CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761400Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761400
PDUFA Goal Date	July 10, 2025
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Team Leader	Naomi Boston, Pharm.D., Risk Management Team Leader
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Review Completion Date	June 30, 2024
Subject	Evaluation of need for a REMS
Established Name	Linvoseltamab-gcpt
Trade Name	Lynozyfic
Name of Applicant	Regeneron Pharmaceuticals, Inc.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed CD3 T cell engager
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)

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EXECUTIVE SUMMARY

This review provides additional analysis beyond what was included in the Division of Risk Management's (DRM) deferral memo, dated August 14,2024.[1] Regeneron Pharmaceuticals, Inc. resubmitted Biologic Licensing Application (BLA) 761400 on January 10, 2025 for Lynozyfic (linvoseltamab-gcpt) with the proposed indication[2] 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, after receiving a Complete Response (CR) letter on August 20,2024, due to the deficiencies in facility inspection.[3] This review by DRM evaluates the proposed REMS for Lynozyfic (linvoseltamab-gcpt). The Applicant submitted the proposed REMS on February 7, 2025, and was amended on June 2, June 20, and June 25, 2025.

The efficacy and safety of linvoseltamab-gcpt were evaluated in Study LINKER-MM1, an open-label, multi-center, multi-cohort study. Based on the efficacy and safety information currently available, the clinical reviewer stated that linvoseltamab-gcpt shows clinically meaningful benefit and recommends approval 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. The major safety concerns in considering the need for a REMS with the use of linvoseltamab-gcpt include cytokine release syndrome (CRS), neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS). These risks will be labeled in a Boxed Warning and Warnings and Precautions.

DRM agrees with the Division of Hematologic Malignancies 2 (DHM2) to determine that a REMS is necessary to ensure the benefits of linvoseltamab-gcpt outweigh the risks of CRS and neurologic toxicity, including ICANS. The REMS determination is supported by the rate of CRS and neurologic toxicity, including ICANS, seen in the clinical trial program for linvoseltamab-gcpt, as well as the concern that in some cases, linvoseltamab-gcpt might be administered in community-based private oncology practices where patients may be less closely monitored. The REMS for linvoseltamab-gcpt is consistent with the REMS for other bispecific T-cell engagers indicated in the treatment for relapsed or refractory multiple myeloma.

The goal of the Lynozyfic REMS is to mitigate the risks of CRS and neurologic toxicity including 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. The Lynozyfic REMS includes the following elements: a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The communication plan will be used to target prescribers and healthcare providers who may be involved in administration of linvoseltamab-gcpt or care for patients treated with linvoseltamab-gcpt. The ETASU include ETASU A (healthcare providers who prescribe linvoseltamab-gcpt are specially certified), and ETASU B (pharmacies and healthcare settings that dispense linvoseltamab-gcpt are specially certified). Prescribers must certify in the REMS to ensure that they receive training about the risks, how to monitor for and manage the risks, and that they provide counseling to patients. Counseling includes providing a wallet card to patients so that patients are aware they should seek medical care if CRS or neurologic toxicity including ICANS symptoms develop outside of a healthcare setting. Pharmacies and healthcare settings must be certified to confirm that prescribers are certified prior to dispensing linvoseltamab-gcpt.

To evaluate if the REMS is functioning as designed, meeting its goal and objectives, and to determine if modifications to the REMS may be needed, the Applicant developed a REMS Assessment Plan. The timetable for submission of assessments is 12 months from the date of the initial approval of the REMS (MM/DD/YYYY) and annually thereafter.. The Division of Mitigation Assessment and Medication Error Surveillance found the REMS Assessment Plan as submitted on June 25, 2025, to be acceptable.

DRM finds the proposed REMS submitted on June 25, 2025, to be acceptable.

1. Introduction

Regeneron Pharmaceuticals, Inc. resubmitted Biologic Licensing Application (BLA) 761400 on January 10, 2025 for Lynozyfic (linvoseltamab-xxxx) with the proposed indication[2] 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, after receiving a Complete Response (CR) letter on August 20,2024, due to the deficiencies in facility inspection.[3] This review provides additional analysis beyond what was included in the Division of Risk Management's (DRM) deferral memo, dated August 14,2024.[1] This application is under review in the Division of Hematologic Malignancies 2 (DHM2). The Applicant's proposed REMS consists of a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments, to ensure the benefits of linvoseltamab-gcpt outweigh the risks of cytokine release syndrome (CRS) and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS).

2. Background

2.1. Product Information

Linvoseltamab-gcpt is a new molecular entity (NME) BLA type 351(a) pathway application.[a] It 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 and some healthy B-lineage cells. In vitro, linvoseltamab-gcpt activated T-cells, caused the release of various proinflammatory cytokines, and resulted in the lysis of multiple myeloma cells. Linvoseltamab-gcpt had anti-tumor activity in mouse models of multiple myeloma.

Linvoseltamab-gcpt is proposed to be supplied as 5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL) single-dose vials. The recommended dosage of linvoseltamab-gcpt is step-up doses of 5 mg, 25 mg, and 200 mg, followed by 200 mg weekly for 10 doses, followed by 200 mg biweekly (every 2 weeks). In patients who have achieved and maintained very good partial response (VGPR) or better at or after Week 24 and received at least 17 doses of 200 mg, the dosing frequency is decreased to 200 mg every 4 weeks, until disease progression or unacceptable toxicity.[b,2] Linvoseltamab-gcpt is not currently approved in any jurisdiction.[4]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2. Regulatory History

The following is a summary of the regulatory history for linvoseltamab-gcpt (BLA 761400) relevant to this review:

- 06/06/2022: Orphan drug designation granted.
- 03/30/2023: Fast Track designation granted.
- 12/22/2023: BLA 761400 submission for linvoseltamab-gcpt with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) received. The Applicant proposed a REMS that consists of CP, ETASU, an implementation system, and a timetable for submission of assessments to ensure the benefits of linvoseltamab-gcpt outweigh the risk(s) of CRS and ICANS.
- 08/20/2024: The Division of Hematology Malignancies 2 (DHM2) issued a Complete Response letter on August 20,2024, due to the deficiencies in facility inspection.[3]
- 01/10/2025: Application resubmitted to the Agency.
- 02/07/2025: The Applicant amended submission for BLA 761400, it included the REMS Document and REMS Appended Materials.
- 05/16/2025: The Agency sent comments on the REMS materials, agreements for the Prescriber Enrollment Form and Pharmacy and Healthcare Setting Enrollment Form, and REMS Supporting Document.
- 05/23/2025: The Applicant requested clarification regarding the REMS Dispense Authorization (RDA) process in REMS operation.
- 06/02/2025: The Applicant amended submission for BLA 761400, it included the REMS Document, REMS Appended Materials and REMS Supporting Document.
- 06/16/2025: The Agency sent comments on the REMS Document, REMS materials, agreements for the Prescriber Enrollment Form and Pharmacy and Healthcare Setting Enrollment Form, REMS Assessment Plan and REMS Supporting Document. The Agency also clarified the RDA process in the response.
- 06/17/2025: The Applicant requested clarification regarding incorporating the RDA process in REMS materials to bring clarity, and the timetable for submission of REMS Assessments.
- 06/17/2025: The Agency clarified the questions from the Applicant.
- 06/20/2025: The Applicant submitted a REMS amendment in response to the IR sent on 06/16/2025.
- 06/24/2025: The Agency issued an IR, requesting the Applicant to remove (b) (4) (b) (4) from the REMS Document and all REMS materials, and to submit a certification of translation demonstrating that the non-English materials are accurate, identical in content, and the translation is correct as a REMS correspondence.
- 06/25/2025: The Applicant amended submission for BLA 761400, including the REMS document, Supporting Document, and all appended materials as full submission.
- 06/26/2025: The Agency issued an IR, reiterating to the Applicant to submit a certification of translation demonstrating that the non-English materials are accurate, identical in content, and the translation is correct as a REMS correspondence.
- 06/27/2025: The Applicant submitted a REMS correspondence in response to the IR sent on 06/26/2025.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Multiple myeloma is the second most common hematological malignancy and is characterized by a clonal proliferation of neoplastic plasma cells within the bone marrow.[5,6] An estimated 131,392 Americans in 2016 were living with MM. The expected number of new cases in the United States in 2025 is 36,110[c], with 12,030 expected deaths due to the disease[d]. Five-year survival for patients diagnosed with MM is approximately 62.4%.[7] MM is the most frequent cancer involving the skeleton, causing osteolytic lesions, bone pain, and pathological fractures that dramatically decrease MM patients' quality of life and survival.[5] Multiple myeloma is more common in men than women and among individuals of African American descent. Myeloma is most frequently diagnosed among people aged 65-74 with the average age of 69.[7] Patients with MM experience a variety of disease-related events and symptoms, such as bone destruction leading to pain, height reduction and body shape changes, and bone marrow failure, renal failure, immunodeficiency, as well as the psychosocial burden of a diagnosis of cancer.[8] A deterioration in quality of life is particularly marked in elderly frail patients, who represent approximately 30% of patients with MM.[9]

3.2. Description of Current Treatment Options

The treatment paradigms and outcomes for patients with MM have changed in the past decade with introduction of several new, more effective, and less toxic therapies more than doubling of the survival.[10] Treatments for MM include autologous stem cell transplantation (ASCT), immunomodulator agents (thalidomide[11], lenalidomide[12], and pomalidomide[13]), proteasome inhibitors (bortezomib[14], carfilzomib[15] and ixazomib[16]) and more recently, the anti-CD38 antibody (daratumumab[17]) and anti-signaling lymphocytic activation molecule F7 (anti-SLAMF7) antibody (elotuzumab[18]). The IMiDs, thalidomide, lenalidomide, and pomalidomide are approved with REMS to mitigate the risk of teratogenicity.[11,11,12] The 2019 National Comprehensive Cancer Network (NCCN) guidelines[19] for multiple myeloma list the following combinations as preferred regimens for primary induction therapy in patients who are candidates for transplantation:

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone (preferred initial treatment in patients with acute renal insufficiency)

Other recommended regimens, according to the NCCN, are as follows:

- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone (category 2B)

Primary therapy for non-transplant candidates are as follows:

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Daratumumab/lenalidomide/ dexamethasone (category 1)

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

- Lenalidomide/low-dose dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone

Other NCCN-recommended regimens for these cases include the following:
- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone
- Daratumumab/bortezomib/melphalan/prednisone (category 1)

Almost all patients eventually relapse despite therapeutic responses to a PI, IMiD or both.[20] A combination regimen of selinexor plus dexamethasone is approved[21] for the treatment of patients with RRMM who received at least four prior therapies and whose disease is refractory to multiple agents, which offers responses of 26.2% in patients with a median duration of response (DoR) of 4.4 months.[22,23] In addition, idecabtagene vicleucel and ciltacabtagene autoleucel are BCMA-directed chimeric antigen receptor (CAR)-T cell therapies approved for RRMM following at least four lines of systemic therapy. The CAR-T therapies required REMS programs with ETASU to mitigate the risks of CRS and neurologic toxicities. The REMS for CAR-T therapies were eliminated on June 26, 2025 because FDA determined a REMS is no longer necessary to ensure the benefits outweigh the risks and to minimize burden on the healthcare delivery system of complying with the REMS.[24,25] Further, there are three bispecific antibody drugs, all given subcutaneously, approved for patients who have received at least 4 prior therapies for the treatment for RRMM that are approved with a REMS with ETASU to mitigate the risks of CRS and neurologic toxicity, including ICANS. Teclistamab approved in 2022, and talquetamab and elranatamab, both approved in August 2023.[26,27,28] Despite substantial progress, RRMM remains a highly resistant disease given its propensity for clonal heterogeneity and its complex interaction with the surrounding bone marrow microenvironment.[29] Treatment for these patients with relapsed or refractory multiple myeloma (RRMM) is complex and there remains no consensus on a clear treatment algorithm.[30]

4. Benefit Assessment

The efficacy of linvoseltamab-gcpt was evaluated in subjects with RRMM in an open-label, multi-center, multi-cohort study (LINKER-MM1; NCT03761108). The study enrolled 105 subjects in the 200 mg cohort who had previously received at least 3 prior therapies, including a PI, IMiD, and anti-CD38 antibody. The study included subjects with Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 and adequate baseline hematologic (absolute neutrophil count > 1 x 10^9/L, platelet count > 50 x 10^9/L, hemoglobin level >8 g/dL), renal (CrCL > 30 mL/min), and hepatic (AST and ALT ≤ 2.5 x ULN, total bilirubin ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN) function. The study excluded subjects with known multiple myeloma brain lesions or meningeal involvement, history of a neurodegenerative condition, history of seizure within 12 months prior to study enrollment, active infection, a history of an allogeneic or autologous stem cell transplantation within 12 weeks, prior BCMA-directed bispecific antibody therapy, prior bispecific T-cell engaging therapy, or prior BCMA CAR-T cell therapy. Subjects had received a median of 5 prior lines of therapy (range: 2 to 13).

The efficacy population included 80 subjects in the 200 mg cohort who received at least four prior lines of therapy. The median age was 71 (range: 37 to 83) years with 30% of subjects 75 years or older; 64% were male and 36% were female; 69% were White, 14% were Black or African American, 13% were Asian, and 2.5% were Hispanic/Latino. The International Staging System (ISS) at study entry was Stage I in 39%, Stage II in 36%, and Stage III in 19%. High-risk cytogenetics (presence of del(17p), t(4;14) and t(14;16)) were present in 40% of subjects. Eighteen percent of subjects had extramedullary disease at

baseline. The median number of prior lines of therapy was 5 (range: 4 to 13); 83% of subjects were refractory to the last line of therapy. Sixty-five percent of subjects received prior stem cell transplantation. Seventy-nine percent of subjects were triple-class refractory (refractory to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody). Thirteen percent of subjects were previously treated with a BCMA antibody-drug conjugate.

Subjects received a step-up dose of 5 mg on Day 1, 25 mg on Day 8, and the first treatment dose of 200 mg on Day 15 of linvoseltamab-gcpt by intravenous infusion. Then, subjects received 200 mg of linvoseltamab-gcpt weekly from Week 4 to Week 13, followed by 200 mg every other week thereafter. After at least 24 weeks, the Phase 2 subjects who achieved a VGPR or greater received 200 mg of linvoseltamab-gcpt every 4 weeks. Subjects were treated until disease progression or unacceptable toxicity. Efficacy was established based on objective response rate (ORR) as determined by blinded independent review committee (IRC), as measured using the International Myeloma Working Group (IMWG) criteria. The efficacy results are summarized in Table 1.[2,31,32,e] The median time to first response was 0.95 months (range: 0.5 to 6 months). With a median follow-up of 13 months among responders, the estimated duration of response (DOR) rate was 89% (95% CI: 77, 95) at 9 months and 72% (95% CI: 54, 84) at 12 months.

