CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761291Orig1s000

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	761291
PDUFA Goal Date	November 28, 2022
OSE RCM #	2021-2487
Reviewer Name(s)	Celeste Karpow, PharmD, MPH Kate Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	October 24, 2022
Subject	Evaluation of Need for a REMS
Established Name	teclistamab
Trade Name	Tecvayli
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Dosing Regimen	1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tecvayli (teclistamab) is necessary to ensure the benefits outweigh its risks. Janssen Biotech, Inc. submitted a Biologic Licensing Application (BLA) 761291 for teclistamab with the proposed indication of treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The FDA approved indication will be 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 risks associated with teclistamab include the following: cytokine release syndrome (CRS), neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), hepatotoxicity, infections, neutropenia, hypersensitivity and other administration reactions, and embryo-fetal toxicity. The risks of concern are CRS and neurologic toxicity including ICANS and these risks will be highlighted in a boxed warning. The Applicant did not initially submit a proposed REMS or risk management plan with this application; however, a REMS was subsequently submitted to address the risks of CRS and neurologic toxicity including ICANS.

The efficacy and safety of teclistamab was evaluated in the single-arm, open-label, multicenter study, MajesTEC-1 (MMY1001). Efficacy was established based on the overall response rate in 68% of patients, with the median time to first response of 1.2 months. The estimated duration of response (DOR) was 90.6% at six months and 66.5% at 9 months.

In the clinical trial, 72% of patients receiving teclistamab experienced CRS, which were mostly Grade 1 events. Similarly, 57% of patients experienced neurologic toxicity, which were mostly Grade 1 or Grade 2 events. In contrast, 6% of patients experienced ICANS in the clinical trial. Risk mitigation activities during the clinical trial included use of pre-medications for step-up dosing, initiating step-up dosing in an inpatient setting, and baseline, pre- and post-dose neurologic exams during step-up dosing and cycle 2 which may have contributed to lower rates of progression of CRS and neurologic toxicity. Dose delays, hospitalization, or permanent discontinuation of Tecvayli may be necessary to manage the toxicities.

DRM and the Division of Hematologic Malignancies II (DHMII) determined a REMS is necessary to ensure the benefits of teclistamab outweigh the risks of CRS and neurologic toxicity, including ICANS. This determination considered the rate of CRS and neurologic toxicity, including ICANS, seen in the clinical trial program for teclistamab, as well as the route of administration and the potential for use by prescribers who may not have experience managing these adverse events in an outpatient setting. Teclistamab is proposed to be administered weekly via subcutaneous injection and the onset of CRS and neurologic toxicity may occur hours or days after the teclistamab dose, a REMS is necessary to ensure all prescribers are trained on how to monitor for these risks and counsel patients to seek prompt supportive care for CRS and neurologic toxicity including ICANS that might occur when a patient is home.

The goal of the Tecvayli REMS is to mitigate the risk of cytokine release syndrome (CRS) and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) by:

- Educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

The Tecvayli REMS includes the following elements: A communication plan, elements to assure safe use (ETASU) A (healthcare providers who prescribe Tecvayli are specially certified), ETASU B (pharmacies and healthcare settings that dispense Tecvayli are specially certified), an implementation system, and a timetable for submission of assessments. The communication plan will be used to target other healthcare providers, in addition to prescribers, who may be involved in administration of Tecvayli or care for patients treated with Tecvayli. Prescribers must certify in the REMS to ensure they receive training about the risks, how to monitor for and manage the risks, and that they provide counseling to patients, including providing patients a wallet card so patients are aware that they should seek medical care should 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 Tecvayli.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] teclistamab is necessary to ensure the benefits outweigh its risks. Janssen Biotech, Inc. (Janssen or the Applicant) submitted a Biologic Licensing Application (BLA) 761291 for teclistamab with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The Agency revised the indication to the treatment of adult patients with RRMM who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. This application is under review in the Division of Hematologic Malignancies 2 (DHM2). The Applicant did not initially submit a REMS with this BLA but proposed a risk mitigation plan that includes routine pharmacovigilance. The prescribing information proposed by the Applicant includes mitigation of cytokine release syndrome (CRS) through a boxed warning and warnings and precautions. On June 29, 2022, the Agency notified the Applicant that a REMS would be necessary to mitigate the risk of CRS and neurologic toxicity. 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 Tecvayli outweigh the risks of CRS and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS).

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

2. Background

2.1. Product Information

The new molecular entity, teclistamab, is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager. Teclistamab will be indicated 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. Teclistamab binds to the CD3 receptor expressed on T-cells and BCMA multiple myeloma cells and some healthy B-lineage cells which results in T-cell activation, release of pro-inflammatory cytokines, and lysis of multiple myeloma cells.

Teclistamab is available as 30 mg/3 mL single-dose vials and 153 mg/1.7 mL single dose vials. When initiating teclistamab, there is a step-up dosing schedule which consists of 0.06 mg/kg on day 1 of treatment followed by 0.3 mg/kg on day 4, followed by the first treatment dose of 1.5 mg/kg may be administered on day 7. Step-up dose 2 and the first treatment dose may be given up to 7 days after step-up dose 1 and step-up dose 2, respectively, to allow for resolution of adverse reactions. The treatment dose, 1.5 mg/kg, is continued as a once weekly subcutaneous injection until disease progression or unacceptable toxicity.[b] The Applicant proposes that teclistamab can be administered in either inpatient or outpatient settings by a healthcare provider.[1,2]

Teclistamab is currently not marketed in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761291 relevant to this review:

- 12/07/2021: Applicant informed at pre-BLA meeting that there is insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks for teclistamab
- 11/24/2020: Orphan Drug designation granted
- 05/26/2021: Breakthrough Therapy designation granted
- 12/28/2021: BLA 761291 submission for treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody received.
- 04/15/2022: Information request sent to Applicant to clarify the Applicant's anticipated outpatient settings of use for teclistamab.
- 4/19/2022: Response to information request received in which the Applicant proposes teclistamab could be given safely in any outpatient setting without restrictions.[1]

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

- 4/26/2022: Mid-cycle communication sent to the Applicant with information requests regarding the use of tocilizumab in patients with CRS.
- 04/28/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the Agency is strongly considering the need for a REMS to ensure the safe use of teclistamab.
- 05/05/2022: Response to information request received which characterizes the patients who experienced CRS but did not receive tocilizumab.
- 05/27/2022: Information request sent to Applicant to clarify the Applicant's intended distribution model in the postmarket setting for teclistamab.
- 06/02/2022:
    - The Agency held a teleconference with the Applicant to inform the Applicant that a REMS will likely be needed and suggested the Applicant begin working on a REMS for this application.
    - Response to information request received in which the Applicant states teclistamab would not be distributed to outpatient retail pharmacies and specialty or mail-order pharmacies. The Applicant specified that teclistamab will be distributed to inpatient hospital pharmacies, hospital outpatient pharmacies, community oncology physician offices that administer subcutaneous anti-cancer therapies, and oncology infusion centers that administer subcutaneous anti-cancer therapies to enable administration by a health care professional (HCP)[2].
- 06/29/2022: The Agency held a teleconference with the Applicant to formally inform the Applicant that a REMS will be needed with a communication plan, ETASU A (prescriber certification), and ETASU B (pharmacy certification). Additionally, the Agency asked the Applicant to provide their rationale explaining why ETASU C is not needed.
- 07/08/2022: The Applicant submitted a proposed REMS consisting of a communication plan, prescriber certification and pharmacy certification. The REMS submission was complete. In addition, the Applicant submitted their rationale why ETASU C is not necessary for this REMS program.
- 07/12/2022: Major amendment acknowledgment letter sent to the Applicant; PDUFA goal date extended by 3 months to November 28, 2022.
- 07/28/2022: The Agency sent preliminary REMS comments to the Applicant.
- 08/01/2022: Janssen submitted a REMS Amendment that included a new and updated REMS Adverse Reaction Management Guide, REMS Knowledge Assessment, REMS Patient Wallet Card, REMS Pharmacy Training Program, and REMS Prescriber Training Program in response to DRM's preliminary REMS review.
- 08/04/2022: Janssen submitted REMS website screenshots.

- 08/05/2022: The Agency sent an information request (IR) to Janssen to request REMS Website screenshots to show the steps that a pharmacist goes through to verify prescriber certification or how authorization to dispense is provided.
- 08/09/2022: Janssen submitted additional REMS website screenshots showing the steps that a pharmacist goes through to verify prescriber certification and how authorization to dispense is provided.
- 09/08/2022: The Agency sent Janssen comments on the REMS document and REMS materials (please see review by Dr. Karpow dated 09/08/2022 for more details on this correspondence).[c]
- 09/13/2022: The Applicant submitted a REMS Amendment that included a REMS document and REMS materials in response to the comments that were sent by the Agency on 09/08/2022. DRM noted that the Applicant proposed new information in the prescriber enrollment form regarding the option for a prescriber to certify in the REMS program (b) (4) Specifically, the Agency asked the Applicant to explain the following:
    - How the wholesaler will verify the person ordering TECVAYLI is a certified prescriber.
    - How you intend to ensure prescribers who select option B are certified prior to prescribing teclistamab.
    - Confirm that prescribers are not intended to be dispensers of TECVAYLI.
- 09/14/2022:
    - Information request sent to Janssen Biotech, Inc. to request the date Janssen intends to have post-login website screenshots available for the Agency's review and the date you expect this part of the website to be functional.
    - The Applicant responded to the information request sent on September 13, 2022
- 09/16/2022:
    - The Agency held a teleconference with the Applicant to express concerns regarding the Applicant's proposal for prescribers to obtain teclistamab (b) (4) The Agency's concerns include prescribers acquiring teclistamab directly from a teclistamab REMS-authorized wholesaler-distributor for administration to patients and (b) (4) Process which may bypass ETASU B, Pharmacy and Healthcare setting Certification that verifies the prescriber is certified prior to dispensing.
    - The Agency sent interim REMS comments to the Applicant.

[c] Karpow, C. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 SEP 08. RCM No.: 2021-2487.

- 09/21/2022: The Applicant submitted a REMS Amendment that included a REMS document and REMS materials in response to the comments that were sent by the Agency on September 16, 2022.
- 09/22/22: An information request was sent to the Applicant to clarify how prescriber certification will be verified and documented prior to dispensing teclistamab to a patient (b) (4)
- 09/23/2022: The Applicant responded to the information request sent on September 22, 2022. DRM noted that the Applicant proposed new information that states, "…all prescribers (b) (4) will be required to enroll in the TECVAYLI REMS as both a prescriber and as a pharmacy and healthcare setting."
- 09/27/2022: An information request was sent to the Applicant to request any stakeholder input regarding (b) (4) Specifically, we requested the following:
    - Anticipated compliance with obtaining a REMS Dispense Authorization (RDA) prior to dispensing for administration
    - How obtaining an RDA prior to dispensing for administration to a patient will fit into prescriber's workflow
    - Define who can serve as an authorized representative
    - Anticipated uptake and market share of teclistamab (b) (4)
    - Describe in detail the Applicant's plan to audit 100% of certified pharmacies or healthcare settings, which will include all (b) (4) prescribers. Also include the action if noncompliance is identified in any of these settings.
- 09/29/2022: The Applicant responded to the information request sent on September 27, 2022 and outlined that they anticipate near 100% compliance, no change in workflow upon certification, the Authorized Representative can be any responsible individual assigned by the pharmacy or healthcare setting who is not a certified TECVAYLI Prescriber, described their anticipated uptake, and outlined their audit plan.
- 10/06/2022: The Applicant submitted a REMS Amendment that included a REMS document and REMS materials in response to the comments that were sent by the Agency on October 5, 2022.
- 10/07/2022: An information request was sent to the Applicant to request a revision to the REMS Document and the Pharmacy and Healthcare Setting Enrollment Form.
- 10/11/2022: The Applicant submitted a REMS Amendment that included a REMS document and REMS materials in response to the information request sent by the Agency on October 7, 2022.
- 10/20/2022: The Agency sent an information request (IR) to Janssen to request labeling revisions. As a result, the Agency also requested that the Applicant ensure the REMS document, REMS Supporting Document and all REMS materials, align with the prescribing information.

- 10/21/2022: The Applicant submitted revised prescribing information and a REMS Amendment that included a REMS document and REMS materials in response to the information request sent by the Agency on October 20, 2022.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Multiple myeloma is a cancer of the blood characterized by proliferation and accumulation of a monoclonal immunoglobulin secreted from the plasma cell.[3,4] Multiple myeloma affects older adults, with the median age typically being in the mid to late 60's to 70's years of age at diagnosis. It is more common in men than women and among individuals of African American descent.[5] Signs of multiple myeloma include hypercalcemia, renal insufficiency, anemia, osteopenia, and osteolytic bone lesions.[4] The American Cancer Society estimates approximately 34,470 new cases of multiple myeloma and approximately 12,640 deaths from multiple myeloma in the United States in 2022.[d,6] According to the National Cancer Institute's SEER database, between 2005-2011, the 5-year survival rate for patients diagnosed with multiple myeloma was 55.6%[e,7].

Although there have been therapeutic advances in treating multiple myeloma, therapy is not curative. As such, patients may relapse or experience refractory disease which is defined as progressing within 60 days of the last treatment in patients who previously achieved at least a minimal response to treatment.[8] Due to the pathology of multiple myeloma, relapses are common. The characteristics of the disease will determine treatment strategy.[8] Specifically, RRMM in which biochemistry suggests an increase in paraprotein concentration with no other symptoms or related organ dysfunction may not need to be treated immediately compared to progressive disease with prominent other symptoms.[8]

Data on the numbers of patients who experience RRMM are sparse, since these patients have much poorer outcomes. A study from 2016, showed that of 511 patients treated for MM over the course of 12 months, 82 patients (16%) experienced early relapse with a median time to relapse of 8 months; approximately 84% of these patients had relapsed in their first regimen after the course of one year.[9] In a retrospective multicenter study, the median overall survival for patients with relapsed multiple myeloma (received at least three lines of therapy, refractory to an immunomodulatory drug and a proteasome inhibitor, and exposed to an alkylating agent) was 13 months.[10]

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

[e] 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.*

3.2. Description of Current Treatment Options

Treatment options for previously treated multiple myeloma include drug therapy, stem cell transplantation, and/or enrollment in a clinical trial. Treatment selection depends on tumor feature, host features, and previous treatment.[11] The National Comprehensive Cancer Network (NCCN) Guidelines for previously treated multiple myeloma include FDA approved products: bortezomib, lenalidomide, carfilzomib, daratumumab, ixazomib, isatuximab-irfc, pomalidomide, bendamustine, liposomal doxorubicin, cyclophosphamide, elotuzumab, selinexor, venetoclax, thalidomide, cisplatin, etoposide, belantamab mafodotin, idecabtegene vicleucel, and ciltacabtagene autoleucel.[12] Therapeutic options for patients with RRMM have improved over the years, however treatment of advanced disease remains difficult. With each relapse, treatments may be less effective due to the emergence of resistance that can occur.[13]

Revlimid (lenalidomide) and Pomalyst (pomalidomide) have REMS and boxed warnings while Doxil (doxorubicin hydrochloride liposome injection) has a boxed warning.[14-16] Lenalidomide and pomalidomide have a REMS with ETASU to prevent the risk of embryo-fetal exposure and to inform prescribers, patients, and pharmacists about the serious risks and safe use conditions and also a boxed warning for hematologic toxicity and venous and arterial thromboembolism.[14] Pomalidomide also has a boxed warning for venous and arterial thromboembolism.[15] Doxorubicin hydrochloride liposome injection has a boxed warning for cardiomyopathy and infusion related reactions.

Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel) are CAR-T drug therapies that have REMS with ETASU to mitigate the risk of CRS and neurological toxicities.[17,18] The REMS include provisions to restrict the drug to certain healthcare settings that have at least two doses of tocilizumab on site prior to infusion for each patient and are ready for administration within two hours.

Blenrep (belantamab mafodotin-blmf) has a REMS with ETASU to manage the risk of ocular toxicity.[19] The REMS includes provisions to educate healthcare providers, monitor patients with verification of ophthalmic exams, and informing patients about the risk of ocular toxicity and need for ophthalmic exams.[19]

A list of products used to treat multiple myeloma include are summarized in Section 10: Appendix.

4. Benefit Assessment

The efficacy and safety of teclistamab was evaluated in a single-arm, open-label, multicenter study of teclistamab administered as monotherapy to patients with relapsed or refractory multiple myeloma, MajesTEC-1 (MMY1001, NCT03145181 [Phase 1] and NCT04557098 [Phase 2]). The protocol included a Part 1 dose escalation cohort and a Part 2 dose expansion cohort. The Part 2 dose expansion cohort was amended to include a phase 2 registrational portion, which evaluated the recommended phase 2 dosing regimen in 3 parallel cohorts that differ based on prior therapies. Inclusion criteria for Part 1 was subjects who had 2 prior lines of therapy which included a proteasome inhibitor and an immunomodulatory agent while the inclusion criteria for Part 2 was subjects who had 3 prior lines of therapy which included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The efficacy population included 110 patients in cohort A of phase 2 who received

1.5 mg/kg subcutaneous once weekly preceded by 0.06 mg/kg and 0.3 mg/kg step-up doses as part of the Phase 2 cohort.[20,21]

The primary endpoint was the overall response rate (ORR) which was achieved in 68% of patients. The median duration of response was 11.5 months. The 6- and 9-month event free rate was 89.7% and 83.3%, respectively.[20] The FDA clinical reviewer concluded the trial supported the efficacy of teclistamab in patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies which included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and recommends accelerated approval based on these data.

5. Risk Assessment & Safe-Use Conditions

The safety of teclistamab was evaluated in MajesTEC-1.[20,21] The safety population in this trial consists of 165 patients who received at least one dose of teclistamab 1.5 mg/kg subcutaneously once weekly preceded by 0.06 mg/kg and 0.3 mg/kg step-up doses. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 6/165 (3.6%) of patients. The rate of dose interruptions due to a TEAE was high and occurred in 120/165 (73%) of patients. However, there were no dose reductions due to TEAEs.

The most frequently reported adverse reactions included pyrexia (76%), CRS (72%), musculoskeletal pain (44%), injection site reaction (37%), fatigue (33%), upper respiratory tract infection (26%), headache (25%), nausea (25%), and diarrhea (21%).[20]

Deaths

As of the clinical cutoff, 40 deaths were reported. Thirty deaths were due to disease progression, one was classified as 'other,' and nine due to an adverse event. Half of these deaths occurred within 30 days after last dose and the other half occurred beyond 30 days after last dose. The fatal TEAEs included hyper viscosity syndrome, Covid-19, general physical health deteriorations, respiratory distress, hemoperitoneum, multiple organ dysfunction syndrome, organ failure, and pneumonia.[22]

Serious TEAEs

Serious TEAEs occurred in 54% of patients who received teclistamab. These included pneumonia (15%), CRS (8%), sepsis (6%), general physical health deterioration (6%), Covid-19 (6%), acute kidney injury (4.8%), pyrexia (4.8%), and musculoskeletal pain (2.4%).[23]

DHM2 determined CRS and neurologic toxicity including ICANS will require a boxed warning and REMS, with additional adverse events to be communicated in the warnings and precautions section. Other adverse reactions that will be communicated in the warnings and precautions include hepatotoxicity, infections, neutropenia, hypersensitivity and other administration reactions, and embryo fetal toxicity.[20] A Medication Guide will also be included as part of labeling.

5.1. Cytokine Release Syndrome

The risk of CRS, which may be life threatening, was identified as a serious risk in the clinical trial. All study participants received premedication with a corticosteroid, e.g., dexamethasone, a histamine-1 (H1)-receptor antagonist, e.g., diphenhydramine, and an antipyretic, e.g., acetaminophen, accompanied by supportive care which included tocilizumab and additional corticosteroids if needed.

