibrators from LLOQ to ULOQ	7	Yes
	Cumulative accuracy (%bias*) from LLOQ to ULOQ	-2 to 2% (%AR = 98 to 102%)	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-8 to 3% (%AR = 92 to 103%)	Yes
	Inter-batch %CV	≤8%	Yes
	Total Error (TE)	≤13%	Yes
Selectivity & matrix effect	Ten multiple myeloma individual lots (samples) tested. No matrix effects observed as all drug naïve (unspiked) samples were below the limit of quantitation. Selectivity at the LLOQ level: Range of observed bias = 0 to 14% (%AR = 100 to 114%) Selectivity at the HQC level: Range of observed bias = 1 to 13% (%AR = 101 to 113%)		Yes

Interference & specificity	Specificity tested at the LLOQ and HQC levels, spiked with increasing concentrations of an unrelated fully human IgG4 monoclonal antibody (REGN2810). Spiking concentrations ranging from 15.63 to 1000 µg/mL. Interference at the HQC level: Range of observed bias = -14 to -2% (AR% = 86 to 98%) Interference at the LLOQ level: Range of observed bias = 3 to 12% (AR% = 103 to 112%)	Yes
Hemolysis effect	Ten individual lots (samples) tested at the LLOQ level: Range of observed bias = -4 to 4% (%AR = 96 to 104%)	Yes
Lipemic effect	Ten individual lipemic lots (samples) tested at the LLOQ level: Range of observed bias = -12 to -3% (%AR = 88 to 97%)	Yes
Dilution linearity & hook effect	Concentration tested = 200 µg/mL of REGN5458 Dilution factors tested: MRD (1:50), 1:250, 1:500, 1:2500, 1:10000 and 1:40000. Dilution factors 1:50, 1:250 and 1:500 were above the limit of quantitation Range of observed bias (for dilution factors 1:2500, 1:10000 and 1:40000) = -20 to -2% (%AR = 80 to 98%)	Yes
Bench-top/process stability	Stability of REGN5458 in human serum evaluated by assessing the recovery of QCs after storage in a 4°C refrigerator for at least 24 hours or at room temperature (20-25°C) for at least 6 hours. Stability at 4°C, 24 hours: %bias = -4 to 3% (%AR = 96 to 103%) Stability at room temperature, 6 hours: %bias = -8 to 1% (%AR = 92 to 101%)	Yes

Freeze-thaw stability	Stability of REGN5458 in human serum evaluated by assessing the recovery of QCs after 8 freeze/thaw cycles. Stability after 8 cycles: %bias = -8 to 2% (%AR = 92 to 102%)	Yes
Long-term storage	Stability of REGN5458 in human serum evaluated by assessing the recovery of QCs stored in -20°C and -80°C freezers up to 24 months. Stability after storage in -20°C freezer, 24 months: %bias = -7 to 12% (%AR = 93 to 112%) Stability after storage in -80°C freezer, 24 months: %bias = -10 to 10% (%AR = 90 to 110%)	Yes
Parallelism	N/A	N/A
Carry over	N/A	N/A
Method performance in clinical study R5458-ONC-1826 (including ISR runs)		
Assay passing rate **Standard curve performance#**	97.1% • Cumulative bias range: 0 to 1% • Cumulative precision: ≤2% CV	Yes
QC performance# **Method reproducibility**	• Cumulative bias range: -5 to -4% • Cumulative precision: ≤8% CV • TE: ≤13% Incurred sample reanalysis was performed in 480 (6%) study samples and 97.9% of samples met the pre-specified ISR acceptance criteria.	Yes
Study sample analysis/stability	The reference standard (used to prepare the standard curve) was stored for up to 1 year. QCs were stored for up to 2 years (as per the long-term stability data provided in the validation report). All study samples were analyzed within 2-years of their collection date.	Yes

* %bias = (%AR-100). All %bias values provided were calculated based on the %AR values reported in the validation report tables referenced.

In the bioanalytical report for Study R5458-ONC-1826 (R5458-ONC-1826-BA-01V1), Table 3 and Table 4 for in- study performance summary of standards and quality controls (QCs) included only the results from

sample analysis assay plates. The standards and QCs performance summaries provided in Appendix C and Appendix D in this response include data from the sample analysis and ISR plates.

Source: Table 1 in Applicant's Response dated 4/15/2024 to FDA IR dated 4/08/2024.