Table 1: Efficacy Results in LINKER-MM1[2,31,32,31]

Efficacy Endpoints	**Linvoseltamab-gcpt N=80**
Objective Response Rate (ORR) % (n) (95% CI)	70% (56) (59,80)
Complete response (CR) or better, % (n) (95% CI)	45% (36) (34,57)
Stringent complete response (sCR), % (n)	39% (31)
Complete response (CR), % (n)	6% (5)
Very good partial response (VGPR) % (n)	19% (15)
Partial response (PR), % (n)	6% (5)
Duration of Response (DOR)[a]	
Median, months (95% CI)	NR (12, NE)
CI=confidence interval; NE=not estimable [a] Based on Kaplan-Meier estimation.	

The clinical reviewer stated that in subjects with RRMM who have received 4 or more prior lines of therapy, linvoseltamab-gcpt has a favorable benefit-risk balance; 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.[31,32,32]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

5. Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for linvoseltamab-gcpt. The safety of linvoseltamab-gcpt was evaluated in Study in the LINKER-MM1 (see Section 4: Benefit Assessment).[2] The safety population included subjects (n=117), who received the step-up dosing regimen. The median duration of treatment was 47 weeks (range 1, 151); 55% of subjects were exposed for 9 months or longer and 36% were exposed for 1 year or longer.

Deaths

In FDA's analysis, 19 subjects (16%) experienced fatal adverse events. Of these 19 events, 9 occurred within 30 days of the last linvoseltamab-gcpt dose and 10 occurred more than 30 days after the last linvoseltamab-gcpt dose. Fatal AEs included infection (n=14; 12%), encephalopathy (n=2; 1.7%) and chronic kidney disease, respiratory failure, and tumor lysis syndrome in one patient each (0.9%). The specific types of fatal infections included sepsis (8 patients), COVID-19 pneumonia (3 patients), Pneumocystis jirovecii pneumonia (1 patient), influenza pneumonia (1 patient), and progressive multifocal leukoencephalopathy (PML; 1 patient).[31]

Serious Adverse Events (SAE)

Serious adverse reactions (SAEs) occurred in 74% of subjects who received linvoseltamab-gcpt. SAEs that occurred in >5% of subjects included cytokine release syndrome (27%), pneumonia (13%), COVID-19 (7%), and acute kidney injury (5%). Permanent discontinuation of linvoseltamab-gcpt due to SAEs occurred in 16% of patients. SAEs leading to discontinuation that occurred in at least 2 patients included sepsis, pneumonia, and encephalopathy. Dosage interruptions or delays of linvoseltamab-gcpt due to SAEs occurred in 74% of patients. SAEs which required a dosage interruption or delay in >10% of patients included neutropenia (29%), upper respiratory tract infection (18%), pneumonia (15%), and COVID-19 infection (11%).[2]

The most common adverse reactions (≥20%) were musculoskeletal pain (53%), cytokine release syndrome (46%), cough (39%), upper respiratory tract infection (35%), diarrhea (35%), fatigue (34%), pneumonia (28%), nausea (23%), headache (22%), and dyspnea (21%). The most common Grade 3 to 4 laboratory abnormalities (≥30%) were decreased lymphocyte count (92%), decreased neutrophil count (47%), decreased hemoglobin (42%), and decreased white blood cell count (31%).[2]

If approved, labeling will include the following risks[f] in the Warnings and Precautions section.

5.1. Cytokine Release Syndrome (CRS):

In the clinical trial, CRS occurred in 46% (54/117) of subjects who received linvoseltamab-gcpt at the recommended dose, with Grade 1 CRS occurring in 35% (41/117) of patients, Grade 2 in 10% (12/117),

[f] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

and Grade 3 in 0.9% (1/117).[g] There were no Grade 4 or 5 events. Clinical signs and symptoms of CRS included, but were not limited to pyrexia, chills, hypoxia, tachycardia, and hypotension. Thirty-eight percent (45/117) of subjects had CRS following step-up dose 1, including 1 subject who experienced Grade 3 CRS; 8% (9/117) had an initial CRS event following a subsequent dose. Seventeen percent (19/113) of subjects developed CRS after step-up dose 2, 10% (11/111) developed CRS after the first full 200 mg dose, and 3.6% (4/110) developed CRS after the second full dose. Recurrent CRS occurred in 20% (23/117) of subjects. The median time to onset of CRS from the end of infusion was 11 (range: -1 to 184) hours after the most recent dose with a median duration of 15 (range: 1 to 76) hours.[2] Infusion-related reactions (IRR) may be clinically indistinguishable from manifestations of CRS. In the subjects who were treated with the recommended step-up dosing regimen and pretreatment medications, the rate of IRR was 9% [11/117 including Grade 2 IRR (4.3%) and Grade 3 IRR (1.7%)].[2]

Labeling instructs healthcare providers to administer pretreatment medications and initiate therapy according to linvoseltamab-gcpt step-up dosing to reduce the incidence and severity of CRS. Healthcare providers should promptly monitor patients for signs and symptoms of CRS after infusion. Labeling also instructs healthcare providers to counsel patients to seek immediate medical attention should signs or symptoms of CRS occur. At the first sign of CRS, healthcare providers should immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care; withhold linvoseltamab-gcpt until CRS resolves and modify the next dose or permanently discontinue linvoseltamab-gcpt based on severity. For IRR, labeling instructs to interrupt or slow the rate of infusion or permanently discontinue linvoseltamab-gcpt based on severity of reaction. Management of CRS to address the safety issues with linvoseltamab-gcpt will be included in Boxed Warning, Warnings and Precautions and the Dosage and Administration section of the label.[2]

Because of the serious risk of CRS, the review team determined a REMS is necessary to ensure the benefits of linvoseltamab-gcpt outweigh this risk.[2] A discussion on the proposed REMS is included in section 7.

5.2. Neurologic Toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):

In the clinical trial, neurologic toxicity occurred in 54% of subjects, with Grade 3 or 4 neurologic toxicity occurring in 8%, at the recommended dose. Neurologic toxicities included ICANS, depressed level of consciousness, encephalopathy, and toxic encephalopathy. The most common clinical signs and symptoms of ICANS are confusion, depressed level of consciousness, and lethargy. ICANS occurred in 8% of subjects who received linvoseltamab-gcpt with the recommended dosing regimen, including Grade 3 events in 2.6%.[g] Most subjects experienced ICANS following step-up dose 1 (5%). Two subjects (1.8%) experienced initial ICANS following step-up dose 2 and one subject developed the first occurrence of ICANS following a subsequent full dose of linvoseltamab-gcpt. Recurrent ICANS occurred in one subject. The median time to onset of ICANS was 1 (range: 1 to 4) day after the most recent dose with a median duration of 2 (range: 1 to 11) days. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

[g] CRS and ICANS were graded based on the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 criteria.

Labeling instructs healthcare providers to monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, Healthcare providers should immediately evaluate the patient; provide supportive therapy and consider further management per current practice guidelines, and withhold linvoseltamab-gcpt until ICANS resolves and modify the next dose or permanently discontinue linvoseltamab-gcpt based on severity. Healthcare providers should counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time. Due to the potential for neurologic toxicity, including ICANS, patients receiving linvoseltamab-gcpt are at risk of confusion and depressed consciousness; labeling also advise patients to refrain from driving, or operating heavy or potentially dangerous machinery, for 48 hours after completion of each of the step-up doses and in the event of new onset of any neurological symptoms, until symptoms resolve. Management of neurologic toxicity including ICANS to address the safety issues with linvoseltamab-gcpt will be included in Boxed Warning, Warnings and Precautions and the Dosage and Administration section of the label.[2]

Because of the serious risk of neurologic toxicity including ICANS, the review team determined a REMS is necessary to ensure the benefits of linvoseltamab-gcpt outweigh this risk.[2] A discussion on the proposed REMS is included in section 7.

5.3. Infections:

In the clinical trial, serious infections, including opportunistic infections, occurred in 42% of subjects, with Grade 3 or 4 infections in 38% and fatal infections in 4%. The most common serious infection reported (≥10%) were pneumonia and sepsis. Two cases of progressive multifocal leukoencephalopathy (PML) occurred in subjects receiving linvoseltamab-gcpt. Labeling instructs healthcare providers to monitor patients for signs and symptoms of infection and immunoglobulin levels prior to and during treatment with linvoseltamab-gcpt and treat appropriately. Healthcare providers should administer prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines, and subcutaneous or intravenous immunoglobulin (IVIG) according to guidelines, including prophylaxis for PJP and herpesviruses. Labeling also instructs healthcare providers to withhold linvoseltamab-gcpt or consider permanent discontinuation of linvoseltamab-gcpt based on severity of the infection.[2]

5.4. Neutropenia:

In the clinical trial, decreased neutrophil count occurred in 62% of subjects with Grade 3 or 4 decreased neutrophil count in 47%. Febrile neutropenia occurred in 8% of subjects. Labeling instructs healthcare providers to monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local guidelines. Healthcare providers should monitor patients with neutropenia for signs of infection and withhold linvoseltamab-gcpt based on severity. [2]

5.5. Hepatotoxicity

In the clinical trial, elevated ALT occurred in 46% of subjects, with Grade 3 or 4 ALT elevation occurring in 6%; elevated AST occurred in 61% of subjects, with Grade 3 or 4 AST elevation occurring in 10% of subjects who received the recommended dose. Grade 3 or 4 total bilirubin elevations occurred in 1.7% of subjects. Liver enzyme elevation can occur with or without concurrent CRS.[2] The Applicant identified

five subjects treated at linvoseltamab-gcpt dose levels ranging from 48 mg to 200 mg who met 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 tumor lysis syndrome (TLS) and sepsis). Per the clinical reviewer, given the identification of compelling alternate diagnoses, the liver function abnormalities in these 5 subjects were found to not meet Hy's law and were determined not to be attributable to drug-induced liver injury (DILI).[31] Labeling instructs healthcare providers to monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated, and withhold linvoseltamab-gcpt or consider permanent discontinuation of linvoseltamab-gcpt based on severity.[2]

5.6. Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal data, linvoseltamab-gcpt can cause fetal harm when administered to a pregnant woman. No animal reproductive or developmental toxicity studies have been conducted with linvoseltamab-gcpt. The proposed label states to advise pregnant women of the potential risk to a fetus. If approved, healthcare providers should advise females of reproductive potential to use effective contraception during treatment with linvoseltamab-gcpt and for 3 months after the last dose.[2]

6. Expected Postmarket Use

If approved, it is expected that linvoseltamab-gcpt will be administered by a healthcare provider in hospital inpatient settings, hospital outpatient settings, and oncology infusion centers. The review team's view is that while multiple myeloma specialists practicing at academic centers may have some experience with the management of CRS and neurotoxicity with the use of CAR T-cell products and bispecific T-cell engagers, community-based oncologists may have limited experience in managing these types of toxicities. Since linvoseltamab-gcpt administration involves a 4-hour infusion for the step-up dose schedule and first 200 mg full dose, linvoseltamab-gcpt will most likely be administered at inpatient settings or hospital-affiliated infusion centers and cancer centers, where patients will likely be monitored. However, the clinical review team has concern that in some cases, linvoseltamab-gcpt might be administered in community-based private oncology practices where patients may be less closely monitored.[1] It is expected that oncologists/hematologists will be the primary prescribers of linvoseltamab-gcpt. Although some prescribers may be familiar with the risks and management of CRS and neurotoxicity including ICANS, there may also be prescribers (primarily those who treat patients in community-based outpatient settings) with limited or no experience in managing CRS and neurologic toxicity including ICANS. As such, some patients might not receive prompt supportive care for CRS or neurologic toxicity if prescribers are not trained and fully aware of the need to monitor for these risks. Until additional evidence is available that shows the prescribing population has generally acceptable knowledge and understanding of the risks and management of CRS and neurotoxicity/ICANS associated with these bispecific antibodies, the review team finds it necessary to ensure all prescribers are trained and aware of the importance of monitoring for these risks and to counsel patients to seek prompt supportive care for CRS and neurotoxicity/ICANS that might occur outside of the treatment setting.[1]

7. Risk Management Activities Proposed by the Applicant

7.1. Review of Applicant's Proposed REMS

The Applicant submitted a complete REMS proposal including a REMS document, REMS materials, and REMS supporting document with the resubmission dated February 7, 2025, amended on June 2, June 20, and June 25, 2025.

7.1.1. REMS Goals

The 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 the signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to Lynozyfic.

Reviewer Comment*: The Applicant's proposed goal for the REMS as submitted on February 7, 2025, was as follows:*

The goal of the Lynozyfic REMS is to mitigate the risks of Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by:

1. *Ensuring prescribers are aware of the importance of monitoring for signs and symptoms of CRS and ICANS in patients exposed to Lynozyfic.*

Initially, the Applicant distinguished CRS and ICANS as serious risks associated with linvoseltamab-gcpt. However, upon review of the clinical trial data and updated labeling, it was determined that linvoseltamab-gcpt, like other previously approved bispecific T-cell engagers such as teclistamab-cqyv, talquetamab-tgvs and elranatamab-bcmm, include the same risks of CRS and neurologic toxicity including ICANS. Since there was a 54% rate of neurologic toxicity and 8% rate of ICANS in the proposed safety population, the Agency's current thinking is to update the labeling with neurologic toxicity including ICANS as one of the major identified safety findings.

7.1.2. Communication Plan

The Applicant proposes to include a Healthcare Provider REMS Letter and a Professional Society REMS Letter, with a REMS Fact Sheet attached, to inform healthcare providers about the Lynozyfic REMS. The letters and Fact Sheet will describe the approved indication, the serious risks of CRS and neurologic toxicity including ICANS, and the importance of monitoring for these risks associated with linvoseltamab-gcpt.

The Healthcare Provider letter targets:

- oncologists
- oncology physician assistants
- oncology nurse practitioners
- hematologists
- oncology nurses

The REMS Letters to Professional Societies targets:

- Advanced Practitioner Society for Hematology and Oncology (APSHO)
- American Geriatrics Society (AGS)
- American Pharmacists Association (APhA)
- American Society of Clinical Oncology (ASCO)
- American Society of Health-System Pharmacists (ASHP)
- American Society of Hematology (ASH)
- American Society for Transplantation and Cellular Therapy (ASTCT)
- Association of VA Hematology/Oncology (AVAHO)
- Eastern Cooperative Oncology Group and American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research group
- HealthTree Foundation
- Hematology Oncology Pharmacy Association (HOPA)
- International Myeloma Foundation (IMF)
- International Myeloma Society (IMS)
- International Society for Experimental Hematology (ISEH)
- Leukemia and Lymphoma Society (LLS)
- Michigan Society of Hematology and Oncology (MSHO)
- Multiple Myeloma Research Foundation (MMRF)
- National Comprehensive Cancer Network (NCCN)
- North American Immuno-Hematology Clinical Education and Research Consortium (NICER Consortium)
- Ohio Hematology Oncology Society (OHOS)
- Oncology Nursing Society (ONS)
- Society for Immunotherapy of Cancer (SITC)
- Society of Hematologic Oncology (SOHO)
- Southwest Oncology Group Cancer Research Network (SWOG CRN).