In patients receiving teclistamab, 72% experienced CRS, despite all patients receiving premedications. Symptoms included pyrexia, chills, headache, and hypotension.[21] Most patients who experienced CRS experienced Grade 1 events (n = 82/165; 50%). Twenty one percent (n = 35/165) of patients experienced Grade 2 CRS and 0.6% (1/165) patients experienced Grade 3 CRS. There were no Grade 4 events or deaths from CRS reported. The median onset of CRS from the last teclistamab dose was 2 days (range 1-6 days). The median duration of CRS was 2 days (range: 1-9 days). Most patients in the clinical trial experienced their first occurrence of CRS following step-up dose 1, step-up dose 2, or first treatment dose.[21] However, two patients experienced their first CRS event following the second treatment dose and two patients experienced their first CRS event following the fourth treatment dose.[21] The latest dose of study treatment associated with CRS onset was at Cycle 3 Day eight.[21] All CRS events resolved in the clinical trial program.

Tocilizumab and corticosteroids were recommended in the study protocol for management of CRS based on the severity of symptoms, however ultimate management was based on physician discretion and standard of care at the study site.[21] The most frequently reported symptoms of CRS were pyrexia, hypoxia, chills, hypotension, sinus tachycardia, and headache.

Sixty-six percent of patients (n = 106/165) received supportive care for CRS. Specifically, 36% of patients (n = 60/165) received tocilizumab, 8% (n = 13/165) received corticosteroids, 13% (n = 21/165) received supplemental low flow oxygen, and 0.6% (n = 1/165) received a single vasopressor. Tocilizumab was administered for 21% of Grade 1 CRS events; 88% of Grade 2 CRS events. Of note, there was no clinically meaningful difference in patients who developed CRS and received tocilizumab compared to patients who did not receive tocilizumab regarding the time to next teclistamab dose, duration of CRS, and rate of dose interruption or dose skips for CRS.[24]

Tocilizumab is not approved for use in bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engagers or for use in Grade 1 or 2 events; therefore, it will not be included in the prescribing information for teclistamab. Recommendations in the prescribing information include initiating therapy according to the step-up dosing schedule and administering pretreatment medications to reduce the risk of CRS. The prescribing information also advises that patients should be hospitalized for 48 hours after administration of all doses within the teclistamab step-up dosing schedule.

5.2. Neurologic Toxicity including ICANS

The risk of neurologic toxicity including ICANS, which may be life threatening, was identified as a serious risk in the clinical trial and was mitigated by neurologic exams at baseline, during step-up dosing, and through Cycle 2, then as clinically indicated. In addition, subjects who experienced Grade ≥2 neurotoxicity were hospitalized for the subsequent 2 doses. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.[20]

In patients receiving teclistamab in the clinical trial, 57% experienced neurologic toxicity. Most patients experienced either Grade 1 or Grade 2 with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients. The most common symptoms of neurologic toxicity were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%). With longer follow-up, Grade 4 seizure and fatal Guillain-Barre syndrome (one patient each) occurred in patients who received teclistamab. The median time to onset of neurologic toxicity was 2 days (range: 1 to 6 days) after the most recent dose. Most neurologic toxicity events (91.7%) resolved. There were no discontinuations or dose reductions due to neurologic toxicity.

ICANS was reported in 6% of patients in the clinical trial program. Most patients experienced ICANS following step-up dose 1 (1.2%), step-up dose 2 (0.6%), or the initial treatment dose (1.8%). All ICANS events were either Grade 1 or Grade 2. The median time to onset of ICANS was 4 (range: 2 to 8) days after the most recent dose and the median duration of ICANS was 3 days (range: 1 to 20 days). Patients exhibiting a confused state and dysgraphia were the most frequent clinical manifestations of ICANS. Recurrent ICANS occurred in 1.8% of patients.

Recommendations in the prescribing information include monitoring patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate the patient and provide supportive therapy based on severity, and withhold or permanently discontinue teclistamab based on the severity of symptoms. The prescribing information also recommends advising patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of the step-up dosing schedule, and in the event of new onset of any neurologic toxicity symptoms until resolves.

6. Expected Postmarket Use

If approved, teclistamab will be administered by a healthcare provider in the following practice settings: inpatient hospital settings, hospital outpatient settings, community oncology physician offices, and oncology infusion centers that administer subcutaneous anti-cancer therapies. It is expected oncologists and hematologists will be the primary prescribers of teclistamab. Although some prescribers may be familiar with the management of the aforementioned risks, there may also be prescribers, with limited or no experience managing CRS and neurologic toxicity including ICANS, primarily those practicing in an outpatient setting. As such, some patients might not receive prompt supportive care for CRS or neurologic toxicity including ICANS if prescribers are not fully aware and educated to monitor for these risks. Furthermore, the convenient subcutaneous route of administration lends teclistamab to be

accessible in a broader range of care and practice settings than other approved products for RRMM. The risks of CRS and neurologic toxicity may be greater if they occur in a setting in which prompt supportive care is not provided or accessible.

While the patient population will have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, these products are not associated with CRS or neurologic toxicity, including ICANS. Therefore, it is unlikely patients will be familiar with CRS and neurologic toxicity, including ICANS. However, CRS associated with teclistamab presents initially with a fever in >95% of patients and we expect patients who would be eligible for teclistamab therapy would be familiar with identifying and monitoring for fevers at home. Oncology patients are often instructed to monitor themselves for fevers as a common symptom of infection due to known complications of cancer therapies such as febrile neutropenia.

7. Risk Management Activities Proposed by the Applicant

To mitigate the risk of CRS and neurologic toxicity, the Applicant initially proposed a Boxed Warning for CRS, included administration of pre-medications in the Dosage and Administration section of the prescribing information and included CRS, neurologic toxicity, and effects on ability to drive and use machines in the Warnings and Precautions section. The Applicant also proposed a Medication Guide and pharmacovigilance plan, consisting of routine risk communication via the prescribing information and routine adverse reactions reporting and signal detection. On July 8, 2022, the Applicant amended their submission to include a REMS; details on the proposed REMS are described in the sections below.

7.1. Review of Applicant's Proposed REMS

The Applicant submitted a REMS comprised of a communication plan, ETASU A (prescriber certification), ETASU B (pharmacy or healthcare setting certification), and a timetable for submission of assessments on July 8, 2022. In response to interim comments and redlined REMS materials from the Agency on July 28, 2022, September 8, 2022, September 16, 2022, and October 5, 2022, the proposed REMS was amended on August 1, 2022, August 4, 2022, August 9, 2022, September 13, 2022, September 21, 2022, October 6, 2022, October 7, 2022, and October 11, 2022. The final REMS document, REMS materials, and REMS Supporting Document were submitted October 21, 2022.

The Applicant's proposed REMS was based on the education to investigators in the clinical trial protocol for monitoring for the reported adverse events of CRS and neurologic toxicity. Below is the overview of the Applicant's proposed REMS, submitted on July 8, 2022 and the changes made during the review of the application.

7.1.1. REMS Goals

The goal of the TECVAYLI REMS is to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by:

- Educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.

Reviewer's Comments:

The Applicant's proposed goals for the REMS as submitted on July 8, 2022, were as follows:

(b) (4)

[redacted]

7.1.2. Communication Plan

The Applicant proposed to send a REMS Healthcare Provider Letter, a Professional Society Letter, and a Fact Sheet to communicate Tecvayli is approved with REMS to mitigate the risk of CRS and neurologic toxicity. The Applicant proposes to send the Fact Sheet with the REMS Letters and provide them during the initial dissemination with healthcare providers for 12 months after Tecvayli approval. The Fact Sheet messaging focuses on the risks of CRS and neurologic toxicity and the REMS program. The Healthcare

Provider letter and REMS Fact Sheet target healthcare providers such as oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology nurses, and pharmacists. The REMS Letters to Professional Societies and REMS Factsheet targets professional societies including the American Society of Clinical Oncology (ASCO); American Society of Hematology (ASH); Oncology Nursing Society (ONS); National Comprehensive Cancer Network (NCCN); Hematology Oncology Pharmacy Association (HOPA); American Pharmacists Association (APhA); American Society of Health-System Pharmacists (ASHP).

The Applicant proposed to send the REMS letters via email within 60 calendar days of the date Tecvayli is first commercially distributed and again 12 months later. If the first email is unsuccessful and depending on the reason, the Applicant proposed to send the REMS letter by mail or a second email within 30 calendar days of the date the first email was sent if a healthcare provider's email address is not available or the email is undeliverable and a second email within 30 calendar days of the date the first email was sent if the first email is marked unopened. The Applicant proposed to email the REMS Letters within 30 calendar days of the date Tecvayli is first commercially distributed, and again 12 months later.

Reviewer's Comments:

We agree with the Applicant's proposal to communicate the serious risks of Tecvayli and that Tecvayli is only available through restricted distribution, by way of the Tecvayli REMS. A communication plan is included in this REMS, in addition to ETASU A and ETASU B, to inform prescribers and other stakeholder about the REMS requirements prior to prescribing Tecvayli and to help prescribers determine patient eligibility. Information on the REMS in these communication materials will include the requirements that prescribers must certify in the REMS program prior to prescribing Tecvayli, pharmacies and healthcare settings must certify in the REMS program prior to dispensing Tecvayli, and the need to monitor for CRS and neurologic toxicity in patients taking Tecvayli.

The Applicant did not originally include Advanced Practitioner Society for Hematology and Oncology (APSHO) and *Society of Hematologic Oncology (SOHO) in the professional societies targeted. The Applicant included APSHO and SOHO in the professional societies targeted per DRM's recommendation.*

In addition, we disagreed with the Applicant's originally proposed 60-day timeline for distribution of communication of the REMS letters via email. Due to the importance of education in this REMS, DRM revised this timeline to 30 days calendar days of the date Tecvayli is first commercially distributed. The Applicant accepted this revision in the REMS submitted on October 11, 2022.

7.1.3. Elements to Assure Safe 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 Tecvayli REMS. To become certified, the prescriber must review the prescribing information, the Prescriber training program, and 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 submit these to the REMS. As part of prescriber certification, the prescriber must agree to counseling the patient on how to recognize and respond to signs and symptoms of CRS and neurologic toxicity using the Patient Wallet Card, complete the Patient Wallet Card, and provide the patient/caregiver with the Patient Wallet Card. The prescriber must also counsel the patient that they should be hospitalized for 48 hours after administration of all doses within the step-up dosing schedule. Lastly, the prescriber must report serious adverse events suggestive of CRS or neurologic toxicity, including ICANS to the REMS program.

Reviewer's comments:

We agree that prescriber training and certification is necessary to ensure the benefits of Tecvayli outweigh the risks. As described above, due to the subcutaneous route, and ease of administration of Tecvayli, we expect broader use of this product by outpatient clinic settings where prescribers may be less familiar with monitoring for and managing CRS and neurologic toxicities. Prescriber certification ensures prescribers are educated on the risks of CRS and neurologic toxicity associated with Tecvayli, the need for monitoring, and the need for patient counseling on the risks of CRS and neurologic toxicity. We also agree with the requirements for certification listed above, which support the goal and objectives of the REMS. The completion of a Prescriber Knowledge Assessment is used to further ensure prescribers understand the risks and requirements of the REMS before prescribing Tecvayli to patients.

The Agency conveyed to the Applicant on July 28, 2022,[f] September 8, 2022,[g] September 16, 2022,[h] and October 4, 2022[i] that changes were necessary to the Healthcare Provider directed materials. Specifically, the Agency recommended the prescriber and pharmacy training materials be separated into two separate training programs, the addition of content to better align with the prescribing information, add a 'Training Outline' slide, add a separate section of the slide deck to address Neurologic Toxicity Including ICANS, revisions and clarifications to the information pertaining (b) (4)

ETASU B: Pharmacy and Healthcare setting Certification

The Applicant proposed Tecvayli is dispensed only from certified pharmacies and healthcare settings. Certified pharmacies and healthcare settings will be required to verify that prescribers are certified by obtaining a REMS Dispense Authorization (RDA) prior to dispensing Tecvayli. Pharmacies and healthcare settings must become certified by designating an authorized representative to complete the certification process, 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 Tecvayli on the REMS requirements using the Pharmacy and Healthcare Setting Training Program.

Reviewer's comments:

We agree with the Applicant's proposal for pharmacy and healthcare setting certification to ensure that prescribers are certified. As currently designed, the role of pharmacy or healthcare setting certification is to verify that prescribers are certified.

On July 28, 2022,[e] September 8, 2022,[f] and October 4, 2022,[h] *we provided comments on the pharmacy and healthcare setting directed materials. Specifically, the Agency recommended the prescriber and pharmacy training materials be separated into two separate training programs, the addition of content to better align with the prescribing information, and the addition of a statement to indicate that*

[f] Karpow, C. Evaluation of Need for a REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 JUL 28. RCM No.: 2021-2487.

[g] Karpow, C. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 SEP 08. RCM No.: 2021-2487.

[h] Karpow, C. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 SEP 16. RCM No.: 2021-2487.

[i] Karpow, C. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 OCT 04. RCM No.: 2021-2487.

Authorized Representatives cannot also be the Certified Prescriber in the Healthcare Setting. The Applicant accepted our revisions.

During the course of the review, the Applicant proposed (b) (4) *We ultimately agreed with the Applicant's proposal for a prescriber's office to become certified as a healthcare setting and carry out the functions of ETASU B as long as the authorized representative is a different individual from the certified prescriber. Therefore, all references to* (b) (4) *were removed from the REMS as prescriber's offices that dispense will be subject to the requirements of pharmacies and healthcare settings that dispense Tecvayli.*

7.1.4. Implementation System

For successful implementation of the REMS, the Applicant proposes to maintain a REMS Call Center and REMS Website to support patients, prescribers, healthcare providers, pharmacies and healthcare settings, and wholesaler-distributors to interface with the REMS. The Applicant will notify stakeholders of successful enrollment in the REMS within one business day. The Applicant will ensure teclistamab 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 to demonstrate the REMS requirements are being met, as well as a database of all certified stakeholders.

Reviewer's Comments: *We agree with the Applicant's proposal to include an implementation system, and provided comments on July 28, 2022,[j] September 8, 2022,[k] and October 4, 2022[l] with recommendations to the implementation system. The Applicant provided a proposed implementation timeline for the REMS program following approval, clarified the audit plan, and made other improvements to the REMS Training, REMS Communications, and REMS Operations. DRM provided feedback to revise the time for the REMS program to contact stakeholders when they are enrolled in the Tecvayli REMS from 7 business days to 1 business day and a requirement to audit pharmacies and*

[j] Karpow, C. Evaluation of Need for a REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 JUL 28. RCM No.: 2021-2487.

[k] Karpow, C. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 SEP 08. RCM No.: 2021-2487.

[l] Karpow, C. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 OCT 04. RCM No.: 2021-2487.

wholesalers-distributors no later than 180 days after the pharmacy or healthcare setting receives their first shipment of TECVAYLI and annually thereafter.

7.1.5. Timetable for Submission of Assessment for the REMS

Janssen must submit REMS assessments to the FDA annually from the date of the initial approval of the REMS.

Reviewer's Comments: *The applicant originally proposed submitting REMS assessments 6 months and 12 months post approval of the REMS, then annually thereafter. The Division of Mitigation and Medication Error Surveillance (DMAMES) and DRM recommend Tecvayli REMS assessments to be submitted beginning at 12 months post approval, then annually thereafter. Evaluation of the REMS strategy to directly affect knowledge will require submission of prescriber surveys. Submission of prescriber survey results with the 6-month assessment report is not feasible due to the time needed for development of the survey protocol and instruments after approval, and subsequent review of these by the Agency. In addition, the Agency will be monitoring cases as they are submitted to the FDA Adverse Event Reporting System (FAERS).*

7.1.6. REMS Materials & Key Risk Messages

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

- Dear Healthcare Provider Letter (PDF and email format): informs healthcare providers of the risks of CRS and neurologic toxicity associated with Tecvayli and provides information on the Tecvayli REMS.
- Dear Professional Society Letter (PDF and email format): informs the healthcare provider members of these societies of the risks of CRS and neurologic toxicity associated with Tecvayli and provides information on the Tecvayli REMS.
- Adverse Reaction Management Guide: provides an easy to access summary for healthcare providers on how to manage the risks of CRS and neurologic toxicity associated with teclistamab.
- Prescriber Enrollment Form: mechanism to enroll the prescriber in the REMS and for the HCP to attest the understand the requirements of the REMS.
- Pharmacy and Healthcare Setting Enrollment Form: mechanism to enroll the pharmacy or healthcare setting in the REMS.
- Training for Prescribers: serves to inform prescribers of the serious risks associated with teclistamab, the REMS requirements, and the responsibilities of the prescriber.
- Training for Pharmacies and Healthcare Settings: serves to inform pharmacy and healthcare setting authorized representatives of the serious risks associated with teclistamab, the REMS requirements, and the responsibilities of the pharmacy and healthcare setting and pharmacy and healthcare setting authorized representative.
- Prescriber Knowledge Assessment: ensures prescribers understand the risks of teclistamab and the requirements of the REMS prior to becoming certified.
- Patient Wallet Card: serves to inform patients on the serious risks associated with teclistamab, 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.

- REMS Fact Sheet: provides a summary of the required REMS safety information and key requirements of the REMS for prescribers, pharmacies and healthcare settings, and wholesaler-distributors.
- REMS Website: serves as a source of information for stakeholders. 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. Pharmacies and healthcare settings will be able to certify in the REMS by completing the pharmacy and healthcare setting training. Upon certification of pharmacies and healthcare settings, pharmacies and healthcare settings will be able to obtain authorization to dispense online. The REMS appended materials, including a link to the Prescribing Information and Medication Guide, will be available and able to be downloaded.

The Applicant did not provide key risks messages with the REMS submission.

Reviewer's Comments: *DRM agrees with the proposed REMS materials. Key risk messages have been drafted by DRM in the REMS Section 8.1.3.*

7.1.7. Supporting Document

The REMS Supporting Document includes the background and the Applicant's rationale for the REMS currently under review. The Supporting Document also contains information on stakeholders' responsibilities in the REMS, how they carry out those responsibilities, and how the REMS will be implemented. The Applicant appended the Audit Plan, Noncompliance Plan, and Pharmacy and Healthcare Setting REMS Dispense Authorization (RDA) REMS Program Website Screenshots to the supporting document.

Reviewer Comments*:*

On October 4, 2022[m] *we provided comments on the REMS Supporting Document. The Applicant accepted our recommendations. Specifically, the Agency recommended all content in the REMS Supporting Document align with the prescribing information and REMS document. The Agency also recommended the addition of a statement to indicate that Authorized Representatives cannot also be the Certified*

[m] Karpow, C. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DRM (US); 2022 OCT 04. RCM No.: 2021-2487.

Prescriber in the Healthcare Setting. We defer review of the Audit and Noncompliance plans which were reviewed by DMAMES under separate cover.[n,o,p]

7.1.8. REMS Assessment Plan

The Applicant initially submitted a REMS Assessment Plan on July 8, 2022, as part of the Tecvayli REMS Supporting Document. This initial Assessment Plan did not capture all metrics necessary to ensure the goal and objectives of the Tecvayli REMS were being met. The Applicant was sent revisions to the Assessment Plan by DMAMES on September 13, 2022 and resubmitted the revised Assessment Plan on September 21, 2022. Additional revisions were required, and DMAMES sent the revisions to the Applicant on October 7, 2022. The Assessment Plan was resubmitted by the Applicant on October 11, 2022.

The assessment plan includes metrics to assess 1) REMS Communication Plan Activities, 2) Program Implementation, 3) REMS certification and enrollment statistics, 4) Utilization Data, 5) REMS compliance, 6) REMS Coordinating Center, 7) Knowledge Assessment, 8) Periodic survey of certified prescribers, 9) Report on key performance indicators (KPI), 10) Summary analysis of all reported cases of CRS and Neurologic toxicity.

The assessment plan includes two KPI's, one as a process indicator and one as an outcome indicator. The process indicator is used to determine if the REMS is being implemented and operating as intended. For this REMS, the process indicator will measure the proportion of dispensed prescriptions that were authorized by the REMS prior to dispensing compared to all dispenses of Tecvayli. The REMS authorization requires both the prescriber and the pharmacy or healthcare setting to be certified. A threshold of 99.9% compliance has been set a priori. The outcome indicator is used to determine if the REMS is producing its intended results. For this REMS, the outcome indicator will measure the proportion of prescriber survey respondents that demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicities including ICANS. A target threshold of ≥ 80% of prescriber survey respondents demonstrating knowledge has been set a priori. Metric 10, a summary analysis of all reported cases of CRS and Neurologic toxicity, will measure the safety-related outcome of all reported cases stratified by grade/severity. This analysis may provide insight into prescribers' awareness or behavior in following the recommendations in the REMS and

[n] Bergquist, B. Evaluation of Proposed REMS for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DMAMES (US); 2022 SEP 13. Nexus ID No.: 2022-71.