19.5. Study 1826 Eligibility Criteria

Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Age ≥18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
3. Confirmed diagnosis of active MM by IMWG diagnostic criteria
4. Patients must have myeloma that is response-evaluable according to the 2016 IMWG response criteria
   a. Phase 1: Patients must have measurable serum or urine markers as defined by the 2016 IMWG response criteria (listed below).
      Measurable disease is defined as 1 or more of the following:
      - Serum M-protein ≥1 g/dL,
      - Urine M-protein ≥200 mg/24-hr, and/or FLC assay with involved FLC level ≥10 mg/dL with an abnormal serum FLC ratio
      - A patient with Immunoglobulin A (IgA) myeloma but without measurable M-protein may be enrolled if quantitative IgA levels are greater than or equal to 400 mg/dL and can be followed longitudinally
      - A patient with non-secretory MM may be considered for enrollment after discussion with the sponsor that includes the feasibility of the plan for response assessment according to IMWG guidelines.
   b. Phase 2: Patients must have measurable serum or urine markers as defined by the 2016 IMWG response criteria (listed below). Up to 20 patients are to be enrolled with measurable extramedullary plasmacytomas in cohort 1, 20 patients with extramedullary plasmacytoma in cohort 2 (measurable disease defined below). All other patients must not have measurable extramedullary plasmacytomas.

   - Measurable disease is defined as 1 or more of the following:
     - Serum M-protein ≥1 g/dL,
     - Urine M-protein ≥200 mg/24-hr, and/or
     - FLC assay with involved FLC level ≥10 mg/dL with an abnormal serum FLC ratio
     - A patient with Immunoglobulin A (IgA) myeloma but without measurable M-protein may be enrolled if quantitative IgA levels are greater than or equal to 400 mg/dl and can be followed longitudinally
   - A plasmacytoma target lesion is defined as: measurable with at least 1 soft tissue lesion

>2 cm in long axis diameter on a CT-scan, MRI, or F-fluorodeoxyglucose positron emissions tomography-computed tomography (FDG PET/CT) and must be longitudinally assessable and not previously irradiated.
- If skin lesions are present, there should be at least 1 lesion >2 cm in long axis diameter as measured with a ruler.

5. Phase 1 Part 1 (Dose Escalation): Patients with MM who have exhausted all therapeutic options that are expected to provide meaningful clinical benefit, either through disease relapse, treatment refractory disease, or intolerance of the therapy, and including either:
   a. Progression on or after at least 3 lines of therapy, or intolerance of therapy, including a PI, an IMiD, and an anti-CD38 antibody, OR
   b. Progression on or after an anti-CD38 antibody and have disease that is "double refractory" to a PI and an IMiD, or intolerance of therapy. The anti-CD38 antibody may have been administered alone or in combination with another agent such as a PI. Refractory disease is defined as lack of response or relapse within 60 days of last treatment.

   Phase 2 (Cohorts 1 and 2): Patients with MM whose disease meets the following criteria:
   a. Progression on or after at least 3 prior lines of therapy including a(n) PI, IMiD, and anti-CD38 antibody, OR
   b. 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 is defined as progression during treatment or within 60 days after completion of therapy, or <25% response to therapy.
6. Adequate hematologic function before dosing as measured by:
   a. Platelet count >50 x 10^9/L for all patients who must have a platelet count 100 x 10^9/L. A patient may not have received a platelet transfusion within 7 days in order to meet this platelet eligibility requirement.
   b. ANC >1.0 x 10^9/L. A patient may not have received granulocyte colony stimulating factor (G-CSF) within 2 days in order to meet this absolute neutrophil count eligibility requirement.
   c. Hemoglobin >8.0 g/dL
7. Adequate renal and hepatic function, defined as:
   a. Total bilirubin ≤1.5 x ULN
   b. Transaminase (ALT, AST) ≤2.5 x ULN
   c. Alkaline phosphatase ≤2.5 x ULN
      - Patients with Gilbert syndrome do not need to meet this total bilirubin requirement provided that the total bilirubin is unchanged from the baseline value.
   d. Serum creatinine clearance by Cockcroft-Gault >30 mL/min
      - A patient with a creatinine clearance by Cockcroft-Gault who does not meet eligibility criteria may be considered for enrollment if a measured creatinine clearance (based on 24-hour urine collection or other

reliable method)
is >30 mL/min.