The Applicant proposes to send the Healthcare Provider REMS letter via email within 30 calendar days of the date linvoseltamab-gcpt is first commercially distributed and again 12 months later. Sending the letter by postal mail and via additional emails will take place depending on whether the emails are undeliverable, unopened, or if the healthcare provider's email address is not available. The Professional Society letter will be disseminated within 30 calendar days of the date linvoseltamab-gcpt is first commercially distributed and again 12 months later with a request that the letter or content be provided to the society's members.

Reviewer Comments:

We agree with the Applicant's proposal to communicate the serious risks of linvoseltamab-gcpt and to inform healthcare professionals that linvoseltamab-gcpt is only available through the REMS.

7.1.3. Elements to Assure Sage Use (ETASU)

The Applicant proposed the following ETASU as part of the REMS requirements:

- ETASU A, Prescriber certification
- ETASU B, Pharmacy and healthcare setting certification

ETASU A: Prescriber Certification

Prior to prescribing the product, the healthcare provider (HCP) must certify in the Lynozyfic REMS. To become certified, the prescriber must review the Prescribing Information, the Prescriber Training Program, and the Adverse Reaction Management Guide. The HCP must then successfully complete the Knowledge Assessment and enroll in the REMS by completing the Prescriber Enrollment Form and submitting these to the REMS. As part of prescriber certification, the prescriber must agree to counsel the patient on how to recognize and respond to signs and symptoms of CRS and neurologic toxicity including ICANS, and the need to report all symptoms suggestive of CRS and neurotoxicity/ICANS to their HCP or emergency room provider immediately. The prescriber must also agree to complete and provide the Patient Wallet Card to the patient, and must report CRS and neurologic toxicity events including ICANS to the REMS program.

Reviewer comments:

The review team agree that prescriber training and certification is necessary to ensure the benefits of linvoseltamab-gcpt outweigh the risks. Please see the review written by this author that outlines the decision-making process for the need, and further alignment for the REMS.[1]

We agree with the requirements for HCP certification listed above to support the goal and objectives of the REMS. During the course of the review, the following requirements proposed by the Applicant for patients to remain in close proximity to the healthcare setting were removed from the REMS and prescribing information. The Prescribing Information was changed to recommend that patients should be hospitalized for 24 hours after administration of the first and second step-up dose. Although this specific aspect of counseling is not a REMS requirement, it is clinically important and therefore is included in the REMS materials. Additionally, the REMS requirements were clarified to ensure patient counseling occurs before the "first step-up dose," because patients should be informed prior to initiation of treatment about how to recognize and respond to signs and symptoms of the risks of CRS and neurotoxicity and the need to report such signs and symptoms to their healthcare provider (HCP) or emergency room provider.

ETASU B: Pharmacy and Healthcare setting Certification

The Applicant proposed that linvoseltamab-gcpt is dispensed only from certified pharmacies and healthcare settings. Pharmacies and healthcare settings become certified by designating an authorized representative to complete the certification process and oversee implementation and compliance with the REMS program. To become certified, the authorized representative must review the Pharmacy and Healthcare Setting Training Program and enroll in the REMS by completing and submitting the Pharmacy and Healthcare Setting Enrollment Form to the REMS program. In addition, the authorized representative must train all relevant staff involved in dispensing linvoseltamab-gcpt on the REMS requirements using the Pharmacy and Healthcare Setting Training Program. Certified pharmacies and healthcare settings verify that prescribers are certified by obtaining a REMS Dispense Authorization (RDA) prior to dispensing linvoseltamab-gcpt.

Reviewer's comments:

Pharmacy and healthcare setting certification is necessary to ensure the prescription was written by a certified HCP. To reduce burden, the pharmacy or healthcare setting must obtain a REMS dispense

authorization (RDA) for the first prescription for each patient to confirm the prescriber is certified in the REMS. For all subsequent prescriptions, the pharmacy or healthcare setting may verify the prescriber is certified through processes and procedures established as a requirement in the REMS such as checking the database of certified prescribers. Further description of these processes are in the communication sent to the applicant on June 16, 2025.[33]

7.1.4. Implementation System

For successful implementation of the REMS, the Applicant proposes to maintain a REMS Coordinating Center, REMS Website, and validated secure database of all REMS participants to support patients, prescribers, healthcare providers, pharmacies and healthcare settings, and wholesaler-distributors to interface with the REMS. The Applicant will notify participants of successful enrollment in the REMS within one business day. The Applicant will ensure linvoseltamab-gcpt is only distributed to certified pharmacies or healthcare settings by wholesaler-distributors who are compliant with the REMS requirements. To ensure compliance, the Applicant will ensure processes and procedures are in place to maintain adequate records that demonstrate the REMS requirements are being met through audits of certified pharmacies/healthcare settings and wholesaler-distributors.

Reviewer's comments:

We agree with the Applicant's proposal to include an implementation system and with the requirements listed above. During the course of the review, the Agency provided edits and comments indicating that changes were necessary to the REMS document related to the authorization for dispensing.[34] *The Applicant's original proposal stated that the Applicant would authorize dispensing based on verification that the prescriber is certified. However, to reduce burden, the Agency recommended pharmacies and healthcare settings would need to obtain authorization only needed for the first prescription for each patient to confirm the prescriber is certified in the REMS. For all subsequent prescriptions, the pharmacy or healthcare setting may verify the prescriber is certified through processes and procedures established as a requirement in the REMS to align with the pharmacy requirements.*[35]

The Applicant also clarified that Wholesalers-Distributors will be distributing the drug only to the certified pharmacies and healthcare settings and certified pharmacies and healthcare settings are allowed to stock the drug; this proposal is acceptable.

Regarding audits, the Applicant's original proposal for the requirement for auditing was (b) (4) *certified pharmacies and healthcare settings,* (b) (4) *The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) disagreed with the audit proposal and on June 16, 2025, informed the Applicant that additional audits are necessary to ensure certified pharmacies and healthcare settings comply with the REMS requirements, and to inform assessment of the REMS. The Applicant was also informed that audits of all wholesalers-distributors are necessary to comply with the REMS requirements, and to inform assessment of the REMS. Refer to DMAMES's memo dated June 26, 2025, for additional details.*[36]

In their response on June 25, 2025, the Applicant revised the audit requirement to align with the Agency's recommendation, as follows:

> *17. Audit all certified pharmacies and healthcare settings no later than 180 calendar days after the pharmacy or healthcare setting receives their first shipment of Lynozyfic and*

annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

18. *Audit all wholesalers-distributors that have distributed Lynozyfic no later than 180 calendar days of being authorized to distribute Lynozyfic and annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.*

This proposal is acceptable. The Agency will recommend the Applicant submit their audit plan and noncompliance plan within 60 days post approval as a REMS Methodology for Agency review.

7.1.5. Timetable for Submission of Assessment for the REMS

The Applicant must submit REMS Assessments 12 months from the date of the initial approval of the REMS (MM/DD/YYYY) and annually thereafter.

Reviewer's comments:

The Applicant's original proposal was that the Applicant must submit REMS Assessments to the FDA annually from the date of the initial approval of the REMS. On June 16, 2025, the Agency informed the Applicant that they must submit REMS Assessments at 6 months and 18 months from the date of the initial approval of the REMS, and every 12 months thereafter from the date of the 18 month submission, to align with recent REMS timetables. Refer to DMAMES's memo dated June 26, 2025, for additional details.[36] *The Applicant responded on June 17, 2025, requesting to keep their original proposal to submit REMS Assessments annually and provided supporting rationale. The Agency agreed with the Applicant's proposal for revising the timetable to annually in our June 17, 2025, response.*

7.1.6. REMS Materials & Key Risk Messages

The Applicant included the following materials as part of the REMS submission:

- Prescriber Enrollment Form: mechanism for the prescriber to enroll and become certified in the REMS, and for the prescriber to agree to comply with all REMS requirements.

- Pharmacy and Healthcare Setting Enrollment Form: mechanism for the authorized representative of the pharmacy or healthcare setting to enroll and have the pharmacy or healthcare setting become certified in the REMS, and for the authorized representative to agree to their responsibilities required by the REMS.

- Prescriber Training Program: informs prescribers about the serious risks associated with linvoseltamab-gcpt and the management of those risks, and the REMS requirements and responsibilities of the prescriber.

- Adverse Reaction Management Guide: provides an accessible summary for prescribers on how to manage the risks of CRS and neurologic toxicity including ICANS associated with linvoseltamab-gcpt.

- Knowledge Assessment: successful completion is a prerequisite for prescriber certification and will help to ensure adequate understanding of the serious risks and key REMS requirements.

- Patient Wallet Card: informs patients about the signs and symptoms of the serious risks associated with linvoseltamab-gcpt, when to seek immediate care, and instructs the patient to present the wallet card to any healthcare professional involved in their care and if they go to the emergency room.

- Training for Pharmacies and Healthcare Settings: informs pharmacy and healthcare setting authorized representatives and staff that dispense of the serious risks associated with linvoseltamab-gcpt, the REMS requirements, and the responsibilities of the pharmacy/healthcare setting and authorized representative.

- Dear Healthcare Provider Letter: informs healthcare providers about the risks of CRS and neurologic toxicity associated with linvoseltamab-gcpt and provides information about the REMS.

- Dear Professional Society Letter: requests that healthcare providers who are members of these societies are informed by the societies of the risks of CRS and neurologic toxicity associated with linvoseltamab-gcpt and provides information about the REMS.

- REMS Fact Sheet: provides an overview of the REMS, the serious risks and management of those risks, and key requirements of the REMS for prescribers, pharmacies and healthcare settings, and wholesaler-distributors.

- REMS Website: serves as a source of information for participants. It allows prescribers, pharmacies and healthcare settings to enroll in the REMS. Healthcare providers will be able to certify in the REMS by completing the prescriber training and submitting the Knowledge Assessment. Authorized representatives for pharmacies and healthcare settings will be able complete the pharmacy/healthcare setting training, receive certification, and manage staff privileges associated with the REMS. Pharmacies and healthcare settings will also be able to obtain authorization to dispense online. The REMS materials, Prescribing Information, and Medication Guide will be available on the website for review and download. The website will also include a REMS participant locator that identifies certified pharmacies/healthcare settings.

Reviewer Comments:

We agree with the proposed REMS materials. These REMS materials will provide education and support the risk messages of the REMS. The REMS materials align with the label. The Applicant also proposed to include non-English versions of the REMS materials and submitted a certification of translation demonstrating that the non-English materials are accurate, identical in content, and the translation is correct as a REMS correspondence.[34]

To maintain consistency among risk messages for bispecific T-cell antibodies that are approved with a REMS, the following key risk messages for linvoseltamab-gcpt are listed below:

Key Risk Messages for Prescribers

- *CRS, including serious life-threatening reactions, can occur in patients receiving Lynozyfic. Initiate treatment with Lynozyfic step-up doing schedule to reduce risk of CRS. Closely monitor patients for signs or symptoms of CRS during treatment. Withhold Lynozyfic until CRS resolves or permanently discontinue based on severity.*

- *Neurologic toxicity, including ICANS and serious life-threatening reactions can occur in patients receiving Lynozyfic. Monitor patients for signs or symptoms of neurologic toxicity including ICANS, during treatment. Withhold Lynozyfic until neurologic toxicity resolves or permanently discontinue based on severity.*

- *Instruct the patient that they should be hospitalized for 24 hours after administration of the first step-up dose, and for 24 hours after administration of the second step up dose.*

- *Before treatment initiation, complete and provide the patient/caregiver with a Patient Wallet Card.*

- *Counsel the patient/caregiver on how to recognize and respond to signs and symptoms of CRS and neurologic toxicity, including ICANS, using the Patient Wallet Card, and having the card at all times.*

Key Risk Messages for Patients

- *There is a risk of CRS and neurologic problems with Lynozyfic.*

- *Carry the Patient Wallet Card with you at all times and show the card to any healthcare professional that treats you.*

- *If you are having any symptoms listed on the patient wallet card, call your doctor, or seek emergency medical attention right away.*

Key Risk Messages for Pharmacies and Healthcare Settings

- *All staff must be trained on dispensing Lynozyfic using the Pharmacy and Healthcare Setting Training Program.*

- *Before dispensing Lynozyfic, staff must verify prescriber is certified in the Lynozyfic REMS.*

7.1.7. REMS Supporting Document

The REMS supporting document includes background information on the benefits and risks of linvoseltamab-gcpt and the Applicant's rationale and goal for the REMS. The supporting document also contains information on the requirements of the REMS and the responsibilities of participants as well as how the REMS will be implemented and assessed.

Reviewer's Comments:

During the course of the review, the Applicant adequately responded to the Agency's comments and updated the supporting document accordingly to align with the REMS requirements. The Applicant added the post login screenshots to the Table of Contents as an appendix to the Supporting Document. Additionally, the supporting document clarified that if the product is administered at a physician office practice, a Certified Prescribers cannot be designated as an Authorized Representative for a certified Pharmacy or Healthcare setting. The Applicant clarified that product distribution to certified pharmacies and healthcare settings is not tied to a specific patient and therefore, may be stocked on shelves without needing to be associated with a patient for dispense.

Key Performance Indicators (KPIs) are the primary metrics or measures that will be used to evaluate the REMS and are essential in determining if the REMS is functioning as designed and meeting its goal and objective. The Applicant proposed in their original submission two KPIs; a process indicator, one to evaluate REMS Operations and a second, an outcome indicator, to evaluate REMS Outcomes. Following are the Applicant proposed KPIs:

a) *REMS Operations: 99.9% of dispenses were authorized by the REMS prior to dispense. REMS authorization for dispense requires both the prescriber and the pharmacy and healthcare setting be certified*

b) *REMS Knowledge: ≥ 80% of prescriber Knowledge survey respondents demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and ICANS*

The Applicant amended one of the KPIs, the REMS Operations on June 2, 2025, by changing from 99.9% to (b) (4) *% of dispenses were authorized by the REMS prior to dispense of the first prescription written by the prescriber. The Agency sent a response on June 16, 2025, that the Agency disagrees and expect to see 99.9% of dispenses were authorized by the REMS prior to dispense of the first prescription written by the prescriber. The Agency also requested the title of Knowledge, Attitude, and Behavior (KAB) surveys to be updated to knowledge survey. The Applicant included a brief description of what actions will be taken if the KPI thresholds are not met, such as a root cause analysis and evaluation of barriers to compliance.*

7.1.8. REMS Assessment Plan

The REMS Assessment Plan was submitted on February 7, 2025, and amended on June 2, June 20 and June 25, 2025. DMAMES provided feedback with suggested changes via information requests sent on June 16, 2025, and June 24, 2025. In response, the Applicant submitted an updated Assessment Plan on June 25, 2025.