[o] Bergquist, B. Evaluation of proposed REMS assessment plan, audit plan and noncompliance plan for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DMAMES (US); 2022 OCT 07. Nexus ID No.: 2022-71.

[p] Bergquist, B. Evaluation of proposed REMS assessment plan, audit plan and noncompliance plan for Tecvayli (teclistamab) (BLA 761291). Silver Spring (MD): FDA, CDER, OSE, DMAMES (US); 2022 OCT 20. Nexus ID No.: 2022-71.

labeling for mitigating the risks of CRS and Neurologic toxicity such as initiating step-up dosing in the hospital setting and use of pre-medications among others.

Reviewer's Comments: *DRM and DMAMES agree that the Assessment Plan submitted on October 11, 2022 is acceptable and captures all necessary metrics. We will use a composite of the process indicator, outcome indicator as well as the safety related outcomes to determine if the REMS is meeting the goals.*

7.1.9. Summary of OPDP Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on August 10, 2022, and completed a consult review on August 26, 2022, by Jennifer Chen.[25] DRM accepted most recommendations and provided them in comments to the Applicant on September 8, 2022. These included aligning the REMS materials with the Boxed Warning and to align the training materials with the Prescribing Information. OPDP had concerns regarding the presentation of risk information on the REMS Fact Sheet, Prescriber Enrollment Form, and REMS Website; however, DRM does not agree with these recommendations for the following reasons:

- The REMS Fact Sheet is not intended to provide a comprehensive look of information related to the REMS, rather it presents some risk information along with an overview of the requirements of the REMS.
- The Prescriber Enrollment Form contains the Prescriber Attestations, which must align with the requirements in the REMS Document and since the REMS does not require the prescriber to provide specific counseling points to the patient, we are not able to include this information as part of the attestations. However, this information is included in the Prescriber Counseling section of the Prescriber Training.
- The purpose of the REMS landing page is to introduce the Tecvayli REMS and brief risk information as related to the REMS.

OPDP accepted our rationale.

7.2 Other Proposed Risk Management Activities

The Applicant did not propose any additional risk management activities.

8. Discussion of Need for a REMS

In the ongoing clinical review, the clinical reviewer recommends accelerated approval of teclistamab based on the efficacy and safety information currently available.

The results from the clinical trial supported the efficacy of teclistamab in patients with RRMM. Due to the relapsing and refractory nature of the disease, treatments may be less effective due to the emergence of resistance that can occur. There remains an unmet need for patients to have access to alternative treatments and therapies after they have relapsed on previous therapies. When compared to approved therapies for patients with four prior lines of therapy, the observed ORR of 68%, duration of response (DOR), and median DOR (not reached with a median of 7.8 months of follow-up) with teclistamab exceeds that of selinexor in combination with dexamethasone (ORR 25.4%, mDOR 3.8

months) and belantamab mafodotin (ORR 31%, mDOR not reached with a median of 6.3 months of follow-up) and approaches the ORR for the two approved BCMA-directed CAR T-cell products (ORR 72% and mDOR 11 months for idecabtagene vicleucel; ORR 97.9% and mDOR 21.8 months for ciltacabtagene autoleucel).[20,26] In addition, teclistamab is available as a convenient subcutaneous route of administration which may allow broader use in community settings and various patient populations.[27]

The most serious risks associated with teclistamab are CRS and neurologic toxicity including ICANS. In the clinical trial setting, all subjects received step-up doses of teclistamab, administration of pre-medications, inpatient initiation of teclistamab, and prompt supportive care for CRS.[28] The incidence of CRS observed in the clinical trial was 72%.[21] Most patients experienced Grade 1 or Grade 2 CRS and one patient experienced Grade 3 CRS.[21] Sixty-six percent of patients required supportive care for CRS in the clinical trial. Although the severity of CRS was relatively low, the high incidence of CRS occurred despite all patients receiving pretreatment medications.

To mitigate the risk of neurologic toxicity, neurologic exams were conducted at baseline, pre- and post-dose during step-up dosing and Cycle 2, then as clinically indicated from Cycle 3 onward in the clinical trial setting. In addition, dose delays, hospitalization for subsequent doses in patients experiencing any Grade ≥2 neurologic toxicity, and permanent discontinuation of study treatment for patients with recurrent Grade 3 or any Grade 4 neurologic toxicity also occurred. The incidence of neurologic TEAEs was 57% and the incidence of ICANS was 6%. The severity of neurologic TEAEs was relatively low with only 1.8% of patients experiencing a Grade 3 neurologic TEAE, however, with longer follow-up, Grade 4 seizure and Guillain-Barre syndrome events occurred in one patient each. The severity of ICANS was low as all ICANS events were either Grade 1 or Grade 2.

Other well-known immunotherapy associated with CRS and neurologic toxicity is the class of CAR-T cell therapy for various hematologic malignancies, which includes Kymriah, Yescarta, Tecartus, Breyanzi, Abecma, and Carvytki.[17,18,29-32] Abecma and Carvytki are approved for RRMM.[17,18] All of these products are approved with REMS with ETASU to mitigate the risk of CRS and neurologic toxicities.[17,18,29-32] Because of the incidence and severity of CRS reported during clinical trials, the REMS for Kymriah, Yescarta, Tecartus, Breyanzi, Abecma, and Carvytki include restricting the product to certain healthcare settings that have at least two doses of tocilizumab on site prior to infusion for each patient and are ready for administration within two hours. Blincyto, a bi-specific T-cell engager, was approved in 2014 for the treatment of acute lymphoblastic leukemia (ALL) with a Communication Plan REMS to mitigate the risks of CRS, neurologic toxicities, and the risk of preparation and administration errors.[33]

Although CRS and neurologic toxicity appear to be common in the treatment for RRMM, teclistamab is unique due to the high incidence of CRS and neurologic toxicity despite risk mitigation activities employed in the clinical trials, and the ease of administration leading to anticipated broader use in community oncology practice settings where healthcare providers may be less familiar with these risks and patients may experience serious adverse events without access to prompt supportive care. In addition, in contrast to the CAR T-cell products, which are a one-time dose and have a complex manufacturing process, teclistamab is a recurrent, subcutaneous, once weekly administration. The risks of CRS and neurologic toxicities were greatest in the first cycles of treatment with teclistamab, but also

occurred in later cycles of treatment, although with less frequency. Therefore, patients treated with teclistamab might be at risk for CRS and/or neurologic toxicities both in the initial and later cycles.

When determining the need for a REMS program, DRM and DHMII considered the estimated size of the population of patients who would receive teclistamab, the seriousness of the disease, the expected benefit of treatment, the seriousness of the adverse events, the expected duration of treatment with teclistamab and that teclistamab is an NME as discussed above. DRM and DHMII determined labeling via the prescribing information and Medication Guide are not sufficient to mitigate the risk of CRS and neurologic toxicity including ICANS and agree a REMS is necessary ensure the benefits outweigh the risks of teclistamab if approved. The weekly subcutaneous route of administration of teclistamab will provide a convenient treatment option compared to other medications approved for RRMM and will allow for broader use of teclistamab in an outpatient oncology setting. While multiple myeloma specialists practicing at academic centers may have experience with the management of CRS and neurotoxicity with the use of CAR T-cell products and Blincyto, there is a potential for broader use of teclistamab by prescribers who may have limited experience in managing CRS and neurologic toxicities. As teclistamab is proposed to be administered weekly via subcutaneous injection and the onset of CRS and neurologic toxicity may occur hours or days after the teclistamab dose, a REMS is necessary to ensure all prescribers are trained on how to monitor for these risks and counsel patients to seek prompt supportive care for CRS and neurologic toxicity including ICANS that might occur when a patient is home.

On June 23, 2022, this application was discussed at the REMS Oversight Committee (ROC) Meeting.[27] DHMII and DRM discussed the benefits and risks of teclistamab, as well as how it may be prescribed in the postmarket setting. DHMII and DRM proposed a REMS that includes a communication plan, ETASU A and ETASU B to mitigate the risks of CRS and neurologic toxicity.[27] A training and communication program is necessary to ensure that all prescribers are educated on the risks and the importance of monitoring patients. Given that patients were monitored in a hospital setting during the step-up dosing regimen for teclistamab, the potential severity of CRS and neurologic toxicity, and the recommendation in the prescribing information for patients to be hospitalized for step-doses, the ROC suggested DRM and DHMII either include ETASU C, in addition to ETASU A and ETASU B or provide a compelling rationale why ETASU C should not be included. DRM and DHMII addressed the ROC's concerns via email with the following rationale:[34]

ETASU C is not necessary for safe use of teclistamab due to the predictable nature of CRS associated with teclistamab. Specifically, CRS associated with teclistamab presents initially with a fever in >95% of patients. Patients who would be eligible for teclistamab are expected to be familiar with identifying and monitoring for fevers at home, and the likely prescribers, consisting of hematologists and oncologists, are expected to have experience in managing febrile neutropenia that develops in the outpatient setting which follows similar management principles. In addition, there may be risk of hospital-acquired infections and additional burden on patients, prescribers and the healthcare system related to mandating hospitalization for these patients.

The Applicant is further evaluating requirements for hospitalization in the ongoing phase 3 MajesTEC-3 trial, which includes an option for outpatient administration of the teclistamab step-up dosing regimen. However, the impact of this is unknown. Therefore, the assessment for not requiring ETASU C is based on the data in the current BLA.

The primary strategy employed in this REMS is to directly affect knowledge through education via ETASU A (prescriber certification) and use of ETASU B (pharmacy and healthcare setting certification), as a mechanism to confirm prescribers are certified. We anticipate that education through the REMS Program, prescribers and other healthcare providers will follow the instructions for administration and adverse reaction management in the prescribing information. Additionally, the review team did not identify any specific requirements for administering teclistamab that would necessitate administration in a specific healthcare setting. Ultimately, DRM and DHMII agree that the decision to hospitalize patients for all doses within the step-up dosing schedule (including when repeat step-up dosing is required due to a dose delay or adverse reaction meeting specified criteria) is best assessed and made by the prescriber and patient, rather than mandating all patients are hospitalized for step-up dosing.

The ROC agreed with the review team's recommendations that a REMS including a communication plan, ETASU A, and ETASU B would be necessary to ensure the benefits of Tecvayli outweigh the risks of CRS and neurologic toxicity.

The minimum necessary REMS elements required include:

1. Communication Plan to target healthcare providers who are likely to prescribe and care for patients treated with Tecvayli
2. Prescriber Certification (ETASU A) to ensure prescribers are educated about the risks, the need to counsel patients
3. Pharmacy Certification (ETASU B) to ensure prescribers are certified prior to dispensing Tecvayli

DRM concludes that based on the review of the proposed REMS received on October 21, 2022, 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 supports safe use of the product.

8.1.1 REMS Materials and Key Risk Messages

The following REMS materials will provide education and support the risk messages of the REMS:

- Healthcare Provider REMS Letter
- Professional Society REMS Letter
- REMS Fact Sheet
- Prescriber Enrollment Form
- Pharmacy and Healthcare Setting Enrollment Form
- Patient Wallet Card
- Prescriber Training Program
- Adverse Reaction Management Guide
- Knowledge Assessment
- Pharmacy and Healthcare Setting Training Program

- REMS Website

Key Risk Messages for Prescribers

- CRS, including life threatening and fatal reactions that can occur in patients receiving Tecvayli. Initiate treatment with Tecvayli step-up doing schedule to reduce risk of CRS. Closely monitor patients for signs or symptoms of CRS during treatment. Withhold Tecvayli until CRS resolves or permanently discontinue based on severity.
- Neurologic toxicity, including ICANS and serious life threating reaction can occur in patients receiving Tecvayli. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment. Withhold Tecvayli until neurologic toxicity resoles or permanently discontinue based on severity.
- Instruct the patient that they should be hospitalized for 48 hours after administration of all doses within the step-up dosing schedule.
- 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 Tecvayli.
- 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 using the Pharmacy and Healthcare Setting Training Program.
- Before dispensing Tecvayli, staff must verify prescriber is certified in the Tecvayli REMS.

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 understand these risks. Based on the high incidence of the CRS and neurologic toxicity and anticipated broader outpatient use of this product, DRM and DHMII agree a REMS consisting of a communication plan, ETASU A, and ETASU B is necessary to ensure that the benefits outweigh the risks. The REMS will also include an implementation system and timetable for submission of assessments.

DRM finds the Applicant's amended proposed REMS received on October 21, 2022 to be acceptable and is appended to this review.

10. Appendices

10.1. Table 1. FDA-Approved Treatments for Multiple Myeloma

Product Name **Year of Approval**	**Indication**	**Dosing and Administration**	**Risk Management Approaches/Boxed Warning,** **Medication Guide**
Bortezomib 05/13/2003	Treatment of adult patients with multiple myeloma and mantel cell lymphoma	The recommended starting dose of VELCADE is 1.3 mg/m2. VELCADE is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL. VELCADE retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with VELCADE and who have relapsed at least six months after completing prior VELCADE treatment. Treatment may be started at the last tolerated dose	Section 5 Warnings and precautions of the prescribing information
Lenalidomide 12/27/2005	in combination with dexamethasone is indicated for the treatment of adult patients with multiple myeloma (MM); maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT); Myelodysplastic Syndromes; Mantle Cell Lymphoma; Follicular Lymphoma; Marginal Zone Lymphoma	25 mg orally once daily on Days 1-21 of repeated 28-day cycles in combination with dexamethasone.	REMS, Boxed Warning
Carfilzomib 07/20/2012	Treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with lenalidomide and dexamethasone, dexamethasone, daratumumab and dexamethasone, or daratumumab and hyaluronidase-fihi and dexamethasone. Indicated as a single agent for the treatment of adult patient with relapsed or refractory multiple myeloma who have received one or more lines of therapy.	Administer Kyprolis intravenously as a 10-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with lenalidomide and dexamethasone until Cycle 12 as shown in Table 1 [see Clinical Studies (14.1)]. The recommended starting dose of Kyprolis is 20 mg/m2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 27 mg/m2 on Cycle 1, Day 8. From Cycle 13, administer Kyprolis on Days 1, 2, 15, 16 until Cycle 18. Discontinue Kyprolis after Cycle 18. Continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity occurs.	Section 5 Warnings and precautions of the prescribing information
Daratumumab 11/16/2015	treatment of adult patients with multiple myeloma: in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in	16 mg/kg actual body weight administered as an intravenous infusion according to specific dosing schedules (See PI).	Section 5 Warnings and precautions of the prescribing information

	patients with relapsed or refractory multiple myeloma who have received at least one prior therapy; in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant; in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant; in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy; in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor; as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.		
Ixazomib 11/20/2015	indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy	4 mg administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle; dose modifications permitted (See PI).	Section 5 Warnings and precautions of the prescribing information
Isatuximab-irfc 03/02/2020	in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor; in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.	10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone, according to the schedule (See PI).	Section 5 Warnings and precautions of the prescribing information
Pomalidomide 02/08/2013	treatment of adult patients with multiple myeloma (MM) in combination with dexamethasone who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy & for Kaposi Sarcoma	4 mg once daily orally with or without food on Days 1 through 21 of each 28-day cycle until disease progression. Give POMALYST in combination with dexamethasone	REMS, Boxed Warning, Medication Guide
Cyclophosphamide 11/16/1959	malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or	When used as the only oncolytic drug therapy, the initial course of Cyclophosphamide Injection for patients	Section 5 Warnings and precautions of the

	diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma; leukemias: chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia (cyclophosphamide given during remission is effective in prolonging its duration); mycosis fungoides (advanced disease); neuroblastoma (disseminated disease); adenocarcinoma of the ovary; retinoblastoma; carcinoma of the breast	with no hematologic deficiency usually consists of 40 mg per kg to 50 mg per kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 mg per kg to 15 mg per kg given every 7 to 10 days or 3 mg per kg to 5 mg per kg twice weekly. When cyclophosphamide is included in combined cytotoxic regimens, it may be necessary to reduce the dose of Cyclophosphamide Injection as well as that of the other drugs.	prescribing information
Elotuzumab 11/30/2015	indicated in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one to three prior therapies; indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.	10 mg/kg administered intravenously every week for the first two cycles (28-day cycle) and every 2 weeks thereafter in conjunction with the recommended dosing of lenalidomide and low-dose dexamethasone as described below. Continue treatment until disease progression or unacceptable toxicity.	Section 5 Warnings and precautions of the prescribing information & Patient Information
Selinexor 07/03/2019	in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; in combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. Diffuse Large B-Cell Lymphoma.	100 mg taken orally once weekly on Day 1 of each week until disease progression or unacceptable toxicity in combination with: Bortezomib 1.3 mg/m2 administered subcutaneously once weekly on Day 1 of each week for 4 weeks followed by 1 week off & Dexamethasone 20 mg taken orally twice weekly on Days 1 and 2 of each week.	Section 5 Warnings and precautions of the prescribing information & Medication Guide
Belantamab mafodotin-blmf 08/05/2020	for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.	2.5 mg/kg of actual body weight given as an intravenous infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity. Dose reduction for adverse reactions is 1.9 mg kg once every 3 weeks.	REMS, Boxed Warning
Idecabtagene vicleucel 03/26/2021	for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.	The recommended dose range is 300 to 460 × 106 CAR-positive T cells.	REMS, Boxed Warning

Ciltacabtagene autoleucel 02/28/2022	for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.	Recommended dose range is 0.5–1.0×10 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10 CAR-positive viable T cells per single-dose infusion.	REMS, Boxed Warning

10.2. Tecvayli REMS Assessment Plan

The REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication Plan

1. REMS communication plan activities (provide data for the 1-year and 2-year assessments only):
    a. Sources of the distribution lists for healthcare providers
    b. Number of healthcare providers targeted stratified by specialty if known
    c. Number of healthcare professional societies targeted, and which healthcare professional societies reported distribution of the REMS letter to their respective members
    d. The number of packets of REMS materials sent by date, attempt, and method of distribution
    e. The number and percentage of emails successfully delivered, opened, and unopened
    f. The number and percentage of mail successfully delivered and returned as undeliverable
    g. The number of REMS Fact Sheets distributed to targeted healthcare providers during the 12 months after TECVAYLI is commercially distributed
    h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed

Program Implementation and Operations

2. Program Implementation (provide data at the 1-year assessment only):
    a. Date of first commercial availability of TECVAYLI
    b. Date the REMS Website went live
        i. Number of total visits and unique visits to the REMS Website
        ii. Number and type of TECVAYLI REMS materials downloaded or accessed
    c. Date the REMS Coordinating Center was fully operational
    d. Date prescribers and pharmacies/healthcare settings were able to complete the REMS certification process (online and by fax)

e. Date of the first prescriber certification

f. Date of the first pharmacy/healthcare setting certification

3. REMS Certification and Enrollment Statistics (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Healthcare Providers

        i. Number of newly certified healthcare providers and number of active (i.e., who have prescribed TECVAYLI at least once during the reporting period) healthcare providers stratified by:

            1. Credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, other)

            2. Specialty (e.g., Oncology, Hematology, Internal Medicine/Family Medicine, Other). If "other" accounts for > 10% of respondents for specialties, provide the most common specialties identified.

            3. Geographic region as defined by the US Census

            4. Method of enrollment (e.g., online, fax, e-mail) for newly certified healthcare providers only

        ii. Number of incomplete prescriber enrollments, and summary of reported reason(s) for not completing

    b. Pharmacies and Healthcare Settings

        i. Number of newly certified pharmacies/healthcare settings and number of active (i.e., who have dispensed or ordered the drug at least once during the reporting period) pharmacies/healthcare settings stratified by:

            1. Type of pharmacy/healthcare setting (e.g., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Oncology Infusion Center, Community Oncology Physician Office, Other). If "other" accounts for > 10% of respondents for type, provide the most common type(s) identified.