8. If previously treated with CAR T therapy or any gene therapy products, patients must have recovered from the toxicities of this therapy
9. Life expectancy of at least 6 months
10. Willing and able to comply with clinic visits and study-related procedures, including serial bone marrow evaluations according to the protocol schedule. A bone marrow aspirate and biopsy, or other tissue infiltrated with malignant plasma cells, must be provided at screening for evaluation of BCMA levels in malignant cells, but demonstration of BCMA levels will not be required for enrollment.
11. Provide informed consent signed by the study patient
12. Able to understand and complete study-related questionnaires

Exclusion Criteria:

A patient who meets any of the following criteria will be excluded from the study:

1. Diagnosis of plasma cell leukemia, primary systemic light-chain amyloidosis (excluding myeloma-associated amyloidosis), Waldenström macroglobulinemia (lymphoplasmacytic lymphoma), or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
2. Patients with known MM brain lesions or meningeal involvement
3. History of neurodegenerative condition, CNS movement disorder, or patients with a history of seizure within 12 months prior to study enrollment are excluded.
4. Cardiac ejection fraction <40% by echocardiogram or multi-gated acquisition scan (MUGA)
5. 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
6. Live or live attenuated vaccines with replicating potential within 28 days prior to first study drug administration. Has received a COVID-19 vaccination (initial series or booster) within 1 week of planned start of study medication or for which the planned COVID-19 vaccinations (initial series or booster) would not be completed 1 week prior to start of study drug.
7. Treatment with any systemic standard or investigational anti-myeloma therapy within 5 half-lives or within 28 days before first administration of study drug, whichever is shorter
8. Prior treatment with BCMA-directed immunotherapies, including BCMA bispecific antibodies and BiTEs. Note: BCMA antibody-drug conjugates are not excluded.
9. Any infection requiring hospitalization or treatment with intravenous (IV) anti-infectives within 2 weeks of first administration of study drug
10. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; or other uncontrolled infection (such as cytomegalovirus [CMV]).
    - Patients with HIV who have controlled infection (undetectable viral load and

CD4 count above 350 cells/microliter either spontaneously or on a stable antiviral regimen) are permitted.
- Patients with hepatitis B (Hepatitis B Surface Antigen Test positive [HepBsAg+]) who have controlled infection (serum HBV DNA polymerase chain reaction [PCR] that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of study drug.
- Patients who are HCV antibody-positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

11. Has known allergy or hypersensitivity to components of REGN5458
12. Known hypersensitivity to both allopurinol and rasburicase
13. History of allogeneic stem cell transplantation at any time, or autologous stem cell transplantation within 12 weeks of the start of study treatment
14. Member of the clinical site study team or his/her immediate family, unless prior approval granted by the sponsor
15. Women of childbearing potential (WOCBP) with a positive serum beta-human chorionic gonadotropin (β-hCG) pregnancy test are ineligible for this study.
16. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
17. Pregnant or breastfeeding women
18. WOCBP* and men** who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose.

    *Highly effective contraceptive measures for women include:
    - stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    - intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    - bilateral tubal ligation
    - vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the study participant and that the partner has obtained medical assessment of surgical success for the procedure)
    - and/or sexual abstinence†, ‡.

    WOCBP are defined as women who are fertile following menarche until becoming post- menopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in

women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months
of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a post-menopausal state.

**Male study participants with WOCBP partners are required to use condoms unless they are vasectomized ¥ or practice sexual abstinence †,‡. Male study participants should not donate sperm during the study, and for at least 6 months after the last dose.

¥ Vasectomized partner or vasectomized study participant must have received medical assessment of the surgical success.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

19. Another malignancy in the past 5 years, except for non-melanoma skin cancer that has undergone potentially curative therapy or in situ cancer, or any other tumor that has been deemed to be effectively treated with definitive local control and with curative intent.
20. Is currently receiving treatment in another interventional study
21. 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

19.6. FDA Grouped Terms

FDA Grouped Term (GT)	Preferred Terms
Abdominal pain (GT)	Abdominal discomfort Abdominal pain Abdominal pain lower Abdominal pain upper Abdominal cramping Stomach pain
Acute kidney injury (GT)	Acute kidney injury Acute renal injury Acute renal failure Renal failure Worsening increased creatinine
Cardiac arrhythmia (GT)	Atrial fibrillation Atrial flutter Bradycardia Sinus bradycardia Sinus tachycardia Tachycardia Ventricular extrasystoles Ventricular tachycardia
Cardiac failure (GT)	Cardiac failure acute Cardiac failure congestive Cardiopulmonary failure Diastolic dysfunction EF decreased Heart failure exacerbation
Colitis	Enterocolitis infectious Enterocolitis infectious: campylobacter Enterocolitis infectious: C diff
Congestion (GT)	Nasal congestion Respiratory tract congestion Sinus congestion
Cough (GT)	Cough Productive cough Upper-airway cough syndrome