Reviewer's Comments:

The Applicant accepted the comments sent by DMAMES via information requests sent on June 16, 2025 and June 24, 2025. The REMS Assessment Plan submitted by the Applicant in their revised REMS Supporting Document on June 25, 2025, did not include any additional changes, and is acceptable. No further revisions are needed at this time. A copy of the agreed upon Lynozyfic REMS Assessment Plan is in Appendix 10.1 and will be included in the Approval Letter. Refer to DMAMES REMS Assessment Plan Review Memo.[36]

7.1.9. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on May 14, 2025, to provide feedback on the content of the REMS materials. The OPDP review was completed by Valerie Guerrier on May 28, 2025.

OPDP recommended to align the language in the REMS materials with the final approved Prescribing Information (PI) and Medication Guide (MG) to accurately reflect the risk information and minimize promotional content. DRM incorporated all recommendations into the REMS materials.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the clinical reviewer stated that linvoseltamab-gcpt shows clinically meaningful benefit and recommends approval 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. Linvoseltamab-gcpt appeared efficacious in its primary outcome of ORR and secondary outcomes of DOR. The clinical reviewer stated that in patients with RRMM who have received 4 or more prior lines of therapy, linvoseltamab-gcpt has a favorable benefit-risk balance; 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.[2,31,32]

The most serious risks associated with linvoseltamab-gcpt are CRS and neurologic toxicity including ICANS. Risk mitigation activities during the clinical study included step-up doses of linvoseltamab-gcpt, initiation of treatment in the inpatient setting, and premedication for CRS for the step-up doses and first full treatment dose.

Because of IV route of administration, the likelihood of patients starting linvoseltamab-gcpt outside of a monitored setting is low, therefore, DRM did not initially agree that a REMS was necessary to ensure the benefits outweigh the risks associated with linvoseltamab-gcpt and considered labeling to be sufficient. Other bispecific T-cell engagers for RRMM approved with a REMS (Elrexfio, Talvey, and Tecvayli) are supplied in subcutaneous formulations and allow "Off-the-Shelf" administration. Given the ease of administration for these products, concerning rates of CRS and neurologic toxicities, and the likelihood of their use in outpatient clinic settings where healthcare providers may be less familiar with the risks and risk mitigation, these products require a REMS to ensure healthcare providers were aware of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicities.[1] Please see Table 1 and Table 2 in the Appendix 10.2 for comparisons of product characteristics and the risks and mitigation of CRS and neurotoxicity/ICANS for the four products.

DHM2's view is that while multiple myeloma specialists practicing at academic centers may have some experience with the management of CRS and neurotoxicity with the use of CAR T-cell products and other bispecific T-cell engagers, community-based oncologists may have limited experience in managing these types of toxicities. Since linvoseltamab-gcpt administration involves a 4-hour infusion for the step-up dose schedule and first 200 mg full dose, linvoseltamab-gcpt will most likely be administered at hospital-affiliated infusion centers and cancer centers, where patients will likely be monitored. However, in some cases, linvoseltamab-gcpt might be administered in private oncology practices where patients may be less closely monitored.[1]

A REMS Oversight Committee (ROC) meeting[h] was held on May 16, 2024, to seek advice on if a REMS is necessary to ensure the benefits outweigh the risks of CRS and neurologic toxicity including ICANS associated with linvoseltamab-gcpt. The ROC vote was 2 "yes" and 2 "no.[37,1] After further discussion with DHM2, DRM agreed with DHM2 to require a REMS with ETASU for linvoseltamab-gcpt that consists of prescriber certification and pharmacy/healthcare setting certification to ensure the benefits outweigh the risks of CRS and neurologic toxicity including ICANS and note that this recommendation is consistent for the bispecific T-cell engagers indicated for RRMM.[1]

The minimum necessary REMS elements required include the following:

- Communication plan to target healthcare providers who are likely to prescribe and care for patients treated with linvoseltamab-gcpt
- Prescriber certification to ensure prescribers are aware of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to linvoseltamab-gcpt
- Pharmacy/Healthcare setting certification to ensure prescribers are certified prior to dispensing linvoseltamab-gcpt

DRM concludes that based on the review of the proposed REMS received on June 25, 2025, the REMS will support actions that will mitigate the risks of CRS and neurologic toxicity, including ICANS. The REMS will ensure that all prescribers are trained on these risks and aware of the importance of monitoring patients to support safe use of the product.

REMS Assessment Reports will be submitted annually from the date of the initial approval of the REMS. The REMS Assessment Plan includes metrics from the following categories: Outreach and Communication Plan, Implementation and Operations, Knowledge, Health Outcomes and/or Surrogates of Health Outcomes, and Overall Assessment of REMS Effectiveness. The totality of the REMS Assessment data will be used to determine whether the REMS is being successfully implemented and functioning as intended.

KPIs are used for evaluating whether the Lynozyfic REMS is functioning as intended and achieving its goal of mitigating the risks of CRS and neurologic toxicity, including ICANS. KPIs have been established to assess the success of the program and to help determine if modifications to the REMS are warranted.

Two types of KPIs will be used:

- Process Indicator – This will assess REMS operations by measuring the number and percentage of first prescriptions dispensed that were authorized by the REMS prior to dispensing, out of all first dispenses. REMS authorization requires certification of both the prescriber and the dispensing pharmacy or healthcare setting. A target threshold of 99.9% has been established a priori for this measure.

[h] As per the 21st Century Review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Office of New Drugs, Surveillance and Epidemiology, and the Office of Regulatory Policy.

- Outcome Indicator – This will evaluate the REMS objective of ensuring prescriber awareness of the need to monitor patients for serious risks. It will be measured through prescriber knowledge surveys. The key outcome indicator is the proportion of prescriber survey respondents who demonstrate knowledge of the importance of monitoring for signs and symptoms of CRS and neurologic toxicity, including ICANS. A target threshold of ≥80% has been set a priori.

KPI thresholds were developed based on experience with similar REMS programs and are intended to ensure that the REMS is operating effectively and achieving its risk mitigation goals.

Health outcome data will include an analysis of all reported cases of CRS and neurologic toxicity, including ICANS, stratified by grade and severity. This analysis of reported adverse events is intended to provide insight into whether the associated risks were mitigated, whether step-up dosing was initiated in an inpatient setting, and whether pre-medication was administered as recommended. Additionally, these data may inform whether patients who experienced an adverse event of interest were monitored in accordance with the guidance outlined in the Prescribing Information. Furthermore, the REMS assessment plan has been designed to incorporate data collected by the REMS Coordinating Center to evaluate whether the REMS program resulted in any unintended burdens on the healthcare system or led to patient access issues.

We anticipate that following education through the REMS program, prescribers and other healthcare providers will be more aware of the risks of CRS and neurologic toxicity including ICANS and will follow the monitoring recommendations in labeling. Based on the review of the proposed REMS received on June 25, 2025, the REMS will support actions to mitigate the risks of CRS and neurologic toxicity including ICANS associated with linvoseltamab-gcpt. The REMS ensures all prescribers are educated to support awareness of the risks and supports safe use of these products.

9. Conclusion & Recommendations

The risk of CRS and neurologic toxicity, including ICANS are serious and potentially life threatening. Therefore, it is necessary for prescribers, pharmacies, health care providers, and patients to be aware of and understand these risks. Based on the incidence of CRS and neurologic toxicity and the potential for broader use of this product in community-based oncology practices, DRM and DHM2 agree that a REMS consisting of a communication plan, prescriber certification, and pharmacy/healthcare setting certification is necessary to ensure that the benefits outweigh the risks of CRS and neurotoxicity including ICANS. The REMS will also include an implementation system and timetable for submission of assessments.

DRM finds the Applicant's amended proposed REMS received on June 25, 2025, to be acceptable for approval, and appended to this review.

10. Appendices

10.1. REMS Assessment Plan

5 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

10.2. Linvoseltamab-gcpt and Other Approved Bisepecific T-cell Engagers Comparison Tables

Table 1: Comparison of CRS incidence of approved bispecific t-cell engagers:

	Linvoseltamab-gcpt %	**Elrexfio (elranatamab-bcmm) %**	**Talvey (talquetamab-tgvs) %**	**Tecvayli (teclistamab-cqyv) %**
	IV	**SQ**	**SQ**	**SQ**
Indication	R/R MM	R/R MM	R/R MM	R/R MM
Major Risk	CRS, NT/ICANS	CRS, NT/ICANS	CRS, NT/ICANS	CRS, NT/ICANS
Overall CRS incidence	46 (54/117)	58	76	72
Grade 1	35 (41/117)	43	57	50
Grade 2	10 (12/117)	14	17	21
Grade 3	0.9 (1/117)	0.5	1.5	0.6
Grade 4	0	0		0
Grade 5	0	0		0 (1 case of fatal MODS, cannot rule out CRS)
Median time to onset of CRS	11 hr (range 1-184 hrs) (all Gr CRS) 5.76 (-1.1 -104.8hrs) hours (Gr ≥3 CRS)	2 (1 to 9) days	27 (range: 0.1 to 167) hours	2 (1 to 6) days

Occurrence of CRS	38% (45/117) after initial (5 mg) dose, 17% (19/113) after intermediate (25 mg) dose, 10% (11/111) after first full dose (200mg), 3.6% (4/110) after second full dose, 2.0% after third full dose or beyond. One Gr3 case after first step-up dose and NO cases of Gr ≥3 CRS with subsequent doses. 3 pts experienced Gr 2 after step-up doses Recurrent CRS (20% (23/117)	first step-up dose (43%) the second step-up dose (19%), 7% after the first treatment dose 1.6% after a subsequent dose	30% with the first 0.4 mg/kg 12% with the first 0.8 mg/kg	step-up dose 1 (42%), step-up dose 2 (35%), the initial treatment dose (24%)
Mean Duration	15 (1-76)hrs	2 (1 to 19) days	17 (range: 0 to 622) hours	2 (1 to 9) days
Anti-IL-6 therapy for CRS (tocilizumab)	41% (22/54) Grade 1: 26% Grade 2: 83% Grade 3: 100%	36% Grade 1: 22% Grade 2: 66% Grade 3: 100%	39.7% Grade 1: 35% Grade 2: 73%	36% Grade 1: 21% Grade 2: 88% Grade 3s: 100%
Risk Mitigation	REMS Submitted	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**

Table 2: Comparison of neurologic toxicity including ICANS incidence of approved bispecific t-cell engagers:

	Linvoseltamab-gcpt %	**Elrexfio (elranatamab-bcmm) %**	**Talvey (talquetamab-tgvs) %**	**Tecvayli (teclistamab-cqyv) %**
	IV	**SQ**	**SQ**	**SQ**
Overall NT/ICANS incidence	54 (NT) 8 (9/117) (ICANS)	59 (NT) 3.3 (ICANS)	55 (NT) 9 (ICANS)	57 (NT) 6 (ICANS)
Grade	NT/ICANS NT : 54% Grade 3-4: 8 ICANS Grade 1: 2.6% Grade 2: 2.6% Grade 3: 2.6% (3/117) Gr4 0 Gr5 0	NT NT: 59% Grade 3-4 – 7% ICANS G1 0.5 G2 1.6 G3 1.1 G4 0 G5 0	NT/ICANS Grade 3-4 - 6	NT Grade ≥3: 2.4
Median time to onset of NT/ICANS	1 (range 1-4) day	ICANS 3 (1 to 4) days	2.5 (range: 1 to 16) days	ICANS 4 (2-8) days

Occurrence of ICANS	5% (6/117) after initial (5 mg) dose, 1.8% (2/113) after intermediate (25 mg) dose, 0% after first thru 6 full doses, 1% (1/99) patient after 7th full dose,	Step-up dose (2.7%), 1 (0.5%) patient had ICANS after the second step-up dose and 1 (0.5%) patient had ICANS after subsequent dose	step-up dose 1 (3%), step-up dose 2 (3%), step-up dose 3 of the biweekly dosing schedule (1.8%), or the initial treatment dose of the weekly dosing schedule (2.6%) (N=156) or the biweekly dosing schedule (3.7%)	step-up dose 1 (1.2%), step-up dose 2 (0.6%), the initial treatment dose (1.8%)
Mean Duration	2 (range 1-11) days	2 (1 to 18) days	2 (range: 1 to 22) days	ICANS 3 (1-20) days
Risk Mitigation	REMS Submitted	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**

11. References

[1] Olickal T. Defer comment on DRM evaluation of the need for a REMS for linvoseltamab-xxxx, BLA 761400, dated August 14, 2024. [Reference ID: 5430309]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed March 11, 2025.

[2] Draft Prescribing Information for linvoseltamab-xxxx as currently edited by the FDA, last updated May 30, 2025.

[3] BLA 761400 Complete Response, dated August 20, 2024. [Reference ID: 5432808]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed April 16, 2025.

[4] Regeneron Pharmaceuticals, Inc. Summary of Clinical Safety of telisotuzumab vedotin-gcpt, BLA 761400, dated December 22, 2023.

[5] Marino S, Petrusca DN, Roodman GD. Therapeutic targets in myeloma bone disease. *Br J Pharmacol.* 2019.

[6] Smith L, McCourt O, Henrich M, et al. Multiple myeloma and physical activity: a scoping review. *BMJ Open.* 2015;5(11):e009576.

[7] *National Institutes of Health* (*NIH*). The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI). https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed July 19, 2020.

[8] Kvam AK, Waage A. Health-related quality of life in patients with multiple myeloma--does it matter? *Haematologica.* 2015;100(6):704-705.

[9] Zweegman S, Engelhardt M, Larocca A. Elderly patients with multiple myeloma: towards a frailty approach? *Curr Opin Oncol.* 2017;29(5):315-321.

[10] Dolloff NG, Talamo G. Targeted therapy of multiple myeloma. *Adv Exp Med Biol.* 2013;779:197-221.

[11] Thalomid. Prescribing Information (last updated 06/2019).

[12] Revlimid. Prescribing Information (last updated 10/2019).

[13] Pomalyst. Prescribing Information (last updated 10/2019).

[14] Velcade. Prescribing Information (last updated 04/2019).

[15] Kyprolis. Prescribing Information (last updated 10/2019).

[16] Ninlaro. Prescribing Information (last updated 11/2016).

[17] Darzalex. Prescribing Information (last updated 09/2019).

[18] Empliciti. Prescribing Information (last updated 10/2019).

[19] NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma. Version 3 2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. 2019 June 19; accesses: July 19, 2020.

[20] Varga C, Laubach JP, Anderson KC, Richardson PG. Investigational agents in immunotherapy: a new horizon for the treatment of multiple myeloma. *British journal of haematology.* 2018;181(4):433-446.

[21] Xpovio. Prescribing Information (last updated 6/2020).