            2. Geographic region as defined by the US Census

            3. Method of enrollment (e.g., online, fax, e-mail) for newly certified pharmacies/healthcare settings only

        ii. Number of incomplete pharmacy/healthcare setting enrollments, and summary of reported reason(s) for not completing

    c. Wholesalers/distributors

        i. Number of wholesalers/distributors contracted to ship and number of active (i.e., have shipped) wholesalers/distributors

4. Utilization Data (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Number of vials sent to certified pharmacies/healthcare settings, stratified by type of pharmacy/healthcare setting

b. Number and percentage of healthcare providers who wrote/ordered prescriptions that were dispensed, stratified by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)

c. Number of dispense authorizations stratified by pharmacy/healthcare setting type

d. Number of RDAs rejected, stratified by:

    i. Reasons and number of denials (numerator) divided by all denials (denominator)

        1. Healthcare provider not certified

        2. Other reasons for denial not categorized above

5. REMS Compliance (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Audits

        i. A copy of the audit plan

        ii. Report of audit findings for each stakeholder

        iii. Number of audits expected, and the number of audits performed

        iv. Documentation of completion of training for relevant staff

        v. Documentation of processes and procedures in place for complying with the TECVAYLI REMS

        vi. Verification for each audited stakeholder's site that the designated Authorized Representative remains the same. If different, include the number of new Authorized Representatives

        vii. Number and type of deficiencies noted for each group of audited stakeholders as a percentage of audited stakeholders

        viii. Confirmation of documentation of completion of training for relevant staff after audit findings indicated training was necessary

        ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

    b. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder (healthcare providers, pharmacies/healthcare settings and wholesalers-distributors), actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS

        i. For those with deficiencies noted, report the number that successfully completed a Corrective and Preventive Actions (CAPA) plan within the timeframes specified in the Noncompliance Plan

        ii. For any that did not complete the CAPA within the timeframe specified in the Noncompliance Plan, describe actions taken

iii. Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

1. Unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
2. Source of the noncompliance data
3. Results of root cause analysis
4. Action(s) that were taken in response

iv. Pharmacies/healthcare settings

1. Number of pharmacies/healthcare settings for which non-compliance with the TECVAYLI REMS is detected (numerator) divided by all pharmacies/healthcare settings dispensing TECVAYLI (denominator)
2. Number and description of pharmacies/healthcare settings that dispensed TECVAYLI to non-certified prescribers, and any corrective and preventative actions taken to prevent future occurrences
3. Number of non-certified pharmacies/healthcare settings that dispensed TECVAYLI (numerator) divided by all pharmacies/healthcare settings that dispensed TECVAYLI
4. Number of prescriptions dispensed by non-certified pharmacies/healthcare settings (numerator) divided by all TECVAYLI prescriptions dispensed (denominator) and the actions taken to prevent future occurrences
5. Summary of audit findings and any action taken and outcome of actions to prevent future occurrences
6. Summary of findings for monitoring conducted during the reporting period, including any CAPA

v. Wholesalers/Distributors

1. Number and description of non-certified pharmacies/healthcare settings that were shipped TECVAYLI, and the number of these that subsequently became certified
2. The number of authorized wholesalers-distributors for which non-compliance with the REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)
3. The number and type of wholesalers-distributors not contracted with Janssen that shipped TECVAYLI and the number of incidents for each
4. The number of contracted wholesalers-distributors suspended and/or unauthorized to distribute for non-compliance with REMS requirements and reasons for such actions

c. Any other TECVAYLI REMS noncompliance, source of report and resulting CAPA

6. REMS Coordinating Center Report (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Number of contacts by stakeholder type (patient/caregiver, certified prescriber, pharmacy/healthcare setting authorized representative or staff, other HCP, wholesaler/distributor, other)

    b. Summary of the reasons for the call(s) by stakeholder type. Limit the summary to the top five reasons for calls by stakeholder group

    c. Description of each call, including stakeholder credentials, that may indicate an issue with product access due to the REMS program, REMS program burden or adverse event

    d. If the summary reason for the call(s) indicates an adverse event related to Cytokine Release Syndrome (CRS) or neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) include details and the outcome of the call(s)

    e. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, health care availability, other

    f. Summary of frequently asked questions (FAQ) by stakeholder credentials type. Limit the summary to the top five FAQs for calls by stakeholder group

    g. Summary of any noncompliance that is identified through coordinating center contacts, source of report and resulting CAPA

    h. Summary of CAPAs resulting from issues identified

    i. Percentage of calls to the REMS Coordinating Center that were answered within 20 minutes

    j. The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered

    k. Percentage of calls to the REMS Coordinating Center where the caller abandoned the call before the call was answered

    l. The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

Knowledge

7. Knowledge Assessment (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Number of completed healthcare provider Knowledge Assessments, including the method of completion

    b. Summary statistics, including mean number of attempts, score, and range of scores and number of attempts to successfully complete the Knowledge Assessment

    c. Summary of most frequently missed questions on the Knowledge Assessment

d. A summary of potential comprehension or perception issues identified with the Knowledge Assessment

8. Periodic Survey of Certified Prescribers (beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report)

   A Knowledge, Attitude and Behavior (KAB) Survey will be conducted with random samples of healthcare providers who prescribe TECVAYLI

   a. Evaluation of understanding of the risks and mitigation strategies of the TECVAYLI REMS as well as compliance with the mitigation strategies

   b. An evaluation of prescriber's knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

9. Report on Key Performance Indicators: The key performance indicators (KPI), or the primary metrics that will be used to evaluate the TECVAYLI REMS, include a process indicator (REMS operations) and an outcome indicator (REMS evaluation of the primary objective)

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

   b. REMS Evaluation of the objective: $\geq$ 80% of prescriber KAB survey respondents demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

Health Outcomes and/or Surrogates of Health Outcomes

10. A summary analysis of all reported cases of CRS and neurologic toxicity including ICANS, stratified by source of report (i.e., spontaneous). (Provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Include the following stratifications by grade/severity in the analysis

       i. Step-up dosing was initiated in the hospital setting. (For those reports that indicate initiation outside of the hospital setting provide the setting if known)

       ii. Pre-medication was administered

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

10.3. References

1. Janssen Biotech, Inc. Response to FDA BLA 761291 Clinical Information Request #12 (Part 1) and Labeling Information Request Received 15 April 2022.
2. Janssen Biotech, Inc. Response to FDA BLA 761291 FDA Information Request #20 Received 27 May 2022.
3. Rollig C, Knop S, Bornhauser M. Multiple myeloma. *Lancet*. May 30 2015;385(9983):2197-208. doi:10.1016/S0140-6736(14)60493-1
4. Pick AM, Rao KV. Multiple Myeloma. In: DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V, eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e*. McGraw-Hill Education; 2020.
5. Cancer Stat Facts: Myeloma. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/mulmy.html
6. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. Jan 2022;72(1):7-33. doi:10.3322/caac.21708
7. Cancer Stat Facts: Myeloma. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Accessed February 25, 2022. https://seer.cancer.gov/statfacts/html/mulmy.html
8. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia*. May 2016;30(5):1005-17. doi:10.1038/leu.2015.356
9. Majithia N, Rajkumar SV, Lacy MQ, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. *Leukemia*. Nov 2016;30(11):2208-2213. doi:10.1038/leu.2016.147
10. Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia*. Nov 2017;31(11):2443-2448. doi:10.1038/leu.2017.138
11. Nijhof IS, van de Donk N, Zweegman S, Lokhorst HM. Current and New Therapeutic Strategies for Relapsed and Refractory Multiple Myeloma: An Update. *Drugs*. Jan 2018;78(1):19-37. doi:10.1007/s40265-017-0841-y
12. <NCCN Guidelines for Multiple Myeloma Version 5.2022 March 9, 2022.pdf>.
13. Bazarbachi AH, Al Hamed R, Malard F, Harousseau JL, Mohty M. Relapsed refractory multiple myeloma: a comprehensive overview. *Leukemia*. Oct 2019;33(10):2343-2357. doi:10.1038/s41375-019-0561-2
14. Revlimid [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated Aug 2021. Accessed March 9, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021880Orig1s064lblrpl.pdf
15. Pomalyst [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated December 2020. Accessed March 9, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204026s028lbl.pdf
16. Doxil [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated Aug 2019. Accessed March 9, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/050718s055lbl.pdf
17. Abecma [Prescribing Information]. U.S. Food and Drug Administration Updated March 2021. Accessed July 7, 2022. https://www.fda.gov/media/147055/download
18. Carvykti [Prescribing Information]. U.S. Food and Drug Administration. Accessed July 7, 2022. https://www.fda.gov/media/156560/download
19. Blenrep [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Updated February 2022. Accessed July 7, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761158s006lbl.pdf

20. Proposed prescribing information for teclistamab as currently edited by FDA. 2022.
21. Janssen Biotech, Inc. Summary of Clinical Safety. 2021.
22. FDA Midcycle Meeting. Division of Hematologic Malignancies II (DHMII).
23. Proposed NDA/BLA Multi-disciplinary Review and Evaluation for teclistamab as currently edited by FDA. 2022.
24. Janssen Biotech, Inc. Response to FDA BLA 761291 Clinical Information Request #16 Received 26 April 2022.
25. Chen J. Office of Prescription Drug Promotion Review of the Proposed Teclistamab (BLA 761291) REMS. 2022.
26. FDA REMS Oversight Committe Meeting. Division of Hematologic Malignancies II (DHMII).
27. REMS Oversight Committee Presentation Executive Summary. Division of Hematologic Malignancies II (DHMII) and Division of Risk Management (DRM).
28. Janssen Biotech, Inc. A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma MajesTEC-1. 2021.
29. Kymriah [Prescribing Information]. U.S. Food and Drug Administration. Accessed July 7, 2022. https://www.fda.gov/media/107296/download
30. Yescarta [Prescribing Information]. U.S. Food and Drug Administration. Accessed July 7, 2022. https://www.fda.gov/media/108377/download
31. Tecartus [Prescribing Information]. U.S. Food and Drug Administration. Accessed July 7, 2022. https://www.fda.gov/media/140409/download
32. Breyanzi [Prescribing Information]. U.S. Food and Drug Administration. Accessed July 7, 2022. https://www.fda.gov/media/145711/download
33. Przepiorka D. Clinical Review for Blincyto (blinatumomab) injection, for intravenous use, BLA 12557. 2014.
34. Rationale for ROC: Why ETASU C is not needed. Division of Hematologic Malignancies II (DHMII) and Division of Risk Management (DRM).

64 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CELESTE A KARPOW
10/24/2022 09:25:00 AM

KATE H OSWELL
10/24/2022 09:45:30 AM

NAOMI S BOSTON
10/24/2022 10:21:32 AM

LAURA A ZENDEL
10/24/2022 11:03:29 AM

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	761291
Nexus REMS ID Number	2022-71
Team Leader	Barbara Bergquist, PharmD (DMAMES)
Acting Deputy Division Director	Jo Wyeth, PharmD (OMEPRM)
Review Completion Date	October 24, 2022
Subject	Memorandum Regarding the Proposed REMS Assessment plan, audit plan and noncompliance plan
Trade Name	Tecvayli
Established Name	teclistamab
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Submission Date	October 21, 2022

Tecvayli (teclistamab) BLA 761291

This memorandum references the Applicant's submission of a revised REMS Supporting Document on October 21, 2022[1] to align with labeling changes to the Prescribing Information as per the Agency's October 20, 2022 communication[2]. The revised REMS Supporting Document included the Tecvayli REMS Assessment Plan, Audit Plan and Noncompliance Plan which is the subject of this memorandum.

Reviewer's comment:

Review of the revised REMS Supporting Document submitted on October 21,2022[1] found no changes to the Tecvayli REMS Assessment Plan, Audit Plan and Noncompliance Plan when compared to the October 11, 2022[3] REMS Supporting Document submission and is acceptable.

The final and agreed upon Tecvayli REMS Assessment Plan is included in Appendix A of our earlier review[4] and will be included in the Tecvayli Approval Letter.

[1] The October 21, 2022 REMS Supporting Document is available at:
BLA761291 (761291 - 0101 - (101) - 2022-10-21 - TRIAGE-1 /Electronic Submission/Gateway) - TECVAYLI REMS Supporting Document with Appendices - pdf clean

[2] October 20, 2022 Labeling Discussion Comments (Carioti, T.) BLA 761291 annotated-draft-labeling-text_FDA edits Oct20 2022. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80690f6e.

[3] The October 11, 2022 REMS Supporting Document is available at:
BLA761291 (761291 - 0098 - (98) - 2022-10-11 - ORIG-1 /REMS/Response to IR) - TECVAYLI REMS Supporting Document with Appendices - pdf clean

[4] Bergquist B. Evaluation of proposed REMS Assessment Plan, Audit Plan, and Noncompliance Plan for Tecvayli (teclistamab), BLA 761291. Silver Spring (MD): FDA, CDER, OMEPRM, DMAMES (US); 2022 Oct 20. Nexus # 2022-71. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80690ed9.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA A BERGQUIST
10/24/2022 09:55:56 AM

JO H WYETH
10/24/2022 09:59:27 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 Diseases
Division of Hematologic Malignancies II

BLA #:	761291
PRODUCT:	TECVAYLI (teclistamab-cqyv), injection, for subcutaneous use
APPLICANT:	Janssen Biotech, Inc.
FROM:	Shan Pradhan, MD, Associate Director for Safety (acting)
DATE:	October 24, 2022

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 TECVAYLI (teclistamab-cqyv) to ensure that the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurologic toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS). In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with a new multiple myeloma (MM) diagnosis in 2022 is 34,470 and 12,640 multiple myeloma-related deaths are expected to occur (American Cancer Society, 2022). In the US, multiple myeloma accounts for approximately 1-2% of all cancers and approximately 17% of hematologic malignancies (American Cancer Society 2021). These estimates are based on key statistics for MM from American Cancer Society's Cancer Statistics Center and the SEER (Surveillance, Epidemiology, and End Results) program of the National Cancer Institute.

B. Despite the availability of multiple treatments, MM remains an incurable disease, with a 5-year survival rate of 56%. Patients with recurrent MM become resistant to current standard of care options and patients who have received multiple lines of therapy and have been treated with major classes of drugs including proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies have poor outcomes.

C. Treatment with teclistamab at step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly resulted in an objective response rate (ORR) of 61.8% (95% CI 52.1, 70.9). At the time of the efficacy data cut-off, with a median follow-up of 7.4 months among responders, median duration of response was not reached (95% CI 9.0, not estimable), and the estimated duration of response (DOR) rate was 90.6% (95% CI 80.3, 95.7) at 6 months and 66.5% (38.8, 83.9) at 9 months.

D. It is expected that adult patients with relapsed or refractory MM who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody would receive treatment with teclistamab until disease progression or unacceptable toxicity.

E. Teclistamab at the recommended dose of step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly (administration is subcutaneous) poses the serious risks of CRS and neurologic toxicities including ICANS. In the pivotal MajesTEC-1 study, CRS and neurologic toxicity were common, occurring in 72% and 57% of patients, respectively, treated with teclistamab at the recommended dose. Fifty percent of patients experienced Grade 1 CRS and 21% of patients experienced Grade 2 CRS (with Grade 2 CRS, intervention such as intravenously administered fluid and/or supplemental oxygen was needed for management). CRS primarily occurred during the initial step-up dosing schedule and occurred despite consistent use of premedications; one patient (0.6%) experienced Grade 3 CRS, 2.4% of patients developed first occurrence of CRS after completion of the step-up dosing schedule, and 33% of patients had recurrent CRS. Sixty-six percent of patients received supportive therapy for management of CRS including intravenously administered fluids in 13%, low-flow oxygen in 13%, vasopressor in 0.6%, tocilizumab in 36%, and steroids in 8%. Neurologic toxicity included headache in 25% of patients, motor dysfunction in 16%, sensory neuropathy in 15%, and encephalopathy in 13%. Grade 3 or 4

neurologic events occurred in 2.4% of patients (headache, vestibular neuronitis, sciatica and spinal cord compression), and there were two additional patients with serious neurologic adverse events of Grade 4 seizure and fatal (Grade 5) Guillain Barré syndrome. Serious neurologic adverse events occurred in 6% of patients, and dose interruption due to neurologic adverse events occurred in 7% of patients. ICANS occurred in 6% of patients. Most ICANS events occurred during initial step-up dosing and 1.8% of patients experienced recurrent ICANS. Concurrent CRS occurred with 41% of ICANS events, and dose interruption due to ICANS occurred in 1.8% of patients. Patients in MajesTEC-1 were monitored closely, with hospitalization required for at least 48 hours following each dose in the initial step-up dosing schedule and for the next dose of teclistamab following events of CRS and neurologic toxicity that met specified criteria based on severity. In addition to CRS and neurologic toxicities including ICANS, teclistamab has been associated with hepatotoxicity, infections, neutropenia, and hypersensitivity and other systemic administration-related reactions.

F. TECVAYLI is a new molecular entity.

The elements of the REMS will be a Communication Plan, elements to assure safe use including ETASU A (healthcare providers who prescribe teclistamab-cqyv are specially certified) and ETASU B (pharmacies and health care settings that dispense teclistamab-cqyv are specially certified), an implementation system, and a timetable for submission of assessments of the REMS.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STACIE A WOODS
10/24/2022 11:08:24 AM

SHAN PRADHAN
10/24/2022 11:12:07 AM

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	761291
Nexus ID Number	2022-71
PDUFA Goal Date	November 28, 2022
Team Leader/Reviewer Name	Barbara Bergquist, PharmD (DMAMES)
Associate Director	Jo Wyeth, PharmD (OMEPRM)
Review Completion Date	October 20, 2022
Subject	Evaluation of proposed REMS assessment plan, audit plan and noncompliance plan
Trade Name	Tecvayli
Established Name	teclistamab
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Submission Date	October 11, 2022

Table of Contents

1. Introduction

This review provides findings from our evaluation of the revised REMS assessment plan, audit plan and noncompliance plan for Tecvayli (teclistamab) that the Applicant included in the REMS Supporting Document (SD) that was submitted on October 11, 2022.

We initiated this review in response to a consult request by the Division of Risk Management (DRM) to provide input on the quantitative and qualitative metrics that will be used to assess if the REMS is meeting its stated goal and objective.

Of note, the Applicant initially submitted the REMS assessment plan, audit plan, and noncompliance plan in their Supporting Document on July 8, 2022[a]; and submitted revised versions on September 21, 2022[b] and October 11, 2022[c] in response to our recommendations on September 13, 2022[d], and October 7, 2022[e], respectively.

2. Background

The Tecvayli application (BLA # 761291) was submitted by Janssen Biotech on December 28, 2021 with a proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior lines, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

2.1 Risk Assessment

A REMS for Tecvayli was determined to be necessary to mitigate the risk of cytokine release syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).[f]

2.2 REMS Goal and Elements

The proposed goal of the Tecvayli REMS is to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by

- Educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS[g]

---

[a] The July 8, 2022 REMS Supporting Document is available at: \\CDSESUB1\EVSPROD\bla761291\0041\m1\us\tecvayli-rems-supporting-doc.docx.

[b] The September 21, 2022 REMS Supporting Document is available at: \\CDSESUB1\EVSPROD\bla761291\0086\m1\us\tecvayli-rems-supporting-doc-tc.docx.

[c] The October 11, 2022 REMS Supporting Document is available at: \\CDSESUB1\EVSPROD\bla761291\0098\m1\us\tecvayli-rems-supporting-doc-tc.docx.

[d] Bergquist B. Review of the proposed REMS for Tecvayli (teclistamab), BLA 761291. Silver Spring (MD): FDA, CDER, OMEPRM, DMAMES (US); 2022 Sep 13. Nexus # 2022-71. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80685842.

[e] Bergquist B. Review of the proposed REMS for Tecvayli (teclistamab), BLA 761291. Silver Spring (MD): FDA, CDER, OMEPRM, DMAMES (US); 2022 Oct 7. Nexus # 2022-71. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8068d160.

[f] Karpow C. Evaluation of Need for a REMS for Tecvayli (teclistamab), BLA 761291. Silver Spring (MD): FDA, CDER, OMEPRM, DRM (US); 2022 (in progress). OSE RCM # 2021-2487.