Chest pain	All PTs containing “chest pain”, except for those indicating musculoskeletal or chest wall pain
COVID-19 (GT)	Coronavirus infection COVID-19 Post-acute COVID-19 syndrome SARS-COVID asymptomatic Suspected COVID-19
Dyspnea (GT)	Dyspnea Dyspnea exertional Shortness of breath
Edema (GT)	Ankle edema Edema Edema peripheral Eye edema Fluid retention Lip edema Localized edema Periorbital edema Peripheral swelling
Encephalopathy (GT)	Agitation Altered state of consciousness Altered mental status Cognitive disorder/impairment Confusional state Confusion Delirium Depressed level of consciousness Disorientation Hallucination Hyperammonemia encephalopathy Lethargy Memory impairment Mental status changes Metabolic encephalopathy Short term memory loss Somnolence Toxic encephalopathy
Fatigue (GT)	Asthenia Fatigue

	Malaise
Febrile neutropenia	Febrile neutropenia Neutropenic fever
Headache	All PTs containing “headache” Migraine
Hemorrhage (GT)	Anal hemorrhage Conjunctival hemorrhage Diarrhea hemorrhagic Ear hemorrhage Epistaxis Hemarthrosis Hematochezia Hematoma Hematoma muscle Hematuria Hemopneumothorax Hemorrhoidal hemorrhage Intestinal hemorrhage Lumbar epidural hematoma Rectal hemorrhage Retroperitoneal hemorrhage Subdural hematoma Upper gastrointestinal hemorrhage Vascular access site hemorrhage
Infusion related reaction	Infusion related reaction IRR related to IVIG
Injection site reaction (GT)	Injection site dryness Injection site erythema Injection site hemorrhage Injection site induration Injection site inflammation Injection site pain Injection site pruritis Injection site rash Injection site reaction Injection site urticaria

Motor dysfunction (GT)	Ataxia Balance disorder Gait disturbance Motor dysfunction Muscle contracture Muscle spasms Muscular Weakness Myoclonus Peripheral motor neuropathy Peroneal Nerve Palsy Tremor
Mucositis (GT)	All PTs containing mucositis Mouth sore Tongue ulceration
Musculoskeletal pain (GT)	Arthralgia Arthropathy Back pain or back ache Bone pain Breast pain Flank pain Generalized pain Lower extremity aches Muscle soreness Musculoskeletal chest pain Musculoskeletal pain Myalgia Neck pain Non-cardiac chest pain Pain in extremity Shoulder pain
Pneumonia (GT)	All PTs containing 'pneumonia', including within another word (e.g. bronchopneumonia) Atypical pneumonia COVID-19 Pneumonia COVID-related lung infection Lower respiratory tract infection

	Lower respiratory tract infection viral Lung infection Pneumocystis jirovecii pneumonia Pneumonia Pneumonia adenoviral Pneumonia bacterial Pneumonia cytomegaloviral Pneumonia fungal Pneumonia influenzal Pneumonia pseudomonal Pneumonia viral
Pneumonitis (GT)	Acute respiratory distress syndrome Chemotherapy induced pneumonitis
Pruritis	All PTs containing “itching” or “pruritis”
Rash (GT)	Acneiform rash Drug-related rash Erythema Palmar-plantar erythrodysesthesia syndrome Rash Rash erythematous Rash macular Rash maculo-papular Rash pustular Symmetrical drug-related interiginous and flexural exanthema
Sensory neuropathy (GT)	Burning sensation Decreased sensation Dysaesthesia Hypoaesthesia Neuralgia Neuropathy peripheral Numbness in fingertips/toes Paraesthesia Parosmia Peripheral sensorimotor neuropathy Peripheral sensory neuropathy

	Polyneuropathy Sensory loss Sciatic pain Tingling of extremity
Sepsis (GT)	Bacteremia- (including pseudomonas, E. coli, campylobacter, S. bovis) Escherichia sepsis Klebsiella sepsis Pseudomonal sepsis Sepsis Septic shock Staphylococcal bacteremia Staphylococcal sepsis Streptococcal sepsis Urosepsis
Skin Exfoliation (GT)	Dermatitis exfoliative Dermatitis exfoliative generalized Skin exfoliation
Thrombosis (GT)	Deep vein thrombosis Mesenteric artery thrombosis Peripheral arterial occlusive disease Pulmonary embolism Superficial vein thrombosis Thromboembolic event Thrombosis
Transaminase elevation (GT)	Alanine aminotransferase increased Aspartate aminotransferase increased
Upper respiratory tract infection (GT)	Acute sinusitis Bronchial infection Bronchitis Bronchitis viral Chronic sinusitis Common cold Head cold Influenza-like illness Nasopharyngitis Parainfluenza infection