[22] Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. *N Engl J Med.* 2019;381(8):727-738.

[23] Combined FDA and Applicant ODAC Briefing Document, The Oncologic Drugs Advisory Committee (ODAC). July 14, 2020; https://www.fda.gov/media/139926/download

[24] Abecma. Prescribing Information (last updated 3/2021).

[25] Carvykti. Prescribing Information (last updated 3/2022).

[26] Tecvayli. Prescribing Information (last updated 5/2024).

[27] Talvey. Prescribing Information (last updated 8/2023).

[28] Elrexfio. Prescribing Information (last updated 8/2023).

[29] Korneev KV, Atretkhany KN, Drutskaya MS, Grivennikov SI, Kuprash DV, Nedospasov SA. TLR-signaling and proinflammatory cytokines as drivers of tumorigenesis. *Cytokine.* 2017;89:127-135.

[30] Mikhael J. Treatment Options for Triple-class Refractory Multiple Myeloma. *Clin Lymphoma Myeloma Leuk.* 2020;20(1):1-7.

[31] Division of Hematology Malignancies 2 (DHM2) Assessment Aid for linvoseltamab-gcpt, BLA 761400, dated August 20, 2024. [Reference ID: 5432800]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed May 9, 2025.

[32] Division of Hematology Malignancies 2 (DHM2) Multi-disciplinary Review and Evaluation (draft) for Re-submission- class 2 linvoseltamab-gcpt, BLA 761400, dated May 30, 2025.

[33] Olickal T. DRM Interim Review of proposed REMS for linvoseltamab-xxxx, BLA 761400, dated June 16, 2025. [Reference ID: 5609107]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 16, 2025.

[34] COR-BLAIR-23 (Labeling Discussion Comments) for linvoseltamab-gcpt, BLA 761400, dated May 16, 2025. [Reference ID: 5592664]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 3, 2025.

[35] Email from DHM2 to Regeneron Pharmaceuticals, Inc. for linvoseltamab-gcpt, BLA 761400, dated June 16, 2025. [Reference ID: 5609228]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 16, 2025.

[36] Kiruthi W, Bergquist B, Crew P. REMS Assessment Plan Review Memo BLA 761400, dated June 26, 2025. [Reference ID: 5615218]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 26, 2025.

[37] REMS Oversight Committee (ROC) Meeting Minutes: Lynozyfic (linvoseltamab-xxxx), BLA 761400. June 16, 2024.

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NAOMI S BOSTON
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LAURA A ZENDEL
06/30/2025 06:31:00 PM

REMS Assessment Plan Review MEMO

Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*****This document may contain information that cannot be released to the public*****

Application Type	BLA
Application Number	761400
Task Tracking Tool Number	2025-12582
Submission Type/Number	Original-1/83
Submission Date	February 7, 2025
Reviewer	Wambui Kiruthi, PharmD, MPH
Team Lead	Barbara Bergquist, PharmD
Associate Director	Page Crew, PharmD, MPH, BCPS
Review Completion Date	June 26, 2025
Non-Proprietary Name	linvoseltamab-gcpt
Proprietary Name	Lynozyfic
Subject	Review of Lynozyfic Risk Evaluation and Mitigation Strategies (REMS) Assessment Plan Memo
Applicant	Regeneron Pharmaceuticals, Inc.

Introduction

This memo is in reference to the Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan for the proposed Lynozyfic REMS (hereafter, Lynozyfic REMS). Refer to the June 16, 2025[a] Agency review for additional background information.

Background and Discussion

On December 22, 2023 the Applicant submitted an original Biologics License Application (BLA) for linvoseltamab-gcpt with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) The Applicant proposed a REMS that consists of communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of linvoseltamab-gcpt outweigh the risk(s) of Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

On August 20, 2024 the Division of Hematology Malignancies 2 (DHM2) issued a Complete Response (CR) letter due to the deficiencies in facility inspection.[c]

On January 10, 2025 the Applicant resubmitted the BLA 761400 for Lynozyfic (linvoseltamab-gcpt) with the same proposed indication to the Agency.[d]

On February 7, 2025 the Applicant submitted an amended submission for BLA 761400, which included the proposed REMS Document and related REMS Materials that were comparable to similar approved products in the drug class.[e] The submission included a proposed REMS Assessment Plan, included within the REMS Supporting Document.

On June 2, 2025 the Applicant submitted an amended submission for BLA 761400 in response to the Agency Information Request dated May 16, 2025. The submission included a revised REMS Document and related REMS Materials and REMS Assessment Plan, included within the REMS Supporting Document.[f]

Review of the REMS Assessment Plan, Audit Requirements, and Timetable for Submission of Assessments

The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed the proposed February 7, 2025 and June 2, 2025 REMS Assessment Plans, Timetable for Submission of

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[a] June 16, 2025, Division of Risk Management (DRM) REMS Review, available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807c2614

[b] December 22, 2023 Original BLA 761400 submission cover letter available at: \\CDSESUB1\EVSPROD\bla761400\0001\m1\us\12-cover-letters\cover.pdf

[c] BLA 761400 Complete Response, dated August 20, 2024. [Reference ID: 5432808]. Available from: Food and Drug Administration (FDA), Document Archiving, Reporting, and Regulatory Tracking System (DARRTS). Accessed June 25, 2025. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80762bd7

[d] January 10, 2025 BLA 761400 resubmission following complete response cover letter available at: \\CDSESUB1\EVSPROD\bla761400\0051\m1\us\12-cover-letters\cover.pdf

[e] February 7, 2025 BLA 761400 amended submission including REMS available at: \\CDSESUB1\EVSPROD\bla761400\0055\m1\us\

[f] June 2, 2025 BLA 761400 amended submission available at: \\CDSESUB1\EVSPROD\bla761400\0066\m1\us\

Assessment for the REMS and the REMS Document audit language, and comments were sent to the Applicant in the June 16, 2025[g] Information Request (IR).

In the June 16, 2025 IR DMAMES included a redlined REMS Assessment plan with comments, along with proposed revisions for the timetable for submission of assessments to be revised to:

> *"Regeneron Pharmaceuticals, Inc. must submit REMS Assessments at 6 months and 18 months from the date of the initial approval of the REMS (MM/DD/YYYY), and every 12 months thereafter from the date of the 18 month submission. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Regeneron Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date."*

And for the audit language to be aligned to REMS with similar risks, and included in the REMS Document as:

> *"17. Audit all certified pharmacies and healthcare settings no later than 180 calendar days after the pharmacy or healthcare setting receives their first shipment of Lynozyfic and annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.*
>
> *18. Audit all wholesalers-distributors that have distributed Lynozyfic no later than 180 calendar days of being authorized to distribute Lynozyfic and annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements."*

On June 17, 2025, the Applicant sent an email correspondence to the Agency with clarification and two questions regarding the incorporation of the REMS Dispensing Authorization (RDA) process into the REMS materials and a proposal to keep their original proposal for the Timetable for Submission of Assessments. Division of Risk Management (DRM) responded to the RDA related question and DMAMES responded to the timetable related question stating: "*We agree with your proposal for the REMS Assessment Timetable to be annually from the date of initial approval of the REMS (MM/DD/YYYY). Revise section IV. titled REMS Assessment Timetable in your REMS Document and revise where applicable in the REMS Supporting Document (including your REMS Assessment Plan) to reflect the change in the timetable for submission of assessments. Include the clean and track change versions in your resubmission for Agency review*."

On June 20, 2025[h], the Applicant submitted an amended submission for BLA 761400 in response to the Agency Information Request dated June 16, 2025 and the June 17, 2025 email correspondence containing a revised timetable to submit REMS Assessments annually from the date of the initial approval of the REMS, and with audit requirements revised as indicated above. Both revisions are acceptable.

DMAMES also reviewed the proposed June 20, 2025 submission including the REMS Assessment Plan and provided additional REMS Assessment Plan comments to the Applicant in the June 24, 2025[i]

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[g]June 16, 2025 Agency Information Request available at:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807c25ec
[h]June 20, 2025 Applicant Submission in Response to June 16, 2025 IR. Available at:
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[i]June 24, 2025 Agency Information Request. Available at:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807c54af

Information Request. The Agency provided additional comments for resubmission clarification in three additional email correspondences also dated June 24, 2025[jkl].

Most recently, on June 25, 2025[m] the Applicant submitted a revised REMS Supporting Document for BLA 761400 in response to the Agency Information Request dated June 24, 2025 which included the proposed revision to the Assessment Plan, which aligns with the Agency's recommendations. This REMS Assessment Plan is acceptable (see Appendix A).

Conclusions and Recommendations

The Applicant accepted the revisions of the proposed Lynozyfic REMS Assessment Plan, from the Agency's Information Requests dated June 16, 2025 and June 24, 2025. We find the REMS Assessment Plan submitted by the Applicant in their amended REMS Supporting Document on June 25, 2025, to be acceptable. We also find the REMS Document audit language and the timetable for submission of assessments to be acceptable. No further revisions or comments are needed at this time from DMAMES. A copy of the agreed upon Lynozyfic REMS Assessment Plan is appended to this memo and will be included in the Letter after an action is taken. The letter will also contain a recommendation for the Applicant to submit their REMS Assessment Methodology to the Agency for review.

[j] June 24, 2025 Agency Correspondence. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807c59bf

[k] June 24, 2025 Agency Correspondence. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807c5e03

[l] June 24, 2025 Agency Correspondence. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807c5e1d

[m] June 25, 2025 Applicant Submission in Response to June 24, 2025 Information Request. Available at: \\CDSESUB1\evsprod\BLA761400\0072

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761400
PDUFA Goal Date	July 10, 2025
Nexus TTT#	2024-7648; 2024-7650
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D. Kate Heinrich Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, Pharm.D.
Acting Division Director	Laura Zendel, Pharm.D.
Review Completion Date	June 16, 2024
Subject	Interim Review of proposed REMS
Established Name	Linvoseltamab-gcpt
Trade Name	Lynozyfic
Name of Applicant	Regeneron Pharmaceuticals, Inc.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed CD3 T cell engager
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) [redacted]

1 Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) and the REMS materials for the new molecular entity (NME) Lynozyfic (linvoseltamab-gcpt). Regeneron Pharmaceuticals, Inc. resubmitted Biologic Licensing Application (BLA) 761400 on January 10, 2025 for Lynozyfic (linvoseltamab-gcpt) with the proposed indication[1] 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, after receiving a Complete Response (CR) letter on August 20,2024, due to the deficiencies in facility inspection[2]. This application is under review in the Division of Hematology Malignancies 2 (DHM2).

The Applicant's proposed REMS submitted on February 7, 2025 and amended on June 2, 2025, are the subject of this review. The proposed REMS consists of a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Lynozyfic outweigh the risk(s) of cytokine release syndrome (CRS) and neurologic toxicity including immune-effector cell associated neurotoxicity syndrome (ICANS). The Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) agree that a REMS with ETASU A (prescriber certification) and ETASU B (pharmacy and healthcare settings certification), is required for the benefits of Lynozyfic to outweigh the risk of CRS and neurologic toxicity including ICANS.[3]

2 Background

General comments on the Applicant's REMS Supporting Document, REMS materials and agreements for the Prescriber Enrollment Form and Pharmacy and Healthcare Setting Enrollment Form were provided on May 16, 2025. On June 2, 2025, the Applicant provided responses to the Agency's comments.

The following materials have been reviewed and comments on these materials are appended to this review:

- REMS Document
- REMS Materials

Additional comments on the REMS Supporting Document will be provided to the Applicant.

3 Comments to the Applicant

The Agency has reviewed your proposed Lynozyfic REMS Document, REMS Supporting Document, and REMS materials submitted on February 7, 2025 and amended on June 2, 2025. We have additional comments on the REMS proposal described below and in the attached redlined REMS Document and materials. Please note that comments on these documents are preliminary and may be revised over the course of the review.

In order to facilitate further review, we ask that you respond to these comments **by June 20, 2025**.

I. REMS Document

Your proposed REMS document follows the draft guidance for Industry Format and Content of the REMS; however, additional edits are necessary to support standardization of the format and content of REMS. In addition, the REMS and all the REMS materials will need to align with final labeling.

Editorial revisions for grammar, consistency, and order were made to the REMS Document. A summary of the significant additions and deletions are listed below.

1. Ensure that "ICANS" is replaced with "neurologic toxicity, including ICANS" throughout the REMS document for consistency with the labeling in the US Prescribing Information (USPI).

   The goal has been revised to include, "neurologic toxicity including" and text (b) (4) is replaced with "exposing" as follows:

   > 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.

2. Prescriber Requirements

   a. The REMS document and materials require clarification regarding when patients must receive counseling and the patient wallet card from the prescriber. The REMS document and REMS materials were changed to state this requirement must occur before the "first step-up dose," because patients should be informed prior to initiation of treatment about how to recognize and respond to signs and symptoms of the risks of CRS and neurotoxicity and the need to report such signs and symptoms to their healthcare provider (HCP) or emergency room provider.

3. Pharmacy and Healthcare Setting Requirements

   a. To reduce burden, the pharmacy or healthcare setting must obtain a REMS dispense authorization (RDA) for the first prescription for each patient to confirm the prescriber is certified in the REMS. For all subsequent prescriptions, the pharmacy or healthcare setting may verify the prescriber is certified through processes and procedures established as a requirement in the REMS such as checking the database of certified prescribers. To account for the change in the RDA requirements, items 5-7 were added. See the redlined REMS document for details.

   b. Please update the supporting document to align with the requirements described above.

   c. Item 8 was revised for clarity and consistency to support standardization of the format and content of a REMS document.

4. Wholesalers-Distributors Requirements

   a. Item 5 was revised for clarity and to support REMS program operation so that wholesalers-distributors submit records of drug distribution to the REMS on a regular basis.

5. Communication Plan

   a. A requirement was added for the Healthcare Provider REMS Letter, Professional Society REMS Letter and Fact Sheet to be disseminated through field-based sales and medical representatives for 12 months from the date linvoseltamab-gcpt is first commercially distributed.

6. Operations

a. To to support the REMS program operations and align with the updated pharmacy requirements, we modified the language of item 1 as follows:

> Authorize dispensing for each patient's first prescription based on verifying the prescriber is certified.

b. The word (b) (4) was revised to "calendar" in item 8 for consistency with other REMS programs as well as for standardization of the format and content of a REMS document.

7. Compliance

a. Audits are necessary to ensure certified pharmacies and healthcare settings comply with the REMS requirements, and to inform assessment of the REMS. Revise audit language for item 17 to include audits of all certified pharmacies and healthcare settings.
b. Similarly, revise the audit language for item 18 to include audits of all wholesaler-distributors that have distributed Lynozyfic no later than 180 calendar days of being authorized to distribute.
c. The requirement, "Take corrective action if noncomplicance is identified," is sufficiently covered in item 15. Hence this statement was removed from the item 18.