[g] See the Tecvayli REMS Document submitted on October 11, 2022 (available at \\CDSESUB1\EVSPROD\bla761291\0098\m1\us\tecvayli-rems-doc-core.docx).

The Applicant's proposed REMS includes a communication plan (CP), Elements to Assure Safe Use (ETASU), an implementation system, and a timetable for submission of assessments.

3. REMS Implementation

This section describes the strategies and resources, requirements, metrics, and process indicators that are needed to ensure that the Tecvayli REMS program can operate as intended.

3.1 Strategies and Resources

To directly affect knowledge is the strategy proposed to achieve the objective of educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.

The stakeholders participating in the REMS include healthcare providers (HCP), pharmacies, healthcare settings (HCS), wholesalers/distributors, and the Applicant (e.g., REMS Coordinating Center).

3.2 Requirements

The proposed requirements to support directly affecting knowledge are described in the Tecvayli REMS Document[g] and include stakeholder training and a communication plan. Education is required for certification, in the form of a REMS Training Program, for HCPs, pharmacies and HCSs. In addition, this strategy requires that HCPs who prescribe must successfully complete the Knowledge Assessment to become certified. To ensure that prescribers received education/training, risk mitigation activities include that prior to dispensing, pharmacies and HCSs must obtain authorization to dispense each prescription by contacting the REMS Program to verify the prescriber is certified.

The communication plan requires the Applicant to disseminate REMS communication materials to those HCPs identified as being likely to prescribe and care for patients treated with Tecvayli.

Quality assurance activities, specifically submission of an audit plan and noncompliance plan for stakeholders participating in the REMS, have been established to assess compliance with REMS program implementation, requirements and operations.

3.3 Implementation Assessment Metrics

Data collected on the REMS requirements are utilized to determine if the REMS is being implemented and operated with fidelity. The Tecvayli REMS Assessment Plan (available from the REMS Supporting Document[c]) requires the Applicant annually report specific metrics. The proposed Tecvayli REMS Assessment Plan metrics that will be used to inform on REMS implementation and operations are as follows:

- **Metric 1- REMS Communication Plan Activities:** data from the reporting of this metric will be utilized to assess if the communication plan was implemented by the Applicant as required to include reporting on communication material dissemination and those HCPs targeted to receive these communication materials.
- **Metric 2- Program Implementation:** data from the reporting of this metric will be utilized to inform on when the product becomes commercially available and that the Applicant established and effectively maintained the REMS website, Coordinating Center and databases needed to support REMS operations.
- **Metric 3-REMS Certification and Enrollment Statistics:** data submitted for this metric will be utilized to determine if stakeholders were reached and able to certify and enroll in the REMS.

This data will also inform on stakeholder demographics to include credentials and specialty for HCPs and type of setting for pharmacies and HCSs. Additionally, this data will measure the extent to which the intended stakeholders are participating in the program. Any known reported reasons why stakeholders are not completing the certification process will be collected to determine whether there are any potential implementation barriers or access issues.

- **Metric 4-Utilization Data**: data submitted for this metric will inform on the demographics of the HCPs who are prescribing and the types of pharmacies/HCSs that are dispensing the product. The risk mitigation activity (dispense authorization) will be evaluated from reported data to include the number of prescriptions received, those received and not authorized and reasons for denials if known.
- **Metric 5-REMS Compliance:** This metric will include submission of the current audit plan, non-compliance plan and reporting of stakeholder non-compliance events. Data reporting on stakeholder noncompliance events is to include, but is not limited to, the source of the noncompliance data, results of root cause analysis and any action(s) taken in response. Analysis of this data will inform on stakeholder compliance with REMS program implementation, requirements and operations.
- **Metric 6-REMS Coordinating Center Report:** data collected will inform on reasons why stakeholders are calling the REMS Coordinating Center, an assessment of reports indicating a burden to the healthcare system or barrier(s) to patient access and an evaluation of the call center with respect to wait times, call volume and abandoned calls.

3.4 Process Indicator

Process indicators are utilized to determine if a REMS is being implemented and operated as intended. For the Tecvayli REMS, the key process indicator will measure the proportion of the risk mitigation activity that is successful (prior to dispensing, pharmacies and HCSs must obtain authorization to dispense each prescription by contacting the REMS Program to verify the prescriber is certified) compared to all dispenses of Tecvayli. The key performance process indicator is included in the Tecvayli REMS Assessment Plan and will be used to assess if the REMS is operating as intended. A target threshold of 99.9% compliance has been set a priori.

- **Metric 9-Report on Key Performance Indicators (KPI):** the KPI to report on REMS operations is:
  - REMS Operations: 99.9% of dispensed prescriptions were authorized by the REMS prior to dispense. REMS authorization for dispense requires both the prescriber and the pharmacy/healthcare setting be certified.

4. REMS Evaluation

This section describes the metrics for the outcomes that will be used to inform whether the Tecvayli REMS is meeting its intended goal and objective.

4.1 Outcome

An assessment of whether the strategy to directly affect knowledge was successful in achieving its intended objective of educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS will be done annually with submission of the REMS assessment report.

4.2 Outcome Assessment Metrics

Short term outcome metrics will inform on HCP's awareness and understanding of the risks, the REMS requirements, and the REMS goal and materials. Health outcomes will include a summary analysis of reported cases of CRS and neurologic toxicity including ICANS. This additional health outcome data can provide insight as to whether the risk was mitigated. The proposed Tecvayli REMS Assessment Plan metrics that will inform on HCP's risk knowledge and health outcomes include:

- **Metric 7-Knowledge Assessment:** Data collected will inform on HCP's completion of the Knowledge Assessment to include the number of attempts needed to achieve the required score of 100% to obtain REMS certification, a summary of the most frequently missed questions and identify potential comprehension or perception issues.
- **Metric 8-Periodic Survey of Certified Prescribers:** A Knowledge, Attitude and Behavior (KAB) survey of a random sample of certified prescriber results will 1) evaluate understanding of the risks, mitigation strategies, and compliance with these strategies and 2) evaluate prescriber's knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.
- **Metric 10-Summary Analysis of all Reported Cases:** Data will include all reported cases of CRS and neurologic toxicity including ICANS, stratified by grade/severity. This analysis will also inform on whether step-up dosing was initiated in the hospital setting and if pre-medication was administered which can provide insight into prescriber's awareness/behavior on the importance of monitoring.

4.3 Outcome Indicator

An outcome indicator is used to determine whether the REMS is producing its intended results. For this REMS, the key outcome indicator will measure the proportion of prescriber survey respondents that demonstrated knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS compared to all prescriber survey respondents. The key performance outcome indicator is included in the Tecvayli REMS Assessment Plan and will be used to determine if the REMS is meeting its stated objective. A target threshold of $\geq$ 80% of prescriber survey respondents demonstrating knowledge has been set a priori.

- **Metric 9-Report on Key Performance Indicators (KPI):** the KPI to report on whether the REMS is meeting its primary objective is:
    - REMS Evaluation of the objective: $\geq$ 80% of prescriber KAB survey respondents demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.

5. Review of Revised Assessment Plan, Audit Plan, and Noncompliance Plan

On October 11, 2022, the Applicant submitted a revised Supporting Document in response to the Agency's October 7, 2022 recommendations on needed changes to the Tecvayli REMS Assessment Plan, audit plan and noncompliance plan.[c]

5.1 REMS Assessment Plan (AP)

The Applicant's revised AP provided in the Supporting Document submitted on October 11, 2022[c] included the Agency's suggested revisions to remove metrics referencing (b) (4),

added and revised metrics to inform on dispense authorizations and product shipments and removed language that described measures to be taken (b) (4). The Applicant made editorial revisions to AP metric 4.d. (informs on REMS dispense authorizations that were rejected) and removed (b) (4). Of note, for metric 9.b the revised AP had a minor editorial error in that the threshold was missing the proposed "equal to" sign (>80% instead of ≥ 80%).

Reviewer's Comments:

The proposed Tecvayli REMS Assessment Plan includes metrics that will inform on whether the REMS is being implemented as intended and if the REMS is achieving its intended results. In addition, the REMS AP includes two key performance indicators (KPIs) proposed by the review team and agreed to by the Applicant (Metric 9); 1) a process indicator that will measure the proportion of the risk mitigation activity that is successful and 2) an outcome indicator which will measure the proportion of prescriber survey respondents that demonstrated knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS. Thresholds for the two KPIs have been set a priori, 99.9 % and ≥ 80%, respectively, and if met would indicate that the REMS is meeting its stated goal and objective.

The updated REMS Assessment Plan submitted on October 11, 2022 included all the Agency's suggested revisions and is acceptable. The final and agreed upon Tecvayli REMS Assessment Plan is included in Section 7 (Appendices) Appendix A. of this review. The final AP will be included in the Tecvayli Approval Letter.

5.2 Audit Plan

The revised audit plan and appended documents included the Agency's recommended revisions to add the REMS Coordinating Center as a stakeholder to be audited, removed language referencing (b) (4) to align with the REMS Document.

Reviewer's comments:

The revised Audit Plan submitted on October 11,2022 includes the Agency's recommended revisions and is acceptable.

5.3 Noncompliance Plan

The revised noncompliance plan included the Agency's recommendation to include the addition of the REMS Coordinating Center as a stakeholder for whom criteria and actions needed to be defined for noncompliance with the REMS.

Reviewer's comments:

The revised noncompliance plan submitted on October 11, 2022 includes the Agency's recommended revision and is acceptable.

6. Conclusions and Recommendations

Our review of the REMS Supporting Document (SD) submitted on October 11, 2022 found that the revised REMS Assessment Plan, audit plan, and noncompliance plan are acceptable.

Evaluation of the REMS will include reporting on two key performance indicators (KPIs), 1) a process indicator that will inform on whether the REMS is being implemented and operating as intended and 2) an outcome indicator that will measure if the REMS is producing its intended results. Thresholds for the two KPIs have been set a priori and if met would indicate that the REMS is meeting its stated goal and objective.

The final and agreed upon Tecvayli REMS Assessment Plan is included in Appendix A of this review and will be included in the Tecvayli Approval Letter.

7. Appendices

7.1 Appendix A: Tecvayli REMS Assessment Plan

Program Outreach and Communication

1. REMS communication plan activities (provide data for the 1-year and 2-year assessments only):
    a. Sources of the distribution lists for healthcare providers
    b. Number of healthcare providers targeted stratified by specialty if known
    c. Number of healthcare professional societies targeted, and which healthcare professional societies reported distribution of the REMS letter to their respective members
    d. The number of packets of REMS materials sent by date, attempt, and method of distribution
    e. The number and percentage of emails successfully delivered, opened, and unopened
    f. The number and percentage of mail successfully delivered and returned as undeliverable
    g. The number of REMS Fact Sheets distributed to targeted healthcare providers during the 12 months after TECVAYLI is commercially distributed
    h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed

Program Implementation and Operations

2. Program Implementation (provide data at the 1-year assessment only):
    a. Date of first commercial availability of TECVAYLI
    b. Date the REMS Website went live
        i. Number of total visits and unique visits to the REMS Website
        ii. Number and type of TECVAYLI REMS materials downloaded or accessed
    c. Date the REMS Coordinating Center was fully operational
    d. Date prescribers and pharmacies/healthcare settings were able to complete the REMS certification process (online and by fax)
    e. Date of the first prescriber certification

f. Date of the first pharmacy/healthcare setting certification

3. REMS Certification and Enrollment Statistics (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Healthcare Providers

        i. Number of newly certified healthcare providers and number of active (i.e., who have prescribed TECVAYLI at least once during the reporting period) healthcare providers stratified by:

            1. Credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, other)

            2. Specialty (e.g., Oncology, Hematology, Internal Medicine/Family Medicine, Other). If "other" accounts for > 10% of respondents for specialties, provide the most common specialties identified.

            3. Geographic region as defined by the US Census

            4. Method of enrollment (e.g., online, fax, e-mail) for newly certified healthcare providers only

        ii. Number of incomplete prescriber enrollments, and summary of reported reason(s) for not completing

    b. Pharmacies and Healthcare Settings

        i. Number of newly certified pharmacies/healthcare settings and number of active (i.e., who have dispensed or ordered the drug at least once during the reporting period) pharmacies/healthcare settings stratified by:

            1. Type of pharmacy/healthcare setting (e.g., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Oncology Infusion Center, Community Oncology Physician Office, Other). If "other" accounts for > 10% of respondents for type, provide the most common type(s) identified.

            2. Geographic region as defined by the US Census

            3. Method of enrollment (e.g., online, fax, e-mail) for newly certified pharmacies/healthcare settings only

        ii. Number of incomplete pharmacy/healthcare setting enrollments, and summary of reported reason(s) for not completing

    c. Wholesalers/distributors

        i. Number of wholesalers/distributors contracted to ship and number of active (i.e., have shipped) wholesalers/distributors

4. Utilization Data (provide data for two previous reporting periods, the current reporting period and cumulatively)

a. Number of vials sent to certified pharmacies/healthcare settings, stratified by type of pharmacy/healthcare setting

b. Number and percentage of healthcare providers who wrote/ordered prescriptions that were dispensed, stratified by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)

c. Number of dispense authorizations stratified by pharmacy/healthcare setting type

d. Number of RDAs rejected, stratified by:

    i. Reasons and number of denials (numerator) divided by all denials (denominator)

        1. Healthcare provider not certified

        2. Other reasons for denial not categorized above

5. REMS Compliance (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Audits

        i. A copy of the audit plan

        ii. Report of audit findings for each stakeholder

        iii. Number of audits expected, and the number of audits performed

        iv. Documentation of completion of training for relevant staff

        v. Documentation of processes and procedures in place for complying with the TECVAYLI REMS

        vi. Verification for each audited stakeholder's site that the designated Authorized Representative remains the same. If different, include the number of new Authorized Representatives

        vii. Number and type of deficiencies noted for each group of audited stakeholders as a percentage of audited stakeholders

        viii. Confirmation of documentation of completion of training for relevant staff after audit findings indicated training was necessary

        ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

    b. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder (healthcare providers, pharmacies/healthcare settings and wholesalers-distributors), actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS

        i. For those with deficiencies noted, report the number that successfully completed a Corrective and Preventive Actions (CAPA) plan within the timeframes specified in the Noncompliance Plan

ii. For any that did not complete the CAPA within the timeframe specified in the Noncompliance Plan, describe actions taken

iii. Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

    1. Unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
    2. Source of the noncompliance data
    3. Results of root cause analysis
    4. Action(s) that were taken in response

iv. Pharmacies/healthcare settings

    1. Number of pharmacies/healthcare settings for which non-compliance with the TECVAYLI REMS is detected (numerator) divided by all pharmacies/healthcare settings dispensing TECVAYLI (denominator)
    2. Number and description of pharmacies/healthcare settings that dispensed TECVAYLI to non-certified prescribers, and any corrective and preventative actions taken to prevent future occurrences
    3. Number of non-certified pharmacies/healthcare settings that dispensed TECVAYLI (numerator) divided by all pharmacies/healthcare settings that dispensed TECVAYLI
    4. Number of prescriptions dispensed by non-certified pharmacies/healthcare settings (numerator) divided by all TECVAYLI prescriptions dispensed (denominator) and the actions taken to prevent future occurrences
    5. Summary of audit findings and any action taken and outcome of actions to prevent future occurrences
    6. Summary of findings for monitoring conducted during the reporting period, including any CAPA

v. Wholesalers/Distributors

    1. Number and description of non-certified pharmacies/healthcare settings that were shipped TECVAYLI, and the number of these that subsequently became certified
    2. The number of authorized wholesalers-distributors for which non-compliance with the REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)

3. The number and type of wholesalers-distributors not contracted with Janssen that shipped TECVAYLI and the number of incidents for each
4. The number of contracted wholesalers-distributors suspended and/or unauthorized to distribute for non-compliance with REMS requirements and reasons for such actions

c. Any other TECVAYLI REMS noncompliance, source of report and resulting CAPA

6. REMS Coordinating Center Report (provide data for two previous reporting periods, the current reporting period and cumulatively)

a. Number of contacts by stakeholder type (patient/caregiver, certified prescriber, pharmacy/healthcare setting authorized representative or staff, other HCP, wholesaler/distributor, other)

b. Summary of the reasons for the call(s) by stakeholder type. Limit the summary to the top five reasons for calls by stakeholder group

c. Description of each call, including stakeholder credentials, that may indicate an issue with product access due to the REMS program, REMS program burden or adverse event

d. If the summary reason for the call(s) indicates an adverse event related to Cytokine Release Syndrome (CRS) or neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) include details and the outcome of the call(s)

e. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, health care availability, other

f. Summary of frequently asked questions (FAQ) by stakeholder credentials type. Limit the summary to the top five FAQs for calls by stakeholder group

g. Summary of any noncompliance that is identified through coordinating center contacts, source of report and resulting CAPA

h. Summary of CAPAs resulting from issues identified

i. Percentage of calls to the REMS Coordinating Center that were answered within 20 minutes

j. The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered

k. Percentage of calls to the REMS Coordinating Center where the caller abandoned the call before the call was answered

l. The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

Knowledge

7. Knowledge Assessment (provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Number of completed healthcare provider Knowledge Assessments, including the method of completion

    b. Summary statistics, including mean number of attempts, score, and range of scores and number of attempts to successfully complete the Knowledge Assessment

    c. Summary of most frequently missed questions on the Knowledge Assessment

    d. A summary of potential comprehension or perception issues identified with the Knowledge Assessment

8. Periodic Survey of Certified Prescribers (beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report)

    A Knowledge, Attitude and Behavior (KAB) Survey will be conducted with random samples of healthcare providers who prescribe TECVAYLI

    a. Evaluation of understanding of the risks and mitigation strategies of the TECVAYLI REMS as well as compliance with the mitigation strategies

    b. An evaluation of prescriber's knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

9. Report on Key Performance Indicators: The key performance indicators (KPI), or the primary metrics that will be used to evaluate the TECVAYLI REMS, include a process indicator (REMS operations) and an outcome indicator (REMS evaluation of the primary objective)

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

    b. REMS Evaluation of the objective: $\geq$ 80% of prescriber KAB survey respondents demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

Health Outcomes and/or Surrogates of Health Outcomes

10. A summary analysis of all reported cases of CRS and neurologic toxicity including ICANS, stratified by source of report (i.e., spontaneous). (Provide data for two previous reporting periods, the current reporting period and cumulatively)

    a. Include the following stratifications by grade/severity in the analysis

        i. Step-up dosing was initiated in the hospital setting. (For those reports that indicate initiation outside of the hospital setting provide the setting if known)

        ii. Pre-medication was administered

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA A BERGQUIST
10/20/2022 03:14:20 PM

JO H WYETH
10/20/2022 03:19:09 PM

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)

A Application Type	BLA
Application Number	761291
Nexus ID Number	2022-71
PDUFA Goal Date	November 28, 2022
Team Leader/Reviewer Name	Barbara Bergquist, PharmD (DMAMES)
Associate Director	Jo Wyeth, PharmD (OMEPRM)
Review Completion Date	October 7, 2022
Subject	Evaluation of proposed REMS assessment plan, audit plan and noncompliance plan
Trade Name	Tecvayli
Established Name	teclistamab
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Submission Date	September 21, 2022

Table of Contents

1. Introduction

This review provides our interim comments on the risk evaluation and mitigation strategy (REMS) for Tecvayli (teclistamab) in response to a consult request by the Division of Risk Management (DRM).

The proposed REMS Supporting Document (SD), specifically the REMS assessment plan, audit plan and noncompliance plan, submitted on July 8, 2022 and revised on September 21, 2022 in response to our September 13, 2022 recommendations[1] is the subject of this review.