	Pharyngitis Respiratory infection Respiratory tract infection viral Rhinitis Rhinovirus infection Rhinoenterovirus RSV infection Sinus drainage Sinusitis Sinusitis bacterial Upper respiratory tract infection Viral upper respiratory tract infection
Urinary tract infection (GT)	Bacteriuria Cystitis Escherichia urinary tract infection Urinary tract infection Urinary tract infection bacterial Enterococcal UTI
Vision changes (GT)	Blurred vision Double vision from a distance

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APPEARS THIS WAY ON ORIGINAL

BLA 761400 Lynozyfic (linvoseltamab-(b) (4))			

Signatures (delete discipline if not part of review)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Liz Garcia-Peterson, PhD	DHOT	Sections: 5	Select one: ☑ Authored ☐ Approved
	Signature: Liz M. Garcia-peterson -S Digitally signed by Liz M. Garcia-peterson -S Date: 2024.06.17 07:23:52 -04'00'			
Nonclinical Team Leader	Michael Manning, PhD	DHOT	Sections: 5	Select one: ☑ Authored ☐ Approved
	Signature: Michael L. Manning -S Digitally signed by Michael L. Manning -S Date: 2024.06.14 16:53:18 -04'00'			
Nonclinical Team Division Director (NME Only)	Haleh Saber, PhD	DHOT	Sections: 5	Select one: ☐ Authored ☑ Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2024.06.14 16:36:39 -04'00'			
Clinical Pharmacology Reviewer	Banu Zolnik, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Banu S. Zolnik -S Digitally signed by Banu S. Zolnik -S Date: 2024.06.18 13:49:54 -04'00'			
Clinical Pharmacology Team Leader	Xiling Jiang, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S Date: 2024.06.18 11:08:07 -04'00'			
Clinical Pharmacology Division Director (NME only)	Brian Booth, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☐ Authored ☑ Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S Date: 2024.06.18 13:55:39 -04'00'			
Pharmacometrics Reviewer	Robyn Konicki, PharmD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Robyn E. Konicki -S Digitally signed by Robyn E. Konicki -S Date: 2024.06.18 12:42:54 -04'00'			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2024.06.18 11:00:09 -04'00'			

Clinical Reviewer	Deepti Telaraja, MD	OOD/DHM2	Sections: All	**Select one:** ☑ Authored ☐ Approved
	Signature: Deepti Telaraja -S Digitally signed by Deepti Telaraja -S Date: 2024.06.28 16:40:00 -04'00'			
Clinical Team Leader	Bindu Kanapuru, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Bindu Kanapuru -S Digitally signed by Bindu Kanapuru -S Date: 2024.06.26 17:00:19 -04'00'			
Statistical Reviewer	Jay Zhao, PhD	OB/DBIX	Sections: 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Jian Zhao -S Digitally signed by Jian Zhao -S Date: 2024.06.17 08:20:44 -04'00'			
Deputy Division Director (OB)	Lisa Rodriguez, PhD	OB/DBIX	Sections: 8	**Select one:** ☑ Authored ☑ Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S Date: 2024.06.14 16:28:40 -04'00'			
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSn, RN, ACNP	OOD/DHM2	Sections: 11	**Select one:** ☑ Authored ☑ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2024.06.20 08:19:19 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Bindu Kanapuru, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
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Division Director (Clinical)	Nicole J. Gormley, MD	OOD/DHM2	Sections: All	**Select one:** ☐ Authored ☑ Approved
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OOD: Office of Oncologic Diseases			
DHOT: Division of Hematology, Oncology, Toxicology			
OCP: Office of Clinical Pharmacology			
DPM: Division of Pharmacometrics			
DCPI: Division of Cancer Pharmacology I			
OB: Office of Biostatistics			
DBIX: Division of Biometrics IX			
DHM2: Division of Hematologic Malignancies 2			
OCE: Oncology Center of Excellence			

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/s/

LAURA C WALL
08/20/2024 11:45:33 AM

MARC R THEORET
08/20/2024 12:23:47 PM