8. REMS Assessment Timetable

a. The timetable for submission of REMS assessments has been revised to: Regeneron Pharmaceuticals, Inc. must submit REMS Assessments (b) (4) months from the date of the initial approval of the REMS (MM/DD/YYYY), and (b) (4) thereafter (b) (4) (b) (4) To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Regeneron Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

II. REMS Materials

General Comments

As the FDA does not review non-English versions of the REMS materials, you must submit a certification of translation demonstrating that the non-English materials are accurate, identical in content, and the translation is correct. You should submit this certification as a REMS correspondence and do not need to submit the foreign language material(s).

For the final PDF compiled file, remove the internal tracking system that is on the bottom of each page.

Agreements

We have made edits to the agreements for the *Pharmacy and Healthcare Setting Enrollment Form* to align with the REMS Document. Please see the separate agreements document with tracked changes.

Fact Sheet and REMS Website

We have added comments on the Fact Sheet and the REMS website to clarify that prescribers should counsel patients on the need to be hospitalized for 24 hours after administration of the first and second step up dose.

Prescriber Training Program

We have made editorial comments on the Prescriber Training Program to correct references and align content with the label.

Please see the tracked changes version of the Fact Sheet, Prescriber Training Program and REMS website.

III. REMS Supporting Document

1. Align the REMS Supporting Document with the REMS Document and label.
2. Remove the post login screenshots from the final compiled REMS materials. Include them as part of the Supporting Document.
3. Key Risk Messages are the most important risk messages related to the REMS goals and objectives. These high level messages are included in the REMS materials where appropriate and broken down by stakeholder. We have developed the key risk messages below. Include these key risk messages in the Supporting Document.

Key Risk Messages for Prescribers

- CRS, including serious life-threatening reactions, can occur in patients receiving Lynozyfic. Initiate treatment with Lynozyfic step-up doing schedule to reduce risk of CRS. Closely monitor patients for signs or symptoms of CRS during treatment. Withhold Lynozyfic until CRS resolves or permanently discontinue based on severity.
- Neurologic toxicity, including ICANS and serious life-threatening reactions can occur in patients receiving Lynozyfic. Monitor patients for signs or symptoms of neurologic toxicity including ICANS, during treatment. Withhold Lynozyfic until neurologic toxicity resolves or permanently discontinue based on severity.
- Instruct the patient that they should be hospitalized for 24 hours after administration of the first step-up dose, and for 24 hours after administration of the second step up dose.
- Before treatment initiation, complete and provide the patient/caregiver with a Patient Wallet Card.
- Counsel the patient/caregiver on how to recognize and respond to signs and symptoms of CRS and neurologic toxicity, including ICANS, using the Patient Wallet Card, and having the card at all times.

Key Risk Messages for Patients

- There is a risk of CRS and neurologic problems with Lynozyfic.
- Carry the Patient Wallet Card with you at all times and show the card to any healthcare professional that treats you.
- If you are having any symptoms listed on the patient wallet card, call your doctor, or seek emergency medical attention right away.

Key Risk Messages for Pharmacies and Healthcare Settings

- All staff must be trained on dispensing Lynozyfic using the Pharmacy and Healthcare Setting Training Program.
- Before dispensing Lynozyfic, staff must verify prescriber is certified in the Lynozyfic REMS.

4. Include a brief description of what actions will be taken if the key performance indicators (KPI) thresholds are not met, such as a root cause analysis and evaluation of barriers to compliance. Include this description under section A. Key Performance Indicators.
5. We disagree with the proposal of revising one of the KPI, REMS operations, from 99.9% to (b)(4)% of dispenses authorized by the REMS prior to dispensing the first prescription written by the prescriber. Since obtaining a RDA prior to the first prescription is a requirement of the REMS, we expect to see 99.9% of dispenses were authorized.
6. Under Section III.D. Implementation System, revise the audit requirement language to align with changes to the REMS Document.
7. Under Section IV. Timetable for Submission of Assessments, revise the timetable to align with the changes to the REMS Document.

IV. REMS Assessment Plan

See the attached redlined REMS Assessment Plan which includes the Agency's revisions, edits, and comments made in tracked changes for your proposed REMS Assessment Plan.

We request that you submit the documents as shown below **by June 20, 2025**:

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word
3	Prescriber Enrollment Form	-
4	Pharmacy and Healthcare Setting Enrollment Form	-
5	Prescriber Training Program	-
6	Adverse Reaction Management Guide	-
7	Knowledge Assessment	-

8	Patient Wallet Card	-
9	Pharmacy and Healthcare Setting Training Program	-
10	Healthcare Provider REMS Letter	-
11	Professional Society REMS Letter	-
12	REMS Fact Sheet	-
13	REMS Website public facing	-
14	Post-login screenshots (non-public)	PDF version
15	Compiled PDF file that **includes the REMS Document and all REMS materials** in their final format	**PDF Version**

V. References

[1] Draft Prescribing Information for linvoseltamab-xxxx as currently edited by the FDA, last updated May 30, 2025.

[2] BLA 761400 Complete Response, dated August 20, 2024. [Reference ID: 5432808]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed April 16, 2025.

[3] Olickal T. Defer comment on DRM evaluation of the need for a REMS for linvoseltamab-xxxx, BLA 761400, dated August 14, 2024. [Reference ID: 5430309]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 9, 2025.

57 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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NAOMI S BOSTON
06/16/2025 11:41:37 AM

LAURA A ZENDEL
06/16/2025 11:48:58 AM

U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Oncologic Disease
Division of Hematology Malignancies 2 (DHM2)

NDA/BLA #s:	761400
Products:	Lynozyfic (linvoseltamab) injection
APPLICANT:	Regeneron Pharmaceuticals, Inc
FROM:	Oladimeji Akinboro, M.D., MPH, Associate Director for Safety
DATE:	June 9, 2025

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for linvoseltamab to ensure that the benefits of the drug outweigh the risks of Cytokine Release Syndrome (CRS) and neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). In reaching this determination, we considered the following:

A. Multiple myeloma accounts for 1-2% of all new diagnoses of cancer in the United States. In 2025, approximately 36,000 patients in the United States will be newly diagnosed with multiple myeloma based on estimates available from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (SEER, 2025; Siegel, 2025). The median age of diagnosis of multiple myeloma in the United States is 69 years; approximately 65% of patients with newly diagnosed multiple myeloma will be aged 65 years and older (SEER, 2025).

   The incidence of multiple myeloma is higher in men (age-adjusted incidence of 8.8 per 100,000) than women (age-adjusted incidence of 6.6 per 100,000) (SEER, 2025). There are considerable differences in the incidence of multiple myeloma by race/ethnicity – the incidence rates of multiple myeloma in non-Hispanic Black males and females are at least twice the respective incidence rates in males and females of other racial/ethnic groups in the United States (SEER, 2025). An analysis of age-adjusted county-level incidence rates of multiple myeloma suggests that there may also be geographic variations in the incidence of multiple myeloma across the United States with higher incidence in parts of the Southeast and New York state and relatively low incidence in the Southwest and the West (Cheung, 2023).

   Despite the differences in the incidence of multiple myeloma by sex and race/ethnicity, the 5-relative survival for multiple myeloma appears similar across sex and racial/ethnic groups in the United States (SEER, 2025). Available data do not demonstrate a consistent pattern of differences in survival outcomes by urbanization status of patients' residence (Mateos, 2023).

B. Multiple myeloma is a serious and life-threatening disease. In 2025, it is estimated that approximately 12,000 adults in the United States will die from multiple myeloma (SEER, 2025). Standard of care treatments for multiple myeloma include several lines of therapies with major classes of drugs that include proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies. Despite the availability of multiple therapies and improvements in the treatment of multiple myeloma, multiple myeloma remains an incurable disease with an estimated 5-year survival of 62% (SEER, 2025).

C. Linvoseltamab is a B-cell maturation antigen (BCMA)-directed CD3 T-cell engaging bispecific monoclonal antibody, i.e., a bispecific T-cell engager (BiTE). The anticipated indication for linvoseltamab is for the treatment of patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including protease inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The data provided in support of the proposed indication are reported from Study 1826 (LINKER-MM1; Study R5458-ONC-1826; NCT03761108), a Phase 1/2 single-arm, multicenter, multicohort trial that evaluated linvoseltamab as a single agent in patients with relapsed or refractory multiple myeloma. The efficacy population comprised 80 patients who had received at least 4 prior lines of therapy and were treated in the Phase 2 portion of Study 1826.

At the time of the data cut-off of September 08, 2023, with median follow-up of 11.3 months in responders, the overall response rate (ORR) in the efficacy population was 70% (95% confidence interval [CI]: 59, 80) while the complete response rate was 45% (95% CI: 34, 57). The median duration of response (DOR) was not reached (95% CI: 12.2 months, not estimable). The estimated DOR rate was 93% at 6 months (95% CI: 82, 97) and 72% at 12 months (95% CI: 54, 84).

The observed ORR, along with the durability of responses, for linvoseltamab in Study 1826 demonstrates substantial evidence of effectiveness in patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including protease inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody population pending the verification and description of the clinical benefit of linvoseltamab in an ongoing confirmatory clinical trial.

D. It is expected that linvoseltamab will be used 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-CD-38 monoclonal antibody.

   The recommended dosage of linvoseltamab, consistent with its dosage in the Phase 2 portion of Study 1826, is expected to be as follows:

   - Initial step-up dose (Step-up dose 1) of 5 mg intravenously (IV) over 4 hours on Day 1, then
   - Step-up dose 2 of 25 mg IV over 4 hours on Day 8, then
   - First full treatment dose of 200 mg IV over 4 hours on Day 15, then
   - Weekly dosing of 200 mg over 1 hour for the second treatment dose and over 30 minutes for subsequent doses, for 10 weekly treatment doses from Week 4 to Week 13, then
   - Biweekly dosing of 200 mg over 30 minutes at Week 14 and then every 2 weeks thereafter.

   It is anticipated that the majority of linvoseltamab doses will be administered, within the first few years of approval, in monitored clinical care settings. Available data from the recent assessments of the REMS programs for the currently approved BiTEs for the treatment of relapsed or refractory multiple myeloma

demonstrate that, as of June 2024, the majority (63%) of BiTE doses for multiple myeloma have been dispensed by either inpatient hospital pharmacies (30%) or oncology infusion centers (33%). Based on this data and given the requirements for inpatient hospitalization immediately following the administration of the first two doses of these BiTEs, it is reasonable to assume that the majority of patients treated with approved BiTEs for multiple myeloma receive their first two doses of the respective BITEs in monitored clinical care settings and that virtually all patients receiving these doses are hospitalized during or immediately after treatment. Experience with the administration of the first few doses of BiTEs for multiple myeloma outside of monitored clinical care settings, such as in free-standing community-based oncology practices that are unaffiliated with hospitals, may therefore be limited.

E. Cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) are recognized immunological adverse reactions (ARs) caused by T-cell engaging therapies such as BiTEs – the class of therapeutic products to which linvoseltamab belongs (van De Donk, 2023; Shimabukuro-Vornhagen, 2021; Tvedt, 2021; Lee, 2019*)*. CRS and ICANS are serious and potentially life-threatening/fatal ARs (Cobb, 2021; Shimabukuro-Vornhagen, 2021; Tvedt, 2021). Majority of cases of CRS and ICANS occur after the first few doses of T-cell engaging therapies (van De Donk, 2023; Shimabukuro-Vornhagen, 2021*)*. Given that CRS (different from '*cytokine storm'*) and ICANS are ARs that have generally been described in the context of treatment with T-cell engaging therapies and other immunological therapies, documented background rates of CRS and ICANS in patients with relapsed or refractory multiple myeloma who are unexposed to T-cell engaging therapies or other immunotherapeutic products are unavailable (Shimabukuro-Vornhagen, 2021; Tvedt, 2021).

   Among the 117 patients in the safety population of Study 1826 who received at least one full dose of linvoseltamab (200 mg IV), 54 patients (46%) experienced any-grade CRS and 23 patients (20%) experienced more than one event of CRS. The maximum CRS toxicity grade in almost all patients who experienced CRS were grades 1 and 2 (*n*=53). However, one patient (0.9%) experienced life-grade 3 CRS, i.e., hypotension requiring vasopressor(s) and/or hypoxia requiring oxygen supplementation at high-flow rates via high-flow nasal cannula, non-rebreather mask or Venturi mask. The occurrence of CRS events was highest after Step-up dose 1 (38%) and it decreased with subsequent doses (17% after Step-up dose 2; 9% after the first full dose; and 5% after the 2nd full dose and beyond). Although the majority of CRS events occurred within 24 hours of treatment with the index dose of linvoseltamab associated with the event, all cases occurred within 8 days of treatment (median time to onset of CRS – 11 hours; range *-1 to* 184 hours). The median duration of CRS was 15 hours (range: 1 to 24 hours). All cases of CRS resolved and there were no long-term sequelae

or complications documented in patients who experienced CRS. There was no treatment discontinuation due to CRS.

Based on FDA's analysis of neurologic toxicity, 54 patients (46%) experienced any grade neurologic toxicity while 9 patients (8%) experienced Grades 3 to 4 neurologic toxicity. These neurologic toxicities, based on grouped terms, were headache (22%), encephalopathy (17%), insomnia (12%), sensory neuropathy (11%), dizziness (9%), and ICANS (8%).

Of the 9 patients (8%) who experienced any-grade ICANS, 3 patients (2.6%) experienced grade 2 or 3 ICANS, i.e., depressed consciousness and/or seizure and/or focal edema on neuroimaging; no patient experienced Grade 4 or fatal ICANS. All but one ICANS events occurred concurrent with CRS; that ICANS event occurred in a patient who experienced an infusion-related reaction. There were no patients in Study 1826 documented to have experienced more than one ICANS event. The majority of ICANS events occurred after Step-up dose 1 (*n*=6) and Step-up dose 2 (*n*=2); one occurred after the 3rd full dose and beyond. The median time to onset of IANS was 3 days (range: 1 to 59 days) while the median duration was 2 days (range: 1 to 11 days). The short- and long-term clinical outcomes, i.e., recovery/resolution and long-term sequelae/complications, respectively, were unavailable for one patient who experienced ICANS (Grade 2). Otherwise, the other cases of ICANS resolved/recovered. One patient required treatment discontinuation due to ICANS (Grade 3).

In Study 1826, protocol-specified risk mitigation measures for CRS and ICANS by phases of prevention were:

- Primary prevention:
  i. Administration of two step-up doses – Step-up dose 1 and Step-up dose 2 on Study Days 1 and 8, respectively, before the first full dose administration on Study Day 15.
  ii. Premedication with acetaminophen prior to each dose, diphenhydramine prior to each dose, and with dexamethasone prior to each of the two step-up doses.
  iii. Administration of the Step-up doses 1 and 2 as well as the first full dose on Study Day 15, each over 4 hours.