2. Background

The Tecvayli application (BLA # 761291) was submitted by Janssen Biotech on December 28, 2021 with a proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior lines, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

A REMS was determined to be necessary to mitigate the risk of cytokine release syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). The Applicant's proposed REMS includes a communication plan (CP) elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2.1 REMS Goal

The Tecvayli REMS goal and objectives[2] are to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by

- Educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

3. Supporting Document

On September 21, 2022, the Applicant submitted a revised Supporting Document (SD) in response to our recommendations on September 13, 2022 for changes to the Tecvayli REMS Assessment Plan, audit plan and noncompliance plan.[3]

The SD also included other materials (e.g., stakeholder audit questionnaire review forms, audit email templates, confirmation letters, follow-up letters, noncompliance notification letters and noncompliance notification letter/CAPA request templates) that are outside the scope of this review.

[1] September 13, 2022, DMAMES (B. Bergquist) Review of proposed Tecvayli (BLA 761291) REMS assessment plan, audit protocol, and noncompliance plan. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80685842.

[2] September 8, 2022, DRM (C. Karpow) Evaluation of proposed Tecvayli (BLA 761291) REMS. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80684300.

[3] The Tecvayli (BLA 761291) REMS Supporting Document submitted on September 21, 2022 is available at: \\CDSESUB1\EVSPROD\bla761291\0086\m1\us\tecvayli-rems-supporting-doc.docx.

3.1 General

On October 5, 2022, the REMS Document[4] was revised to include removal of language pertaining to the [redacted] (the Agency agreed with the Applicant's proposal for prescribers [redacted] to have their office enroll as a healthcare setting). The REMS document was also changed from having pharmacies and healthcare settings audited at 180 calendar days after they begin dispensing to after they receive their first shipment and annually.

Reviewer's comment:

- *The revised SD needs further revision to align with the revised REMS Document to 1) remove [redacted] and 2) timing of stakeholder audits.*

3.2 REMS Prescriber Surveys

The revised SD included a description of REMS prescriber surveys with protocol and survey questionnaires to be provided to the Agency at least 90 days prior to survey implementation. Results of prescriber surveys will be reported beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report.

Reviewer's comments:

- *The revised SD pertaining to prescriber surveys [redacted] as per our September 13, 2022 recommendations is acceptable.*

3.3 Audit Plan

The revised audit plan and appended documents[5] included the Agency's recommended addition of the REMS Coordinating Center and healthcare settings as stakeholders to be audited. The revised audit plan also includes language referencing the prescriber [redacted] including the addition of prescribers as a stakeholder to be audited. The timing of stakeholder audits was stated as, "pharmacies and healthcare settings will be audited no later than 180 calendar days after the pharmacy or healthcare setting begins dispensing Tecvayli".

Reviewer's comments:

- *Review of the revised SD audit language and the audit plan indicate that revisions are needed to align the SD and audit plan with the revised REMS Document as described in section 3.1. of this review to remove* [redacted]
- [redacted] *to be audited to align with the revised REMS Document. Those prescribers wishing to dispense are to have their office enroll as a healthcare setting. As a certified healthcare setting, they are required to be audited annually.*
- *Revision to the audit language in the SD and the audit plan is needed to align with the revised REMS Document to change the timing of the audit language from* [redacted] *" to, "…after the pharmacy or healthcare setting receives their first shipment of Tecvayli and annually…".*

[4] October 5, 2022 DRM (C. Karpow) REMS Review.
[5] The audit plan submitted on September 21, 2022 is available at: \\CDSESUB1\EVSPROD\bla761291\0086\m1\us\tecvayli-rems-audit-plan.docx

- *The revised SD includes the REMS Coordinating Center as a stakeholder to be audited, but is not included in the audit plan. The audit plan needs further revision to include the REMS Coordinating Center as a stakeholder to be audited.*

3.4 Noncompliance Plan

The revised noncompliance plan[6] included the Agency's recommendation to include the addition of healthcare settings as a stakeholder.

Reviewer's comments:

- *The revised SD includes the REMS Coordinating Center as a stakeholder to be audited, but is not included in the noncompliance plan. The noncompliance plan needs further revision to include the REMS Coordinating center as a stakeholder for whom criteria and actions need to be defined for noncompliance with the REMS.*

4. REMS Assessment Plan

The Applicant's proposed revised REMS Assessment Plan (AP)[7] included metrics stratified by assessment categories: Program Outreach and Communication Plan, Program Implementation and Operations, Knowledge, and Health Outcomes and/or Surrogates of Health Outcomes. Additions to the revised AP included (b) (4) and measures to be taken to increase prescriber survey sample size in the event the target is not achieved. In addition, the SD includes a table (Table 2: Tecvayli REMS Assessment Plan) which maps the goal and objective of the REMS to the REMS requirements, materials, assessment plan category, metrics, data sources/analytic tools, frequency of metric reporting, performance threshold and methodology/protocol location. The final AP will be included in the Tecvayli Approval Letter.

Reviewer's Comments:

The submitted AP needs revision to inform on the goal, objective and REMS requirements and to align with the revised REMS Document. This reviewer's suggested changes (summarized by metric numbering where indicated below) include the following:

- *The Applicant included the Agency's September 21,2022 recommended metric revisions in their revised AP.*
- *The Agency requested that the Applicant include how the REMS will be evaluated in the event that the target REMS prescriber survey sample size is not achieved given the REMS strategy is*

[6] The noncompliance plan submitted on September 21, 2022 is available at: \\CDSESUB1\EVSPROD\bla761291\0086\m1\us\tecvayli-rems-noncompliance-plan.docx

[7] The proposed REMS Assessment Plan submitted on September 21, 2022 is available from the Supporting Document (Section 3.6), available at: \\CDSESUB1\EVSPROD\bla761291\0086\m1\us\tecvayli-rems-supporting-doc.docx.

knowledge based. In response, the Applicant included measures to be taken for future survey waves to increase prescriber survey sample size in the event the target sample size is not achieved. These measures should be included in the survey protocol, not the AP, and initiated with survey wave 1 as indicated if response rate is low.

- ***Metric 2**: **Program Implementation:** Needs revision to metric 2.d and 2.f to align with the Pharmacy and Healthcare Setting Enrollment Form by adding healthcare setting to the metric.*
- ***Metric 3: REMS Certification and Enrollment Statistics:*** [redacted] *needs to be removed to align with the revised REMS Document.*
- ***Metric 4: Utilization Data:** Added and revised metrics to inform on dispense authorizations and product shipments. Removed* [redacted] *to align with the revised REMS Document.*
- ***Metric 5: Compliance:** Removed* [redacted] *to align with the revised REMS Document.*
- ***Metric 8: Periodic Survey of Certified Prescribers:** Revised to remove language that described* [redacted] *These measures should be included in the survey protocol, not the AP,* [redacted]

5. Conclusions and Recommendations

Our review of the REMS Supporting Document (SD) revised on September 21, 2022 identified the need for further revisions as discussed in Sections 3 and 4 of this review. The assessment plan, audit plan, and noncompliance plan require revisions to be consistent with changes made to the REMS document and capture additional data needed to inform whether the REMS is meeting its goal and objective.

6. Comments For The Applicant

We have the following comments on the revised Tecvayli REMS Supporting Document (SD) submitted on September 21, 2022, specifically the Tecvayli REMS Assessment Plan, audit plan and noncompliance plan. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within one business day that addressed these comments. Include the REMS Supporting Document and appended materials submitted as Word Track changes version, a Word clean version, and a pdf version.

Supporting Document (SD)

The submitted SD needs revisions to align with the revised REMS Document and capture additional data needed to inform whether the REMS is meeting its goal and objective:

- General
  - The SD needs further revision to align with the revised REMS Document [redacted]
  - Revisions are needed to align language referencing the timing of stakeholder audits with the revised REMS Document.
- Audit Plan
  - Remove all references [redacted] to align with the revised REMS Document.

    - Remove (b) (4) to align with the revised REMS Document.
    - The revised SD includes the REMS Coordinating Center as a stakeholder to be audited but is not included as a stakeholder in your audit plan. Add the REMS Coordinating Center as a stakeholder to be audited in the audit plan.
    - Revise the audit language to align with the revised REMS Document to change the timing of the audit language from (b) (4) " to, "…after the pharmacy or healthcare setting receives their first shipment of Tecvayli and annually…".
- Noncompliance Plan
    - The revised SD includes the REMS Coordinating Center as a stakeholder to be audited but is not included as a stakeholder in your noncompliance plan. Add the REMS Coordinating Center as a stakeholder for whom criteria and actions need to be defined for noncompliance with the REMS.

Tecvayli REMS Assessment Plan Comments

The submitted assessment plan (AP) needs revision to inform on the REMS goal, objective and requirements and to align with changes to the REMS Document. Suggested changes and edits (summarized by our proposed metric numbering below) include the following:

- **Metric 2**: **Program Implementation:** Revised metric 2.d and 2.f to align with the Pharmacy and Healthcare Setting Enrollment Form by adding healthcare setting to the metric.
- **Metric 3: REMS Certification and Enrollment Statistics:** Removed (b) (4) to align with the revised REMS Document.
- **Metric 4: Utilization Data:** Added and revised metrics to inform on dispense authorizations and product shipments. Removed (b) (4) to align with the revised REMS Document.
- **Metric 5: Compliance:** Removed (b) (4) to align with the revised REMS Document.
- **Metric 8: Periodic Survey of Certified Prescribers:** Removed (b) (4) These measures should be included in the survey protocol, not the AP (b) (4)

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA A BERGQUIST
10/07/2022 02:37:12 PM

JO H WYETH
10/07/2022 02:39:32 PM

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	761291
PDUFA Goal Date	November 28, 2022
OSE RCM #	2021-2487
Reviewer Names	Celeste Karpow, PharmD, MPH, Risk Management Analyst Kate Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	October 4, 2022
Subject	Evaluation of Proposed REMS
Established Name	teclistamab
Trade Name	Tecvayli
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Dosing Regimen	1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule

1. Introduction

This review by the Division of Risk Management (DRM) provides our interim comments on the risk evaluation and mitigation strategy (REMS) and REMS materials submitted on July 8, 2022; amended on August 1, 2022, August 4, 2022, August 9, 2022, September 13, 2022, and September 21, 2022 for the new molecular entity (NME) Tecvayli (teclistamab). Janssen Biotech, Inc. submitted a Biologic Licensing Application (BLA) 761291 for teclistamab with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. This application is under review in the Division of Hematologic Malignancies II (DHMII). 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 teclistamab outweigh the risks of cytokine release syndrome and neurologic toxicity, including ICANS.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for BLA 761291 relevant to this review[a]:

07/28/2022: DRM's preliminary REMS review sent to Applicant.

08/01/2022: Janssen Biotech, Inc. submitted a REMS Amendment that included a new and updated REMS Adverse Reaction Management Guide, REMS Knowledge Assessment, REMS Patient Wallet Card, REMS Pharmacy Training Program, and REMS Prescriber Training Program in response to DRM's preliminary REMS review.

08/04/2022: Janssen Biotech, Inc. submitted REMS website screenshots.

08/05/2022: Information request sent to Janssen Biotech, Inc. to request REMS Website screenshots to show the steps that a pharmacist goes through to verify prescriber certification or how authorization to dispense is provided.

08/09/2022: Janssen submitted additional REMS website screenshots showing the steps that a pharmacist goes through to verify prescriber certification and how authorization to dispense is provided.

09/08/2022: DRM sent Janssen comments on the REMS document and REMS materials (please see review by Dr. Karpow in DARRTS on 09/08/2022 for more details on this correspondence).

09/13/2022: The Applicant submitted a REMS Amendment that included a REMS document and REMS materials in response to the comments that were sent by the Agency on 09/08/2022. DRM noted that the Applicant proposed new information in the prescriber enrollment form regarding the option for a prescriber to certify in the REMS program (b) (4)

[a] For additional regulatory history, please see DRM review(s) dated 7/28/2022, 9/8/2022.

(b) (4) . Specifically, the Agency asked the Applicant to explain the following:

- How the wholesaler will verify the person ordering TECVAYLI is a certified prescriber.
- How you intend to ensure prescribers who select option B are certified prior to prescribing teclistamab.
- Confirm that prescribers are not intended to be dispensers of TECVAYLI.

9/14/2022:

- Information request sent to Janssen Biotech, Inc. to request the date Janssen intends to have post-login website screenshots available for the Agency's review and the date the applicant expects this part of the website to be functional.
- The Applicant responded to the information request sent on September 13, 2022.

09/16/2022: The Agency held a teleconference with the Applicant to express concerns regarding the Applicant's proposal for prescribers to obtain teclistamab (b) (4) The Agency's concerns include prescribers acquiring teclistamab directly from a teclistamab REMS-authorized wholesaler-distributor for administration to patients (b) (4) which may bypass ETASU B, Pharmacy and Healthcare setting Certification that verifies the prescriber is certified prior to dispensing.

09/21/2022: The Applicant submitted a REMS Amendment that included a REMS document and REMS materials in response to the comments that were sent by the Agency on September 16, 2022.

09/22/2022: An information request was sent to the Applicant to clarify how prescriber certification will be verified and documented prior to dispensing teclistamab to a patient (b) (4)

09/23/2022: The Applicant responded to the information request sent on September 22, 2022. DRM noted that the Applicant proposed new information that states, "…all prescribers utilizing (b) (4) will be required to enroll in the TECVAYLI REMS as both a prescriber and as a pharmacy and healthcare setting."

09/27/2022: An information request was sent to the Applicant to request any stakeholder input (b) (4). Specifically, we requested the following:

- Anticipated compliance with obtaining a REMS Dispense Authorization (RDA) prior to dispensing for administration
- How obtaining an RDA prior to dispensing for administration to a patient will fit into prescriber's workflow
- Define who can serve as an authorized representative
- Anticipated uptake and market share of teclistamab (b) (4)

- Describe in detail the Applicant's plan to audit 100% of certified pharmacies or healthcare settings, (b) (4). Also include the action if noncompliance is identified in any of these settings.

  09/29/2022: The Applicant responded to the information request sent on September 27, 2022 and outlined that they anticipate near 100% compliance, no change in workflow upon certification, the Authorized Representative can be any responsible individual assigned by the pharmacy or healthcare setting who is not a certified TECVAYLI Prescriber, described their anticipated uptake, and outlined their audit plan.

3. Comments to the Applicant

The following comments and attached REMS Document, Healthcare Provider REMS Letter, Professional Society REMS Letter, REMS Fact Sheet, Prescriber Enrollment Form, Pharmacy and Healthcare Setting Enrollment Form, Prescriber Training Program, Pharmacy and Healthcare Setting Training Program, REMS Website, and REMS Supporting Document are based on our review of the proposed REMS submitted by Janssen Biotech, Inc. on July 8, 2022, August 1, 2022, August 4, 2022, August 9, 2022, September 13, 2022, and September 21, 2022. To facilitate our review, please address the following comments and resubmit your REMS as an amendment by close of business October 6, 2022. These comments should not be considered as final edits to the REMS. Comments on the REMS Supporting Document and REMS Assessment Plan will be forthcoming. All REMS materials must align with the final approved labeling.

REMS Document

Healthcare providers who prescribe TECVALYI must:

- We agree with your proposal for prescribers (b) (4) to have their office enroll as a healthcare setting. Therefore, remove the added language (b) (4) because it is covered in section 3, Pharmacies and Healthcare Settings that Dispense.

Wholesalers-distributors that distribute TECVAYLI must:

- In items 1 and 3, delete (b) (4) for consistency with the IR responses received on September 23, 2022 and September 29, 2022.

REMS Operations

- The time period to notify prescribers, pharmacies and healthcare settings after they become certified should be shortened. Revise this statement to, "Notify prescribers, pharmacies and healthcare settings within 1 calendar day after they become certified in the REMS."
- It is unclear why you deleted the statement, "Provide certified prescribers access to the database of certified pharmacies and healthcare settings." We recommend you include this statement that indicates there is a database of pharmacies and healthcare settings that are certified for prescribers to access.

REMS Compliance

- Delete the statement, [redacted]
- Revise the statement, "[redacted] to "Audit all certified pharmacies and healthcare settings within 180 calendar days after the pharmacy or healthcare setting receives their first shipment of TECVAYLI and annually to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements."

Healthcare Provider REMS Letter and Professional Society REMS Letter

- Ensure you submit the Healthcare Provider REMS Letter and Professional Society REMS Letter in both print and email formatted PDFs with REMS materials shown as embedded links.

REMS Fact Sheet

- Ensure references to [redacted] are deleted for consistency with the IR response received on September 29, 2022.

Prescriber Enrollment Form

- Delete the boxed question, [redacted] as this is not necessary since the dispensing functionality will be captured as a certified Pharmacy or Healthcare setting.
- Add the statement, "Certified Prescribers cannot also be the Authorized Representative for my Healthcare Setting." to the Instructions box. Ensure this statement appears before the Attestations on the Prescriber Enrollment Form.
- Delete the [redacted]
- Delete the following [redacted]
  - [redacted]
  - [redacted]

Pharmacy and Healthcare Setting Enrollment Form

- Add the statement, “Authorized Representatives cannot also be a Certified Prescriber.” to the Instructions box. Ensure this statement appears before the Attestations on the Pharmacy and Healthcare Setting Enrollment Form.

Prescriber Training Program

- Ensure references to (b) (4) are deleted for consistency with the IR response received on September 29, 2022.
- On slide 7, add a statement similar to, “Certified Prescribers cannot also be the Authorized Representative in the Healthcare Setting.”

Pharmacy and Healthcare Setting Training Program

- On slide 7, add a statement similar to, “Authorized Representatives cannot also be the Certified Prescriber in the Healthcare Setting.” for consistency with the IR response received on September 29, 2022.

REMS Website

- Website screenshots that show how pharmacy or healthcare setting staff create an account that is linked to the certified pharmacy or healthcare setting are absent. Clarify whether staff are able to create an account online to obtain an RDA or not. If staff are able to create an account, submit website screenshots that show how pharmacy or healthcare setting staff create an account and how it is linked to the certified pharmacy or healthcare setting and make corresponding changes to the pharmacy training slides (slide 8) with your next REMS submission. Please also include screenshots depicting the “staff management” tab on the AR screenshots.
- The website screenshots contain presentations of other REMS materials that need to be updated. Apply our comments on the REMS materials to similar presentations in the REMS Website screenshots (e.g., Prescriber Enrollment Form, Pharmacy and Healthcare Setting Enrollment Form, Prescriber Training Program).

REMS Supporting Document

- Additional revisions to the assessment plan are forthcoming.
- Ensure all content in the REMS Supporting Document aligns with the USPI and the REMS document.
- The description of Tecvayli can be improved in the Background section to align with the USPI. Specifically, we recommend you revise the statement, (b) (4)

  to, “TECVAYLI is a bispecific B-cell maturation antigen (BCMA)-directed and CD3-directed T-cell engager available for subcutaneous injection” for consistency with the USPI.
- Add a statement in section 3.3.2. Pharmacies and Healthcare Settings That Dispense TECVAYLI Must Be Certified that indicates the authorized representative must be a different individual than the certified prescriber for consistency with the for consistency with the IR response received on September 29, 2022. Also include the information from the IR response received September 29, 2022 in the Supporting Document.

The Agency requests you accept all tracked changes to the Word documents provided. **If you make additional revisions, submit a track changed Word version of the revised document(s) to the Agency for review in addition to the formats outlined in the table below.** The Agency requests you submit the REMS documents as shown below **by close of business October 6, 2022**:

	Materials	**Required Formats**
1.	REMS Document	Clean MS Word & Tracked MS Word
2.	REMS Supporting Document	Clean MS Word, Tracked MS Word, & a Clean PDF file that includes the REMS Supporting document and non-public facing website screenshots
3.	DHCP REMS Letter in both print and email versions	--
4.	Professional Society REMS Letter	--
5.	REMS Fact Sheet	--
6.	Prescriber Enrollment Form	--
7.	Pharmacy and Healthcare Setting Enrollment Form	--
8.	Patient Wallet Card	--
9.	Prescriber Training Program	--
10.	Pharmacy and Healthcare Setting Training Program	--
11.	Prescriber Knowledge Assessment	--
12.	Adverse Reaction Management Guide	--
13.	Website	--
14.	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	Clean PDF

47 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CELESTE A KARPOW
10/05/2022 10:41:24 AM

KATE H OSWELL
10/05/2022 10:56:54 AM

NAOMI S BOSTON
10/05/2022 11:30:37 AM

LAURA A ZENDEL
10/05/2022 12:17:08 PM

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	761291
PDUFA Goal Date	November 28, 2022
OSE RCM #	2021-2487
Reviewer Names	Celeste Karpow, PharmD, MPH, Risk Management Analyst Kate Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	September 16, 2022
Subject	Evaluation of Proposed REMS
Established Name	teclistamab
Trade Name	Tecvayli
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Dosing Regimen	1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule

1. Introduction

This review by the Division of Risk Management (DRM) provides our interim comments on the risk evaluation and mitigation strategy (REMS) and REMS materials submitted on July 8, 2022; amended on August 1, 2022, August 4, 2022, August 9, 2022, and September 13, 2022 for the new molecular entity (NME) Tecvayli (teclistamab). Janssen Biotech, Inc. submitted a Biologic Licensing Application (BLA) 761291 for teclistamab with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. This application is under review in the Division of Hematologic Malignancies II (DHMII). 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 teclistamab outweigh the risks of cytokine release syndrome and neurologic toxicity, including ICANS.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for BLA 761291 relevant to this review[a]:

07/28/2022: DRM's preliminary REMS review sent to Applicant.

08/01/2022: Janssen Biotech, Inc. submitted a REMS Amendment that included a new and updated REMS Adverse Reaction Management Guide, REMS Knowledge Assessment, REMS Patient Wallet Card, REMS Pharmacy Training Program, and REMS Prescriber Training Program in response to DRM's preliminary REMS review.

08/04/2022: Janssen Biotech, Inc. submitted REMS website screenshots.

08/05/2022: Information request sent to Janssen Biotech, Inc. to request REMS Website screenshots to show the steps that a pharmacist goes through to verify prescriber certification or how authorization to dispense is provided.

08/09/2022: Janssen submitted additional REMS website screenshots showing the steps that a pharmacist goes through to verify prescriber certification and how authorization to dispense is provided.

09/08/2022: DRM sent Janssen comments on the REMS document and REMS materials (please see review by Dr. Karpow in DARRTS on 09/08/2022 for more details on this correspondence.

09/13/2022: The Applicant submitted a REMS Amendment that included a REMS document and REMS materials in response to the comments that were sent by the Agency on 09/08/2022. DRM noted that the Applicant proposed new information in the prescriber enrollment form regarding the option for a prescriber to certify in the REMS program (b) (4)

[a] For additional regulatory history, please see DRM review(s) dated 7/28/2022, 9/8/2022.

(b) (4) Specifically, the Agency asked the Applicant to explain the following:

- How the wholesaler will verify the person ordering TECVAYLI is a certified prescriber.
- How you intend to ensure prescribers who select option B are certified prior to prescribing teclistamab.
- Confirm that prescribers are not intended to be dispensers of TECVAYLI.

9/14/2022:

- Information request sent to Janssen Biotech, Inc. to request the date Janssen intends to have post-login website screenshots available for the Agency's review and the date you expect this part of the website to be functional.
- The Applicant responded to the information request sent on September 13, 2022

09/16/2022: The Agency held a teleconference with the Applicant to express concerns regarding the Applicant's proposal for prescribers to obtain teclistamab (b) (4) Pharmacy and Healthcare setting Certification that verifies the prescriber is certified prior to dispensing.

3. Comments to the Applicant

The following comments and attached Prescriber Training Program, Knowledge Assessment, and REMS Website are based on our interim review of the proposed REMS submitted by Janssen Biotech, Inc. on July 8, 2022, August 1, 2022, August 4, 2022, August 9, 2022, September 13, 2022. To facilitate our review, please address the following comments and resubmit your REMS as an amendment by September 21, 2022. These comments should not be considered as final edits to the REMS. Comments on the REMS Supporting Document and REMS Assessment Plan will be forthcoming. All REMS materials must align with the final approved labeling.

Prescriber Training Program

- We added slide 3, "Training Outline." Since there are multiple topics covered in this training and the "Training Outline" slides helps the reader know what the topics will be access them quickly. Consider including the corresponding slide numbers with each bullet on this slide.
- Delete "and Neurologic Toxicity Including ICANS" from slide 8 and add a separate section slide for "Neurologic Toxicity Including ICANS" in between slides 13 and 14 to correspond with Slide 3, Training Outline.
- Move the (b) (4) outlined in Slide 3, at the end of the slide deck. Revise content and add additional slides if appropriate.

Knowledge Assessment

- Question 9 can be improved. Revise the question to, "If CRS is suspected during treatment with TECVAYLI, in addition to withholding TECVAYLI until CRS resolves, which of the following supportive measures should be considered:" In addition, revise answer choice B to, "Intravenous fluid support" because hypotension is a key feature of CRS whereas DIC is much less common. Lastly, add "coagulopathy" to answer choice C.

REMS Website

- As currently presented the 'login' is absent from the first PDF of your REMS Website homepage. It is important for the 'login' button to be readily available on the REMS Website homepage. Ensure there is a 'login' button readily available on the REMS Website homepage.

In addition, as discussed at the teleconference on 09/16/2022, the agency requests you submit a proposal to address how a prescriber will certify in the REMS program (b) (4) This proposal must ensure teclistamab will be acquired and dispensed only by certified prescribers and/or healthcare settings. Please update these changes to all affected documents in the REMS program (i.e., the REMS Document and relevant REMS materials), as well as in the REMS Assessment Plan in the REMS Supporting Document. This proposal for (b) (4) should also be detailed in the REMS Supporting Document to show how prescriber certification will be verified prior to dispensing for administration to patients.

The Agency requests you accept all tracked changes to the Word documents provided. If you make additional revisions, submit a track changed Word version of the revised document(s) to the Agency for review in addition to the formats outlined in the table below. The Agency requests you submit the REMS documents as shown below **by September 21, 2022**:

	Materials	**Required Formats**
1.	REMS Document	Clean MS Word & Tracked MS Word
2.	REMS Supporting Document	Clean MS Word & Tracked MS Word
3.	DHCP REMS Letter	Clean MS Word & Tracked MS Word (if applicable)
4.	Professional Society REMS Letter	Clean MS Word & Tracked MS Word (if applicable)
5.	REMS Fact Sheet	Clean MS Word & Tracked MS Word
6.	Prescriber Enrollment Form	Clean MS Word & Tracked MS Word
7.	Pharmacy and Healthcare Setting Enrollment Form	Clean MS Word & Tracked MS Word (if applicable)
8.	Patient Wallet Card	--

9.	Prescriber Training Program	Clean MS PowerPoint & Tracked MS PowerPoint
10.	Pharmacy and Healthcare Setting Training Program	Clean MS PowerPoint & Tracked MS PowerPoint (if applicable)
11.	Prescriber Knowledge Assessment	--
12.	Adverse Reaction Management Guide	--
13.	Website	Clean PDF
14.	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	Clean PDF

24 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CELESTE A KARPOW
09/16/2022 04:27:33 PM

KATE H OSWELL
09/16/2022 04:28:53 PM

NAOMI S BOSTON
09/16/2022 04:41:35 PM

LAURA A ZENDEL
09/16/2022 04:43:29 PM

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)

Application Type	BLA
Application Number	761291
Nexus ID Number	2022-71
Sequence Number, Date Received	Original-1 received July 8, 2022 (sequence 0041)
PDUFA Goal Date	November 28, 2022
Team Leader/Reviewer Name	Barbara Bergquist, PharmD (DMAMES)
Acting Deputy Division Director	Jo Wyeth, PharmD (DMAMES)
Review Completion Date	September 13, 2022
Subject	Evaluation of Proposed REMS
Trade Name	Tecvayli
Established Name	teclistamab
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Submission Date	July 8, 2022

Table of Contents

1. Introduction

This review by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) provides our interim comments on the risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tecvayli (teclistamab) in response to a consult request by the Division of Risk Management (DRM). The proposed REMS Supporting Document (SD) submitted on July 8, 2022, specifically the REMS assessment plan, audit protocol, and noncompliance plan are the subject of this review.

2. Background

Application BLA # 761291; Tecvayli (teclistamab) was submitted by Janssen Biotech on December 28, 2021 with a proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior lines, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. A REMS was determined to be necessary to mitigate the risk of cytokine release syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). The Applicant's proposed REMS includes a communication plan (CP) elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2.1 REMS Goal

The Tecvayli REMS goal and objectives were revised to the following[1]: to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by

- Educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

3. Supporting Document

The Applicant's July 8, 2022 Supporting Document (SD) (available at: BLA761291 (761291 - 0041 - (41) - 2022-07-08 - ORIG-1 /REMS Correspondence) - 1 Administrative Information and Prescribing Information) included a description of REMS Prescriber and Pharmacist Surveys, a timetable for assessment of the REMS, REMS assessment plan, an audit protocol and a noncompliance plan.

3.1 REMS Prescriber and Pharmacist Surveys

The Applicant proposed conducting surveys of certified prescribers and with pharmacists in certified pharmacies to assess awareness and understanding of the risks, the REMS requirements and the REMS goals and materials. It was proposed that these surveys would be developed after REMS approval and provided to the Agency at least 90 days before implementation. Results of stakeholder surveys were to be reported every two years beginning with the 2-Year Tecvayli REMS Assessment Report.

Reviewer's comments:

- *Due to revisions to the REMS Document, including the goal and objectives as described in section 2.1 in this review, the SD should be revised to include:*

[1] September 8, 2022, DRM (C. Karpow) REMS Review

- *Remove* [redacted] *to be surveyed as the revised objective of the REMS is to educate prescribers, and no longer includes ensuring that pharmacies are educated.*
- *Implementation of surveys with the* [redacted] *REMS assessment report is not acceptable. The REMS strategy being utilized to achieve its desired goal is to directly affect knowledge. Surveys are needed to evaluate if the REMS is meeting its desired objective of educating prescribers and should be implemented and results reported in the 1-Year REMS assessment report.*
- *As the strategy for the REMS is knowledge based, the Applicant will be asked to include in their survey protocol how the REMS will be evaluated in the event that the target REMS prescriber survey sample size is not achieved.*
- *The timetable for submission of assessments needs revision from* [redacted] *to at 1-Year and annually thereafter. Evaluation of the REMS strategy to directly affect knowledge will require submission of prescriber surveys. Submission of prescriber survey results* [redacted] *assessment report is not feasible due to the time needed for development of the survey protocol and instruments after approval, and subsequent review of these by the Agency.*

3.2 Audit Protocol

The audit protocol[2] includes the REMS requirements, audit methodology, audit frequency and audit reporting to include a definition and examples of audit classifications (critical, major and minor). Appended to the audit protocol are a pharmacy audit questionnaire (Appendix 1), a pharmacy audit questionnaire review form (Appendix 2), wholesaler-distributor audit questionnaire (Appendix 3), wholesaler-distributor audit questionnaire review form (Appendix 4), [redacted] and wholesaler-distributors (Appendix 6), on site audit report sample template (Appendix 7), audit confirmation letter (Appendix 8), and audit follow-up letters (Appendix 9) for pharmacies and wholesaler-distributors (Appendix 10, 11) respectively, and non-compliance notification letters/CAPA request for pharmacies (Appendix 12) and wholesalers-distributors (Appendix 13).

Reviewer's comments:

Preliminary review of the audit protocol indicate that revisions and additional information is needed to ensure that REMS processes and procedures are in place, functioning, and support the REMS requirements and to align with the revised REMS Document. Preliminary comments and recommended revisions include:

- *The REMS Coordinating Center should be included as a stakeholder to be audited*
- *Revisions of the SD, the audit protocol and appended documents are needed to include healthcare settings as a stakeholder to be audited where indicated to align with the revised REMS Document*
- *The audit protocol and appended documents need revision to align with the revised REMS goal, objectives and requirements as per the revised REMS Document.*

[2] The audit protocol submitted on July 8, 2022 is available at: \\CDSESUB1\EVSPROD\bla761291\0041\m1\us\rems-audit-protocol.docx.

- *The audit methodology needs revision to include healthcare settings as a stakeholder to be audited. The proposed timing of remote audits of pharmacies and wholesaler-distributors within 180 calendar days after first dispense or authorization to distribute, respectively, and annually thereafter, is acceptable.*

3.3 Noncompliance Plan

The noncompliance plan[3] includes the purpose, roles and responsibilities of the Compliance Assessment Committee (CAC), a description of noncompliance events and actions to be taken for noncompliance. Appended to the noncompliance plan are noncompliance notification letter/CAPA request templates for pharmacies (Appendix 1) and wholesalers-distributors (Appendix 3) and CAPA request noncompliance notification templates for pharmacies (Appendix 2) and wholesalers-distributors (Appendix 4).

Reviewer's comments:

Preliminary review of the noncompliance plan indicate that revisions are needed to align with the revised REMS goal, objectives and requirements as per the revised REMS Document. We have the following preliminary comments and recommended revisions:

- *Revisions are needed to align the noncompliance plan with the revised REMS Document. This should include the addition of healthcare settings as a stakeholder.*
- *The description of noncompliance events should be revised to have these events be described by stakeholder and align with the revised REMS requirements.*

4. REMS Assessment Plan

The Applicant's proposed REMS Assessment Plan (AP)[4] included metrics stratified by assessment categories; Program Outreach and Communication Plan, Program Implementation and Operations, Knowledge, and Health Outcomes and/or Surrogates of Health Outcomes. The SD includes a table (Table 2: Tecvayli REMS Assessment Plan) which maps the objectives of the REMS to the REMS requirements, materials, assessment plan category, metrics, data sources/analytic tools, frequency of metric reporting, performance threshold and methodology/protocol location. The final AP will be included in the Tecvayli Approval Letter.

Reviewer's Comments:

The submitted AP needs revision to inform on the revised goal, objective and REMS requirements and to align with the revised REMS Document. This reviewer's suggested changes (summarized by our proposed metric numbering where indicated below) include the following:

- *Revised the alignment of AP metrics by assessment categories where indicated*

[3] The noncompliance plan submitted on July 8, 2022 is available at: \\CDSESUB1\EVSPROD\bla761291\0041\m1\us\rems-noncompliance-plan.docx.

[4] The proposed REMS Assessment Plan submitted on July 8, 2022 is available from the Supporting Document (section 3.6), available at: \\CDSESUB1\EVSPROD\bla761291\0041\m1\us\tecvayli-rems-supporting-doc.docx.

- *Revised the timeframe for data to be provided to include two previous, current and cumulative reporting periods where indicated*
- *Revised to remove providing assessment data at* (b) (4) *to align with submission of assessments beginning at 1-Year from the date of approval and annually thereafter*
- *Revised the Applicant's proposed assessment category, "Program Outreach and Communication* (b) (4) *to remove,* (b) (4) *as this is an assessment category for alignment of AP metrics and not the communication plan*
- *Revised* (b) (4) *to "pharmacies and healthcare settings" where indicated to align with the revised REMS Document*
- *Table 2: Tecvayli REMS Assessment Plan is not acceptable. This table needs to be revised to align with the revised REMS Document, REMS SD and the REMS AP.*
- ***Metric 1: REMS communication plan activities**: Revised to provide data for the 1-year and 2-year assessments only. Removed submission* (b) (4) *Added stratification of healthcare providers (HCP) targeted to include by specialty if known.*
- ***Metric 2**: **Program Implementation:** Revised to provide data in the 1-Year assessment only. Revised to include the addition of metrics to inform on the REMS website to include the number of visits to the REMS website and the types of REMS materials being downloaded or accessed.*
- ***Metric 3: REMS Certification and Enrollment Statistics:** Revised to align reporting of these metrics by stakeholder. Additional metrics were added to inform on whether stakeholders were "active" and provided definitions of, "active" by stakeholder, to add geographic region and to stratify HCPs data by credentials and specialty and pharmacies/healthcare settings by type.*
- ***Metric 4: Utilization Data:** Added metrics on prescription authorizations and included demographics of the associated prescribers to inform on the utilization and characteristics of those prescribers associated with Tecvayli use*
- ***Metric 5: Compliance:** Expanded, aligned and updated metrics by audit and noncompliance. Addition of metrics to inform and align with the revised REMS Document requirements and added/revised metrics to include reporting of numerators and denominators to determine the percentage(s) of noncompliance where indicated.*
- ***Metric 6: REMS Coordinating Center:** Expanded and added metrics to inform on stakeholder wait time for calls to be answered, assessment of reports indicating a burden or barrier to patient access, addition of metric to inform and provide details on any calls received where the summary reason indicated an adverse event related to CRS or neurologic toxicity including ICANS.*
- ***Metric 7: Knowledge Assessment**: Aligned under the Knowledge assessment category. Addition of metrics to inform on any potential comprehension or perception issues identified, to report the number of completed HCP KAs and method of completion.*
- ***Metric 8: Periodic Survey of Certified Prescribers:** Revised to include submission of surveys beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report. Expanded to include language that surveys should be conducted with random samples of HCPs who prescriber or dispense Tecvayli, added a metric to provide an evaluation of prescriber's knowledge of the revised REMS objective (the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS).*
- ***Metric 9: Report on Key Performance Indicators:** Added key performance indicator metrics to be the primary metrics that will be used to evaluate if the REMS is meeting its stated goal and objective. A process indicator was added to evaluate if the REMS is operating as intended to mitigate the risks. A threshold of 99.9 % compliance with the process indicator is expected. An outcome indicator was added to determine if the REMS is meeting its stated objective of*

educating prescribers on the importance of monitoring patients for signs and symptoms of these risks. A threshold of 80% correct response rate for the outcome indicator was set to align with recommendations in the Agency's REMS Assessment: Planning and Reporting Guidance for Industry[5].

- ***Metric 10: A Summary Analysis of All Reported Cases of CRS and Neurologic Toxicity Including ICANS:*** *Revised to align with language from the revised REMS Document. To further inform on adverse outcomes, expanded this metric to include in the analysis a stratification by grade/severity of whether step-up dosing was initiated in the hospital setting and if pre-medication was administered.*

5. Conclusions and Recommendations

DMAMES has reviewed the proposed REMS Supporting Document (SD) submitted on July 8, 2022, specifically the REMS assessment plan, assessment plan table, audit protocol, and noncompliance plan and have provided edits and needed additions as discussed in section 3 and 4 of this review. The assessment plan, assessment plan table, audit protocol, and non-compliance plan require revisions to be consistent with changes made to the REMS document and capture additional data needed to inform whether the REMS is meeting its goal and objective.

6. Comments For The Applicant

We have the following comments on the proposed Tecvayli REMS Supporting Document (SD) submitted on July 8, 2022, specifically the Tecvayli REMS Assessment Plan, audit protocol and noncompliance plan. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 3 business days that addressed these comments. Include the REMS Supporting Document; include a Word Track changes version, a Word clean version, and a pdf version of all appended materials.

Supporting Document (SD)

The submitted SD needs revisions to align with the revised REMS Document, including the revised goal, objective and requirements. Suggested changes to the SD should include:

- REMS Prescriber and Pharmacist Surveys
  - Remove (b) (4) to be surveyed as the revised objective of the REMS is to educate prescribers, (b) (4) .
  - Implementation of surveys with the (b) (4) REMS assessment report is not acceptable. The REMS strategy being utilized to achieve its desired goal is to directly affect knowledge. Surveys are needed to evaluate if the REMS is meeting its desired objective of educating prescribers and should be implemented and results reported in the 1-Year REMS assessment report.

[5] The January 2019 REMS Assessment: Planning and Reporting Guidance For Industry is available at: https://www.fda.gov/media/119790/download

- As the strategy for the REMS is knowledge based, include in your SD how the REMS will be evaluated in the event that the target REMS prescriber survey sample size is not achieved.
- The timetable for submission of assessments needs revision from (b) (4) to at 1-Year and annually thereafter. Evaluation of the REMS strategy to directly affect knowledge will require submission of prescriber surveys. Submission of prescriber survey results with the (b) (4) assessment report is not feasible due to the time needed for development of the survey protocol and instruments after approval, and subsequent review of these by the Agency.