- Secondary prevention:
  iv. Hospitalization for 24-48 hours for observation in an inpatient/monitored setting for after Step-up doses 1 and 2 (duration of hospitalization differed by protocol version – later protocol versions permitted administration of Step-up doses 1 and 2 in a monitored setting rather than mandating inpatient setting and those protocol versions also permitted monitoring for 24 hours after Step-up doses 1 and 2).

- Tertiary prevention:
  v. Treatment of CRS with supportive care, systemic corticosteroids and/or tocilizumab (anti-IL-6 monoclonal antibody).

In addition to CRS and neurologic toxicity including ICANS, other serious adverse reactions with linvoseltamab are infections, neutropenia, hepatoxicity, and embryo-fetal toxicity.

The 3 BiTEs that are currently approved for the treatment of relapsed or refractory multiple myeloma – teclistamab-cqyv (BCMA/CD3-targeting BiTE; BLA 761291), talquetamab-tgvs (G-protein-coupled receptor class 5 member D [GPRC5D]/CD3-targeting BiTE; BLA 761342), and elranatamab-bcmm (BCMA/CD3 targeting-BiTE; BLA 761345) – were all approved with, and currently have, REMS that each have the goal of mitigating the risks of CRS and ICANS. The rates of CRS observed with linvoseltamab were comparable to the CRS rates observed with these approved BiTEs. Similarly, the rates of neurologic toxicity (particularly Grade 3 events) observed with linvoseltamab were either comparable, or higher than the rates observed with these approved BiTEs. The elements of the respective REMS for each of these approved BiTEs for relapsed or refractory multiple myeloma comprise the following:

- Communication Plan
- Elements to assure safe use, including ETASU A (special certification of prescribing healthcare providers) and ETASU B (special certification of dispensing pharmacies and healthcare settings)

F. Linvoseltamab is a new molecular entity. The safety database for linvoseltamab in the sole clinical trial supporting its BLA – Study 1826 – is limited, comprising of 117 patients. The documentation of the serious risks of CRS and ICANS as established serious ARs with BiTEs in general from prior clinical trials notwithstanding, a REMS for linvoseltamab will facilitate the safe use of linvoseltamab for its proposed indication until further data emerge regarding the incidence and outcomes of CRS and ICANS with linvoseltamab in the postmarketing setting that may guide subsequent regulatory action with respect to risk mitigation for these serious ARs.

The REMS program for linvoseltamab will comprise of:

1. A Communication Plan.
2. Elements to assure safe use (ETASU), including:
   - ETASU A: healthcare providers who prescribe linvoseltamab are specially certified.
   - ETASU B: pharmacies and healthcare settings that dispense linvoseltamab are specially certified.

3. An implementation system.
4. A timetable for submission of assessments of the REMS.

References:

- Cheung JT, Zhang W, Chiu BC. Geospatial analysis of population-based incidence of multiple myeloma in the United States. *Cancer Epidemiol.* 2023;83:102343.
- Cobb DA, Lee DW. Cytokine release syndrome biology and management. *Cancer J.* 2021;27(2):119-125.
- Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant.* 2019;25(4):625-38.
- Mateos M, Ailawadhi S, Costa LJ, Grant SJ, Kumar L, Mohty M, Aydin D, et al. Global disparities in patients with multiple myeloma: a rapid evidence assessment. *Blood Cancer J.* 2023;13(1):109.
- SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2025 Apr 16. [cited 2025 May 9]. Available from: https://seer.cancer.gov/statistics-network/explorer/. Data source(s): U.S. Mortality Data (1969-2023), National Center for Health Statistics, CDC.
- Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. *J Immunother Cancer.* 2018;6(1):56.
- Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin.* 2025;75(1):10-35.
- Tvedt THA, Vo AK, Bruserud O, Reikvam H. Cytokine release syndrome in the immunotherapy of hematological malignancies: the biology behind and possible clinical consequences. *Clin Med.* 2021;10(21):5190.
- van de Donk NWCJ, Zweegman S. T-cell-engaging bispecific antibodies in cancer. *Lancet.* 2023;402(10396):142-58.

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/s/

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OLADIMEJI A AKINBORO
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Office of Prescription Drug Promotion

Internal Consult

******Pre-decisional Agency Information******

To: Kate Oswell, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Valerie Guerrier, Regulatory Review Officer, OPDP

CC: Jina Kwak, Team Leader, OPDP
Candido Alicea, Safety Regulatory Project Manager, OSE
Naomi Boston, Team Leader, DRM
CDER-OPDP-RPM

Date: May 28, 2025

Re: BLA 761400
LYNOZYFIC™ (linvoseltamab-gcpt) injection, for intravenous use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

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Materials Reviewed

OPDP has reviewed the following proposed REMS materials for LYNOZYFIC™:

- Healthcare Provider (HCP) REMS Materials:
  - LYNOZYFIC REMS Prescriber Enrollment Form
  - LYNOZYFIC REMS Pharmacy and Healthcare Setting Enrollment Form
  - LYNOZYFIC REMS Prescriber Training
  - LYNOZYFIC REMS Adverse Reaction Management Guide
  - LYNOZYFIC REMS Knowledge Assessment
  - LYNOZYFIC REMS Pharmacy and Healthcare Setting Training
  - LYNOZYFIC REMS Letter for Healthcare Providers
  - LYNOZYFIC REMS Letter for Professional Societies
  - LYNOZYFIC REMS Fact Sheet

- Direct-to-Consumer (Patient) REMS Materials:
  - LYNOZYFIC REMS Patient Wallet Card

- LYNOZYFIC REMS Website

The version of the draft REMS materials used in this review were sent from DRM by Kate Oswell via email on May 14, 2025. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for LYNOZYFIC.

General Comment

Please remind Regeneron Pharmaceuticals, Inc. that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.Lynozyficrems.com and toll-free number 1-855-212-6391. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone.

Comments are provided using the draft product labeling (Prescribing Information and Medication Guide) for Lynozyfic accessed via SharePoint on May 27, 2025.

OPDP notes that the current Lynozyfic Prescribing Information (PI) and Medication Guide (MG) are still being reviewed by DMH2. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label for Lynozyfic.

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS pieces:

- **LYNOZYFIC REMS Prescriber Training**
  - Slide eight of the LYNOZYFIC REMS Prescriber Training presents patient counseling information for prescribers.
    - **Risk**
      - This presentation minimizes risks by omitting material information from the draft PI for Lynozyfic. According to the DOSAGE AND ADMINISTRATION, *Important Administration Instructions* subsection of the draft PI, it states, "Due to the risk of CRS and neurologic toxicity, including ICANS, patients **should be hospitalized** for 24 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose" (emphasis added). In addition, OPDP notes the crossed-out statement, (b) (4) aligns with the PATIENT COUNSELING INFORMATION section of the draft PI. Therefore, OPDP recommends revising this presentation to include this material information.

  - Slide 15 of the LYNOZYFIC REMS Prescriber Training presents recommended pretreatment medications for Lynozyfic.
    - **Risk**
      - This presentation minimizes risks by omitting material information regarding pretreatment medication recommendations of Lynozyfic. Specifically, the DOSAGE AND ADMINISTRATION, *Recommended Pretreatment Medications* subsection of the draft Lynozyfic PI states (in pertinent part, emphasis added), "Administer the following pre-treatment medications . . . to reduce the risk of CRS **and/or IRR**." Therefore, OPDP recommends revising this presentation to include this material information.

  - Slide 16 of the LYNOZYFIC REMS Prescriber Training presents CRS management for Lynozyfic.
    - **Risk**
      - This presentation minimizes risks by omitting material information regarding CRS management of Lynozyfic. Specifically, the WARNINGS AND PRECAUTIONS section of the draft Lynozyfic PI states (in pertinent part, emphasis

added), "**At the first sign of CRS, immediately evaluate patients for hospitalization**." Therefore, OPDP recommends revising this presentation to include this material information.

- Slide 23 of the LYNOZYFIC REMS Prescriber Training presents ICANS management for Lynozyfic.
  - **Risk**
    - This presentation minimizes risks by omitting material information regarding neurologic toxicity, including ICANS, management of Lynozyfic. Specifically, the PATIENT COUNSELING INFORMATION section of the draft Lynozyfic PI states, "Advise patients to **immediately** contact their healthcare provider if they experience any signs or symptoms of neurologic toxicity" (emphasis added). Therefore, OPDP recommends revising this presentation to include this material information.

- **LYNOZYFIC REMS Patient Wallet Card**
  - Page two of the LYNOZYFIC REMS Patient Wallet Card includes the statement, "**You should be monitored for potential side effects for 24 hours after the first dose of LYNOZYFIC**" (emphasis original).
    - **Risk**
      - This statement minimizes risks by omitting material information. According to the "**What is the most important information I should know about LYNOZYFIC?**" section of the draft MG, "**Due to the risk of CRS and neurologic problems**, you will receive LYNOZYFIC on a "step-up dosing schedule" and <u>should be hospitalized for 24 hours after the first and second "step-up" doses</u>" (bolded emphasis original, underlined emphasis added). Therefore, OPDP recommends revising this statement to include this material information.

- **LYNOZYFIC REMS Fact Sheet**
  - Page two of the LYNOZYFIC REMS Fact Sheet states, "Administer pretreatment medications and initiate therapy according to LYNOZYFIC step-up dosing to reduce the risk of CRS as outlined in the Prescriber Training Program."
    - **Risk**
      - This statement minimizes risks by omitting material information regarding pretreatment medication recommendations of Lynozyfic. Specifically, the DOSAGE AND ADMINISTRATION, *Recommended Pretreatment Medications* subsection of the draft Lynozyfic PI states (in pertinent part, emphasis added), "Administer the following

pre-treatment medications . . . to reduce the risk of CRS **and/or IRR**." Therefore, OPDP recommends revising this statement to include this material information.

- Page two of the LYNOZYFIC REMS Fact Sheet includes the following statements:

(b) (4)

  - **Risk**
    - These statements minimize risks by omitting material information Specifically, the DOSAGE AND ADMINISTRATION, *Important Administration Instructions* subsection of the draft PI states, "Due to the risk of CRS and neurologic toxicity, including ICANS, patients **should be hospitalized** for 24 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose" (emphasis added). OPDP recommends revising these statements to include this material information.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

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/s/

VALERIE GUERRIER
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Division of Risk Management (DRM)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761400
PDUFA Goal Date	August 22, 2024
OSE RCM #	2024-7648; 2024-7650
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Laura Zendel, Pharm.D.
Review Completion Date	August 14, 2024
Subject	Defer comment on the REMS for linvoseltamab-xxxx
Established Name	linvoseltamab-xxxx
Trade Name	Lynozyfic
Name of Applicant	Regeneron Pharmaceuticals, Inc.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed CD3 T cell engager
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) [redacted]

Table of Contents

1 Introduction

This purpose of this memo is to defer the Division of Risk Management (DRM) review of the risk evaluation and mitigation strategy (REMS) for linvoseltamab-xxxx, BLA 761400.

On December 22, 2023, Regeneron Pharmaceuticals, Inc (the Applicant) submitted BLA 761400 for linvoseltamab-xxxx with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) The Applicant's proposed REMS consists of communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of linvoseltamab-xxxx outweigh the risks of cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS).

2 Regulatory History

The following is a summary of the regulatory history for linvoseltamab-xxxx (BLA 761400) relevant to this review:

- 06/06/2022: Orphan drug designation granted
- 03-30-2023: Fast Track designation granted.
- 12/22/2023: BLA 761400 submission for linvoseltamab-xxxx with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) received.
- 04/11/2024: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the REMS is still under review. A complete review of the REMS, in conjunction with the full clinical review of the BLA, is necessary to determine that this REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act. The major identified safety findings include CRS, neurologic toxicity including ICANS, hepatic toxicity, and infections. A determination of whether the proposed risk management strategies are adequate, and whether additional mitigation strategies may be required to support a positive benefit risk for linvoseltamab are under review.
- 06-24-2024: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Late-cycle meeting that The assessment of the need for REMS is currently under review. FDA comments on the proposed REMS will be provided following completion of review. Agency also informed the Applicant that dollowing a recent inspection of (b) (4) (b) (4) (FEI (b) (4)), listed in the application, FDA conveyed deficiencies to the representative of the facility. Satisfactory responses from the facility are needed before the application can be approved.

- 07-09-2024: The Division of Hematology Malignancies 2 (DHM2) issued a ”Deficiencies Preclude Discussion” letter stating that the Agency identified deficiencies that preclude discussion of labeling and anticipated postmarketing requirements (PMRs) and known postmarketing commitments (PMCs) at this time.[2]

3 Benefit Assessment

The effectiveness of linvoseltamab-xxxx was evaluated in patients with relapsed or refractory multiple myeloma (RRMM) in an open-label, single arm, phase 1/2, multi-center, multi-cohort study LINKER-MM1 (Study R5458-ONC-1826; NCT03761108). The study included patients who had previously received at least 3 prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 antibody. The study excluded patients with a history of an allogeneic stem cell transplantation, autologous stem cell transplantation within 12 weeks, prior BCMA-directed bispecific antibody therapy, prior bispecific T-cell engaging therapy, and prior BCMA CAR-T cell therapy. Linvoseltamab was administered using a step-up dosing regimen. Patients received linvoseltamab-xxxx 5 mg at week 1 and 25 mg at week 2 intravenous infusion. Linvoseltamab was administered over 4-hours for the step-up doses and first full dose. After step-up dosing, patients received 200 mg of linvoseltamab-xxxx weekly for 12 doses, followed by 200 mg every other week for 5 doses. After at least 24 weeks, the Phase 2 patients who achieved a very good partial response (VGPR) or greater received 200 mg of linvoseltamab-xxxx every 4 weeks. Patients were treated until disease progression or unacceptable toxicity.[1]

The efficacy population included 80 patients from the Phase 2 portion of the study who received the recommended dose of linvoseltamab-xxxx and who had received at least four or more prior lines of therapy including a PI, an IMiD, and an anti-CD38 antibody. Efficacy was established based on objective response rate (ORR) as determined by blinded independent review committee (IRC), as measured using the International Myeloma Working Group (IMWG) criteria. The median time to first response was 0.95 months (range: 0.5 to 6 months).[1] The ORR in the primary efficacy population (n=80) was 70% (95% CI: 59.2, 78.9). With median follow-up duration of 11.3 months, the median duration of response was not reached (95% CI: 12.2, NE).[1] The demonstration of efficacy and durability in the population of patients with RRMM represents clinical benefit in this population.[3]

4 Risk Assessment & Safe-Use Conditions

The safety of linvoseltamab-xxxx was evaluated in LINKER-MM1 (see section 3: Benefit assessment).[1] The most notable safety concerns with linvoseltamab are cytokine release syndrome (CRS) and neurologic toxicity.

Cytokine Release Syndrome (CRS)

CRS occurred in 46% of patients in the safety population (n=117). CRS severity was a maximum of Grade 1 in 35%, Grade 2 in 10%, and Grade 3 in 0.9%. There were no Grade 4 or 5 events. The majority of CRS events occurred during the step-up dosing period; 38% of patients experienced an event following the initial dose and 17% of patients experienced an event following the intermediate dose. The first occurrence of a CRS event outside of the step-up dosing period

occurred in 4.3% of patients. However, for all CRS events overall, 21% occurred outside of the step-up dosing period. Twenty percent of patients experienced more than 1 CRS event. The median time to onset of the first CRS event from the most recent prior dose was 11 hours and median duration of the first CRS event was 14 hours. Dose reductions due to CRS occurred in 4.3% of patients, dose interruptions due to CRS occurred in 4.3% of patients, and no CRS events led to treatment discontinuation. [1,3]

The protocol recommended consideration of tocilizumab for CRS management in patients with comorbidities for Grade 1 CRS, for symptoms >4 hours for Grade 2 CRS, and for all Grade 3 or higher CRS events. Of those who experienced CRS, 41% of patients received tocilizumab and 22% received corticosteroids.[3]

Neurologic Toxicity including Immune-effector-cell associated neurotoxicity syndrome (ICANS)

Neurologic TEAEs, defined by FDA analysis as all preferred terms in the nervous system disorder or psychiatric disorder system organ classes (SOCs), occurred in 54% of patients. The most frequent neurologic TEAEs (occurring in >10% of patients, based on grouped terms, including some terms outside of nervous system disorder and psychiatric disorder SOCs) were headache (22%), encephalopathy (17%), insomnia (12%), and sensory neuropathy (11%). Grade 3-4 neurologic TEAEs occurred in 8% of patients and 1 Grade 5 event (acute encephalopathy) occurred.[1,3]

Immune-effector-cell associated neurotoxicity syndrome (ICANS) occurred in 8% of patients. Grade 1, 2, and 3 ICANS events each occurred in 2.6% of patients and no Grade 4 or 5 events occurred. All but one event occurred concurrent with CRS, and the other event occurred in a patient who experienced IRR.[1,3]

5 Summary of the Risk Management Proposals and Discussion on the Need for a REMS

The Applicant included a proposed REMS with their application. The goal of the Applicant's proposed REMS is to mitigate the risk of CRS and ICANS, by ensuring prescribers are aware of the importance of monitoring patients for signs and symptoms of CRS and ICANS in patients exposed to linvoseltamab. The elements of the proposed REMS for linvoseltamab are the same as those required in the Elrexfio REMS and the Tecvayli and Talvey REMS, and include the following:

- Communication Plan: serves to inform the likely prescribers as well as oncology nurses about the REMS, the risks of CRS and ICANS, and safe use.
- ETASU A, Prescriber Certification: Prescribers review training materials and enroll in the REMS. Prescribers agree to counsel patients before initiation of treatment and report events of CRS and ICANS to the REMS.
- ETASU B, Pharmacy and Health Care Setting Certification: Pharmacies/healthcare settings that dispense the product review training materials, enroll in the REMS, and verify the prescriber is certified before dispensing. Pharmacies/healthcare settings report events of CRS and ICANS to the REMS. Wholesalers-distributors distribute only to certified pharmacies and healthcare settings.

- Timetable for submission of assessments.

The Division of Hematology Malignancies 2 (DHM2) believes that a REMS is necessary to ensure the benefits of linvoseltamab outweigh the risks of CRS and neurologic toxicity including ICANS.[3] DHM2's view is that while multiple myeloma specialists practicing at academic centers may have some experience with the management of CRS and neurotoxicity with the use of CAR T-cell products and bispecific T-cell engagers, community-based oncologists may have limited experience in managing these types of toxicities. Since linvoseltamab administration involves a 4-hour infusion for the step-up dose schedule and first 200 mg full dose, linvoseltamab will most likely be administered at hospital-affiliated infusion centers and cancer centers, where patients will likely be monitored. However, in some cases, linvoseltamab might be administered in private oncology practices where patients may be less closely monitored. Therefore, DHM2 agrees with the Applicant's proposed REMS to mitigate the risks of CRS and neurologic toxicity including ICANS to ensure prescribers are aware of the importance of monitoring patients exposed to linvoseltamab for signs and symptoms of CRS and ICANS.[3] DHM2 additionally states that requiring a REMS for linvoseltamab maintains consistency in risk mitigation for similar products that treat RRMM.

DRM did not initially agree that a REMS was necessary to ensure the benefits outweigh the risks associated with linvoseltamab and considered labeling to be sufficient. Other bispecific T-cell engagers approved with a REMS (Elrexfio, Talvey and Tecvayli) are supplied in subcutaneous formulations and allow "Off-the-Shelf" administration. Given the ease of administration for these products, concerning rates of CRS and neurologic toxicities, and the likelihood of their use in outpatient clinic settings where healthcare providers may be less familiar with the risks and risk mitigation, these products require a REMS to ensure healthcare providers were aware of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicities.

Linvoseltamab is proposed to be available as an intravenous infusion that requires compounding and is administered over 4-hours for the step-up doses and first full dose. DRM believes that the likelihood of a patient starting this medication outside of an inpatient setting or setting where monitoring would occur is low, as the labeling will recommend that patients should be monitored for 48 hours for the first dose and 24 hours for the second dose.[3] The highest incidence of CRS is during the initial dose and first step-up dose leading DRM to expect that patients are likely to be in a monitored setting at the time they are at highest risk for adverse events.

The language in the proposed label is similar to other approved bispecific T-cell engagers and includes [3]:

- A Boxed Warning for CRS and neurotoxicity including ICANS
- Important Dosing Information (section 2.1 of the proposed label[1])
  - Linvoseltamab should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS).
  - Due to the risk of CRS and neurologic toxicity, including ICANS, review team is considering adding language in section 2.1, "Due to the risk of CRS

and neurologic toxicity, including ICANS, patients should be hospitalized for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose".

- Recommendations for monitoring in labeling that mirror the clinical trial protocol
- Guidelines for Grading and Management of both CRS and ICANS

Additionally, we note that other intravenously administered bi-specific T-cell engagers such as Lunsumio (Mosunetuzumab), Columvi (glofitamab), and Blincyto (blintumomab) are also associated with CRS and neurologic toxicity. Lunsumio and Columvi were approved without a REMS, and Blincyto's REMS was released in 2022. These products are approved for different indications than linvoseltamab. Blincyto was approved in 2014 for the treatment of acute lymphoblastic leukemia, Lunsumio was approved in December 2022 for the treatment of relapsed or refractory follicular lymphoma, and Columvi was approved in June 2023 for the treatment of relapsed or refractory large B-cell lymphoma.[3] DHM2 supports a different approach to risk mitigation for these products based on the indication as they stated that patients with RRMM are more likely to be treated in community settings compared to other indications including relapsed or refractory follicular lymphoma or refractory large B-cell lymphoma. Because of the similar routes of administration IV infusion, DRM expects RRMM patients would receive this product in a monitored setting as recommended in the label. The release of the Blincyto REMS was supported by the communication plan requirements being fulfilled and knowledge surveys of healthcare professionals demonstrated acceptable understanding of the risks of CRS and neurologic toxicities.[4,5]

Further, the availability of non-REMS training materials developed by professional societies supported rationale to remove prescriber training requirements for chimeric antigen receptor (CAR) T-cell products. On March 14, 2024, the Breyanzi (lisocabtagene maraleucel) REMS was modified to remove training requirements to minimize the burden on the healthcare delivery system of complying with the REMS. This modification is one product in the class modification of REMS for BCMA- or CD 19-directed genetically modified autologous T-cell immunotherapies.[6,7] Other examples of literature available outside of a REMS, includes "Bispecific T cell engager-associated CRS and ICANS literature" in UpToDate and journals.[8,9,10] Continuing Education training for prescribers and pharmacists are available on bispecific T-cell engagers and their risks via the National Comprehensive Cancer Network (NCCN) Continuing Education[11], Society for Immunotherapy of Cancer[12], Mayo Clinic School of Continuous Professional Development[13] and Pharmacy Times Continuing Education Programs.[14] We are encouraged that information about these risks is making its way into professional guidelines and educational materials that are available to the broader prescribing population for hematology and oncology.

A REMS Oversight Committee (ROC) meeting[a] was held on May 16, 2024, to seek advice on if a REMS is necessary to ensure the benefits outweigh the risks of cytokine release syndrome (CRS) and neurologic toxicity including immune-effector cell associated neurotoxicity syndrome (ICANS) associated with linvoseltamab-xxxx. The ROC vote was 2 "yes" and 2 "no.[15] ROC members representing the Office of New Drugs (OND) and the Office of Surveillance and

[a] As per the 21st Century Review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Office of New Drugs, Surveillance and Epidemiology, and the Office of Regulatory Policy.

Epidemiology (OSE) agreed with DMH2's position to require a REMS until additional data is obtained that would support community-based oncologists are sufficiently knowledgeable about the risks and how to manage CRS and ICANS. Other ROC members did not agree that a REMS was needed in this situation, since similar products with similar administration settings and comparable adverse event profiles do not have a REMS, and requiring a REMS for this product may appear to be inconsistent with previous Agency actions for similar products. Since the ROC did not reach a consensus on whether a REMS was necessary for linvoseltamab to ensure the benefits outweigh its risks, the ROC recommended to reconvene the discussion between DHM2 and DRM to determine whether a REMS is necessary to ensure the benefits outweigh the risks of CRS and neurologic toxicity including ICANS associated with linvoseltamab-xxxx.[3,15]

After further discussion with DHM2, DRM aligned with DHM2 to require a REMS for linvoseltamab and note that this recommendation is consistent for the bispecific T-cell engagers indicated for RRMM.

6 Conclusion

Due to the safety findings of CRS and neurologic toxicity including ICANS, DRM aligned with DHM2's conclusion that a REMS with ETASU is needed to ensure the benefits of linvoseltamab outweigh the risks in the post-marketing setting. The regulatory action for this application is anticipated to be a Complete Response as recommended by the Office of Pharmaceutical Quality (OPQ) [16,17]:

> *The data submitted in this application are not sufficient to support a conclusion that the manufacture of LYNOZYFIC is well-controlled and will lead to a product that is pure and potent. From a chemistry, manufacturing and control (CMC) standpoint, OPQ is recommending a Complete Response letter[18] be issued to Regeneron Pharmaceuticals, Inc., to outline the deficiencies noted below and the information and data that will be required to support approval. During a recent inspection of* (b) (4) (b) (4) *(FEI:* (b) (4) *), listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.*

Given the manufacturing issues precluding approval of linvoseltamab, the labeling and REMS were not finalized. An evaluation of the proposed REMS for linvoseltamab-xxxx will be undertaken by DRM after the Applicant addresses the deficiencies in the CR letter. Please send DRM a new consult request at such time. This serves to close the existing consult request to DRM for linvoseltamab-xxxx under BLA 761400.

7 References

[1] Draft Prescribing Information for linvoseltamab-xxxx, BLA 761400 as currently edited by the FDA, last updated May 22, 2024.

[2] Deficiencies Preclude Discussions Letter, dated July 9, 2024. [Reference ID: 5410568]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed July 18, 2024.

[3] REMS Oversight Committee (ROC) meeting: ROC Presentation Executive Summary for linvoseltamab-xxxx, BLA 761400. May 16, 2024.

[4] Pratt B. Division of Risk Management's (DRM) REMS Modification Rationale Review for blinatumomab, BLA 125557, dated October 6, 2022. [Reference ID: 5057129]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 7, 2024.

[5] Division of Hematology Malignancies 2 (DHM2). Supplement Approval for blinatumomab, BLA 125557, dated December 5, 2022. [Reference ID: 5088408]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed June 28, 2022.

[6] Food and Drug Administration (FDA). Drug Databases. REMS. Breyanzi (lisocabtagene maraleucel), BLA #125714. Update History. REMS last update: 03/14/2024. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=405. Accessed June 7, 2024.

[7] Alimchandani M. Center for Biologics Evaluation and Research (CBER). Risk Evaluation and Mitigation Strategies (REMS) Modification Memorandum. Justification for class modification of REMS for BCMA- or CD19-directed genetically modified autologous T cell immunotherapies, dated February 23, 2024.

[8] UpToDate. Cytokine release syndrome (CRS). Bispecific T cell engager-associated CRS. https://www.uptodate.com/contents/cytokine-release-syndrome-crs?search=bispecific%20T-cell%20engagers%20crs&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1#H655196148. Accessed June 7, 2024.

[9] Shah D, Soper B, Shopland L. Cytokine release syndrome and cancer immunotherapies - historical challenges and promising futures. Front Immunol. 2023;14:1190379.

[10] Leclercq G, Steinhoff N, Haegel H, De Marco D, Bacac M, Klein C. Novel strategies for the mitigation of cytokine release syndrome induced by T cell engaging therapies with a focus on the use of kinase inhibitors. Oncoimmunology. 2022;11(1):2083479.

[11] National comprehensive cancer network (NCCN) Continuing Education. Revolutionzing Hematolgic Cancer Treatment: The Promise of Bispecific T-cell engagers. https://education.nccn.org/node/94566. Accessed June 7, 2024.

[12] Society for Immunotherapy of cancer. A Focus on Cellular Therapies, T cell Engagers and TIL Therapies. https://www.sitcancer.org/education/aci/cellular-therapies. Accessed June 7, 2024.

[13] Mayo Clinic School of Continuous Professional Development. Online CME Cources. May Clinic Pharmacy Grand Rounds Podcast. Pharmacy Podcast Episode 160 : When Drugs BITE Back: Managing Toxicities of Bispecific T-Cell Engagers. https://ce.mayo.edu/online-education/content/pharmacy-podcast-episode-160-when-drugs-bite-back-managing-toxicities-bispecific-t-cell. Accessed June 7, 2024.

[14] Pharmacy Times Continuing Education. T-Cell Engaging Bispecific Antibodies: Preparing Oncology Pharmacists to Optimize Patient Care. https://www.pharmacytimes.org/courses/t-cell-engaging-bispecific-antibodies-preparing-oncology-pharmacists-to-optimize-patient-care-enduring. Accessed June 7, 2024.

[15] REMS Oversight Committee (ROC) Meeting Minutes: Lynozyfic (linvoseltamab-xxxx), BLA 761400. June 16, 2024.

[16] Roelofs BA. Office of Pharmaceutical Quality. Quality Executive Summary Addendum for linvoseltamab-xxxx, BLA 761400, dated July 14, 2024. [Reference ID: 5415469]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed July 18, 2024.

[17] Memorandum of Late-Cycle meeting minutes for linvoseltamab-xxxx, BLA 761400, dated June 25, 2024. [Reference ID: 5402882]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed July 18, 2024.

[18] Complete Response (draft). The Division of Hematology Malignancies 2 (DHM2), dated July 18, 2024.

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/s/

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