- Audit Protocol
  - The REMS Coordinating Center should be included as a stakeholder to be audited
  - Revise the SD, the audit protocol and its appended documents to include healthcare settings as a stakeholder to be audited where indicated
  - Revise the audit protocol and its appended documents to align with the revised REMS goal, objectives and requirements as per the revised REMS Document.
  - Revise the audit methodology to include healthcare settings as a stakeholder to be audited.
  - The proposed timing of stakeholder audits (within 180 calendar days after first dispense or authorization to distribute, and annually thereafter) is acceptable.
- Noncompliance Plan
  - Revise the noncompliance plan to align with the revised REMS Document. This should include the addition of healthcare settings as a stakeholder.
  - The description of noncompliance events should be revised to have these events be described by stakeholder and align with the revised REMS requirements.

<u>Tecvayli REMS Assessment Plan Comments</u>

The submitted assessment plan (AP) needs revision to inform on the REMS goal, objective and requirements and to align with changes to the REMS Document. Suggested changes and edits (summarized by our proposed metric numbering below) include the following:

(b) (4)

9 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA A BERGQUIST
09/13/2022 12:20:43 PM

JO H WYETH
09/13/2022 12:57:51 PM

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	761291
PDUFA Goal Date	November 28, 2022
OSE RCM #	2021-2487
Reviewer Names	Celeste Karpow, PharmD, MPH, Risk Management Analyst Kate Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	September 8, 2022
Subject	Evaluation of Proposed REMS
Established Name	teclistamab
Trade Name	Tecvayli
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Dosing Regimen	1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule

1. Introduction

This review by the Division of Risk Management (DRM) provides our interim comments on the risk evaluation and mitigation strategy (REMS) and REMS materials submitted on July 8, 2022; amended on August 1, 2022, August 4, 2022, and August 9, 2022 for the new molecular entity (NME) Tecvayli (teclistamab). Janssen Biotech, Inc. submitted a Biologic Licensing Application (BLA) 761291 for teclistamab with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. This application is under review in the Division of Hematologic Malignancies II (DHMII). 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 teclistamab outweigh the risks of cytokine release syndrome and neurologic toxicity, including ICANS.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for BLA 761291 relevant to this review:

12/07/2021: Applicant informed at pre-BLA meeting that there is insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks for teclistamab.

11/24/2020: Orphan Drug designation granted.

05/26/2021: Breakthrough Therapy designation granted.

12/28/2021: BLA 761291 submission for treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody received.

04/15/2022: Information request sent to Applicant to clarify the Applicant's anticipated outpatient settings of use for teclistamab.

04/19/2022: Response to information request received in which the Applicant proposes teclistamab could be given safely in any outpatient setting without restriction.

04/26/2022: Mid-cycle communication sent to the Applicant with information requests regarding the use of tocilizumab in patients with CRS.

04/28/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the Agency is strongly considering the need for a REMS to ensure the safe use of teclistamab.

05/05/2022: Response to information request received which characterizes the patients who experienced CRS but did not receive tocilizumab.

05/27/2022: Information request sent to Applicant to clarify the Applicant's intended distribution model in the postmarket setting for teclistamab.

06/02/2022:

- The Agency held a teleconference with the Applicant to inform the Applicant that a REMS will likely be needed and suggested the Applicant begin working on a REMS for this application.
- Response to information request received in which the Applicant states teclistamab would not be distributed to outpatient retail pharmacies, specialty, or mail-order pharmacies. The Applicant specified that teclistamab will be distributed to inpatient hospital pharmacy, hospital outpatient pharmacy, community oncology physician offices that administer subcutaneous anti-cancer therapies, and oncology infusion centers that administer SC anti-cancer therapies to enable administration by a health care professional (HCP).

06/29/2022: The Agency held a teleconference with the Applicant to formally inform the Applicant that a REMS will be needed with a communication plan, ETASU A, and ETASU B which constitutes a major amendment, moving the PDUFA date from August 28, 2022 to November 28, 2022. Additionally, the Agency asked the Applicant to provide their rationale explaining why ETASU C is not necessary for their proposed REMS program.

07/08/2022: The Applicant submitted a proposed REMS consisting of a communication plan, prescriber certification and pharmacy certification. The REMS submission was complete. In addition, the Applicant submitted their rationale why ETASU C is not necessary for this REMS program.

07/12/2022: Major amendment acknowledgment letter sent to the Applicant; PDUFA goal date extended by 3 months to November 28, 2022.

07/28/2022: DRM's preliminary REMS review sent to Applicant.

08/01/2022: Janssen Biotech, Inc. submitted a REMS Amendment that included a new and updated REMS Adverse Reaction Management Guide, REMS Knowledge Assessment, REMS Patient Wallet Card, REMS Pharmacy Training Program, and REMS Prescriber Training Program in response to DRM's preliminary REMS review.

08/04/2022: Janssen Biotech, Inc. submitted REMS website screenshots.

08/05/2022: Information request sent to Janssen Biotech, Inc. to request REMS Website screenshots to show the steps that a pharmacist goes through to verify prescriber certification or how authorization to dispense is provided.

08/09/2022: Janssen submitted additional REMS website screenshots showing the steps that a pharmacist goes through to verify prescriber certification and how authorization to dispense is provided.

3. Materials Reviewed

Janssen submitted REMS materials on July 8, 2022, August 1, 2022, August 4, 2022, and August 9, 2022. This review captures DRM's interim comments on:

- All submissions received to date
- Comments DRM received on August 30, 2022 from the Office of Regulatory Policy (ORP) and the Office of Chief Counsel (OCC) on the REMS document
- Comments DRM received on August 26, 2022 from the Office of Prescription Drug Promotion (OPDP) REMS Consult Review signed in DARRTS by Jennifer Chen on the REMS materials.

Materials Reviewed:

1. REMS document
2. Healthcare Provider REMS Letter
3. Professional Society REMS Letter
4. REMS Factsheet
5. Prescriber Training Program
6. Knowledge Assessment
7. Adverse Event Management Guide
8. Prescriber Enrollment Form
9. Pharmacy Training Program
10. Pharmacy Enrollment Form
11. Patient Wallet Card
12. REMS Website, including pharmacy portal

Comments on the REMS Supporting Document and REMS Assessment Plan will be forthcoming.

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

OPDP's comment below is applicable to several REMS materials, including the Patient Wallet Card, Prescriber Enrollment Form and Factsheet:

OPDP Comment: This presentation minimizes risk information as it does not include the following content from the WARNING AND PRECAUTION section of the Prescribing Information: "Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves." Therefore, OPDP recommends revising this presentation to include this material information.

DRM Response: DRM does not agree that this presentation of material from the label is necessary on the Patient Wallet Card, Prescriber Enrollment Form or Factsheet.

The purpose of the wallet card is two-fold:

1) for the patient to show all their healthcare providers to inform them that they are taking TECVAYLI, in particular, medical staff at emergency facilities and

2) as a reminder for patients of the symptoms of CRS and neurologic toxicity and to seek immediate medical assistance if experiencing any symptoms.

The wallet card is a physically small communication tool and content is limited to the most important information related to its purpose.

The Prescriber Enrollment Form contains the Prescriber Attestations, which must align with the requirements in the REMS Document. The REMS program does not require the prescriber to counsel the patient to refrain from driving or operating heavy machinery during Tecvayli treatment. Therefore, we are not able to include this information as part of the attestations. However, this information does appear in the Prescriber Training when discussing prescriber counseling to the patient.

The Factsheet is not intended to provide a comprehensive look of information related to the REMS. The Factsheet presents some risk information along with an overview of the requirements of the REMS, as an introduction to the Tecvayli REMS. The content related to prescriber counseling is described in more detail in the Prescriber Training, which is required for prescriber certification.

REMS Website

OPDP Comment: OPDP noted the presentation of the REMS Website landing page minimizes risks by omitting material information from the BOXED WARNING section of the Prescribing Information regarding the REMS risks. Therefore, OPDP recommends revising these presentations to include this material information.

DRM Response: DRM does not agree that a full presentation of the Boxed Warning is appropriate on the REMS landing page. The purpose of the REMS landing page is to introduce the Tecvayli REMS and brief risk information as related to the REMS. The functionality of the landing page is directly related to the amount of content presented. Healthcare providers can locate the resources they need for certification in the REMS and relevant REMS materials to pass along safety information, such as the wallet card, to patients. Visitors to the REMS website need a clearly laid out, streamlined site to be able to navigate and find information quickly before giving up and leaving the site. In addition, prescribers are required to take Prescriber Training which contains detailed risk information and is accessible through the REMS website.

DRM will communicate our responses to OPDP.

5. Comments to the Applicant

The following comments and attached redlined Tecvayli REMS Document and REMS materials are based on our interim review of the proposed REMS submitted by Janssen Biotech, Inc. on July 8, 2022, August 1, 2022, August 4, 2022, and August 9, 2022. To facilitate our review, please address the following comments and resubmit your REMS as an amendment by September 12, 2022. These comments should not be considered as final edits to the REMS. Comments on the REMS Supporting Document and REMS Assessment Plan will be forthcoming. All REMS materials must align with the final approved labeling.

REMS Document

Revised REMS Goals

The Applicant's proposed goals for the REMS as submitted on July 8, 2022, were as follows:

(b) (4)

The Agency's thinking regarding how to write REMS goals is changing to focus the REMS goals to align with public health prevention goals such as: 1) primary prevention (prevent), 2) secondary prevention (screen), 3) tertiary prevention (manage), and/or informed benefit-risk decision making. This REMS, as designed, uses a prescriber training program to ensure prescribers are educated on the risks of CRS, neurologic toxicity including ICANS, and how to monitor for these risks as we anticipate potentially wider use of this product given the subcutaneous route and ease of administration compared to other products for the proposed indication.

The new goals and objectives of the REMS are as follows:

The goal of the TECVAYLI REMS is to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by:

- Educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.

General Comments for the REMS Document

- Healthcare settings are not included as dispensers in the REMS document. Based on the IR response received from Janssen Biotech, Inc. on June 2, 2022, you indicate there are healthcare settings such as community oncology physician offices and oncology infusion centers that will likely dispense teclistamab instead of a pharmacy. Therefore, "Pharmacies" was revised to "Pharmacies and healthcare settings" throughout the REMS document. Ensure this revision is reflected in all instances that reference pharmacies.

- The abbreviated Applicant's name, "Janssen" was used throughout the REMS document. We do not abbreviate the Applicant's name, therefore, "Janssen" was replaced with "Janssen Biotech, Inc." throughout the REMS document.

- Ensure that "neurological toxicity" is replaced with "neurologic toxicity, including ICANS" throughout the REMS document for consistency with the labeling in the USPI.

- The order of REMS stakeholders can be improved in the statement, "Janssen Biotech, Inc. (Janssen) must ensure that prescribers, pharmacies, patients, and wholesalers-distributors comply with the following requirements:"

Revise the statement to read, “Janssen Biotech, Inc. must ensure that prescribers, patients, pharmacies, healthcare settings and wholesalers-distributors comply with the following requirements:” for consistency with the REMS document template. Ensure this revision is reflected throughout the REMS document.

- Ensure the Prescriber Training Program and the Pharmacy and Healthcare Setting Training Programs are differentiated throughout the REMS document. In addition, ensure that the Adverse Reaction Management Guide is only mentioned in sections relevant to prescribers.

REMS Document Subsection A:

“Healthcare providers who prescribe TECVALYI must:”

- The statement, “Review the TECVAYLI Prescribing Information” can be improved. Revise this statement to read, “Review the drug’s Prescribing Information.” for consistency with the REMS document template.

- The statement, “Review the Prescriber and Pharmacy Training Program and Adverse Reaction Management Guide provided by the REMS” can be improved. (b) (4) We recommend this statement reads, “Review the Prescriber Training Program and Adverse Reaction Management Guide.”

- The statement, “Counsel the patient on how to recognize and respond to signs and symptoms of CRS and neurologic toxicities, using the Patient Wallet Card and the need to report all symptoms of suggestive of CRS and neurological toxicities to their healthcare provider immediately. Provide a copy of the Patient Wallet Card to the patient.” can be improved for clarity and readability. Define all abbreviations when first mentioned and numbering the specific counseling points. Revise this statement to read, “Counsel the patient on 1) how to recognize and respond to signs and symptoms of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), 2) the need to report all symptoms of suggestive of CRS and neurologic toxicity including ICANS to their healthcare provider or emergency room provider immediately, and 3) to carry Patient Wallet Card at all times.”

- The statement (b) (4) ” is no longer necessary since the USPI recommends that patients be hospitalized for 48 hours after administration of all step-up doses. Delete this statement from the REMS document.

- The statement, “Counsel all patients on the importance of the Patient Wallet Card and that they should carry it with them at all times” can be improved. Counseling patients about the Patient Wallet Card is now addressed in a previous item. Therefore, we recommend you revise this statement to read, “Complete the Patient Wallet Card and provide the Patient Wallet Card to the patient” to avoid redundancy.

- The “At all times” section is absent. We recommend you add an “At all times section” that includes the statement, “Report serious adverse events suggestive of CRS or neurologic toxicity

including ICANS to the REMS" for consistency with the prescriber and pharmacy and healthcare setting enrollments forms and to ensure serious adverse events suggestive of CRS or neurologic toxicity including ICANS are reported to the REMS.

"Patients who are prescribed TECVAYLI"

- Move the heading, "Patients who are prescribed TECVAYLI" immediately below the "Healthcare providers who prescribe TECVALYI must" heading.

- The "At all times" and "Have the Patient Wallet Card with you" statements can be improved. This sentence does not address circumstances when the patient should disclose Tecvayli use for ongoing disease treatment. We recommend revising this sentence to further clarify the circumstances when the patient should disclose Tecvayli use for ongoing disease treatment. Revise this statement to read, "Have the Patient Wallet Card with you and inform other healthcare providers about treatment with TECVAYLI."

"Pharmacies and healthcare settings that dispense TECVAYLI must"

- The statement, "Have the authorized representative review the Prescriber and Pharmacy Training Program and Adverse Reaction Management Guide provided by the REMS" can be improved. Delete, "Prescriber and" since there is now a separate pharmacy training program. In addition, delete, "and Adverse Reaction Management guide provided by the REMS" as this is unnecessary for pharmacies. We recommend this statement reads, "Have the authorized representative review the Pharmacy and Healthcare Setting Training Program."
- Delete the statement, (b) (4)
- The statement, "Train all relevant staff involved in dispensing TECVAYLI on the REMS requirements using the Prescriber and Pharmacy Training Program and the Adverse Reaction Management Guide." can be improved. Delete, "Prescriber and" since there is now a separate pharmacy training program. In addition, delete, "and Adverse Reaction Management guide provided by the REMS" as this is unnecessary for pharmacies. We recommend this statement reads, "Train all relevant staff involved in dispensing TECVAYLI on the REMS requirements using the Pharmacy and Healthcare Setting Training Program."
- Delete the statement, (b) (4)
- Based on your response to our information request received on August 1, 2022, this REMS program will have a Pharmacy REMS Dispense Authorization (RDA) functionality. Therefore, we recommend you revise the statement, "Verify that the prescriber is certified through the REMS." to read, "Obtain authorization to dispense each prescription by contacting the REMS Program to verify the prescriber is certified" to align with the REMS Dispense Authorization process.
- The statement to report serious adverse events suggestive of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) should be moved to the top of the "At all times section" for prominence. In addition, we recommend you revise the statement to read, "Report serious adverse events suggestive of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) to the REMS."

"Wholesalers-distributors that distribute TECVAYLI must"

- In the "At all times" section, combine statements 4 and 5 into one item for brevity and clarity. Revise statements 4 and 5 to read, "Maintain records of all TECVAYLI distribution and that all processes and procedures are in place and are being followed."

REMS Document Subsection B:

REMS Training

- The REMS training statements are absent. Include the following REMS training statements for consistency with the REMS document template:

    - "**Janssen Biotech, Inc. must provide training to healthcare providers who prescribe TECVAYLI.** The training includes the following educational materials: Prescriber Training Program, Adverse Reaction Management Guide, and Knowledge Assessment. The training must be provided online."

    - "**Janssen Biotech, Inc. must provide training to pharmacies and healthcare settings that dispense TECVAYLI.** The training includes the following educational material: Pharmacy and Healthcare Setting Training Program. The training must be provided online."

REMS Communications

- Revise the Target Audience to read, "Healthcare providers including oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, and oncology nurses who are likely to prescribe and care for patients treated with TECVAYLI"
- For first approvals, (b) (4) Revise these statements to read, "E-mail within 30 calendar days of the date TECVAYLI is first commercially distributed and again 12 months later" and "Disseminate within 30 calendar days of the date TECVAYLI is first commercially distributed and again 12 months later through the following professional societies and request the letter or content be provided to their members."
- Delete the statement, (b) (4)
- Include Advanced Practitioner Society for Hematology and Oncology (APSHO) and Society of Hematologic Oncology (SOHO) in the list of professional societies.
- The inclusion of "and prominently display" in the statement, (b) (4) is unnecessary. Revise this statement to read, "Disseminate at Professional Meetings where Janssen Biotech, Inc. has a presence for 12 months from the date TECVAYLI is first commercially distributed."
- Delete the REMS Website items from the REMS Communications section. The REMS Website will be addressed in the REMS Operations Section.

REMS Operations

- Revise the statement, [redacted] to read, "Authorize dispensing for each prescription based on verifying the prescriber is certified" to align with the recommendation above about the RDA.
- Revise the statement, "Make the REMS Website fully operational and all REMS materials available through the website and the REMS Coordinating Center, upon request" to read "Make the REMS Website fully operational and all REMS materials available through the website and the REMS Coordinating Center by the date TECVAYLI is first commercially distributed." This ensures that the REMS website is fully operational by the date TECVAYLI is first commercially distributed and reduces the burden on stakeholders to request REMS materials from the REMS Coordinating Center.
- Revise the statement, [redacted] to read, "Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the TECVAYLI REMS" for clarity.
- Revise the statement, [redacted]" to read, "Ensure prescribers, pharmacies and healthcare settings can enroll in the REMS online, by fax and e-mail." The REMS Program should have capabilities to support online, fax and e-mail enrollment without request to ensure enrollment is least burdensome.
- A statement to address verification of prescriber certification is absent. Therefore, we recommend you add a statement that reads, "Ensure pharmacies and healthcare settings are able verify the prescriber is certified by phone and online."
- A statement to indicate pharmacies and healthcare settings that are certified for prescribers is absent. Therefore, we recommend you add a statement that reads, "Provide certified prescribers access to the database of certified pharmacies and healthcare settings."
- A statement to indicate prescribers that are certified for pharmacies and healthcare settings is absent. Therefore, we recommend you add a statement that reads, "Provide certified pharmacies and healthcare settings access to the database of certified prescribers."
- A statement to require reporting of CRS and neurologic toxicity including ICANS to FDA is absent. Therefore, we recommend you add a statement that reads, "Report CRS and neurologic toxicity including ICANS as soon as possible to the FDA but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under applicable FDA regulations."

REMS Compliance

- A statement about how to address noncompliance is absent. Therefore, we recommend you add a statement that reads, "Establish a plan for addressing noncompliance with REMS Program requirements."
- Delete the statement, [redacted] as it is duplicative with item #14.
- The statement, [redacted]

[redacted] (b) (4) ” can be improved so it is clear to the reader when the 180 calendar day clock starts.

We recommend this statement to be revised to “Audit all certified pharmacies and healthcare setting no later than 180 calendar days after the pharmacy or healthcare settings begins dispensing TECVAYLI to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements. Certified pharmacies must also be included in Janssen’s ongoing annual audit plan.”

- Revise the statement, “Take reasonable steps to improve implementation of and compliance with the requirements in the TECVAYLI REMS based on monitoring and evaluation of the TECVAYLI REMS” to read, “Take reasonable steps to improve operations of and compliance with the requirements in the TECVAYLI REMS based on monitoring and evaluation of the TECVAYLI REMS” for clarity.

REMS Assessment Timetable

- Delete the reference to specific times in the first sentence of the REMS Assessment Timetable. Revise the first sentence to read, “Janssen Biotech, Inc. must submit REMS Assessments to the FDA annually from the date of the initial approval of the REMS (MM/DD/YYYY).”

REMS Materials

Overall Comments

- We note that your proposed labeling is currently being reviewed by the FDA. All REMS communication materials must be revised to be consistent with the final FDA approved labeling and resubmitted for review.
- We have provided an Attestation Document with language for the enrollment forms that aligns with the REMS Document. Replace the current proposed attestations with these attestations.

Healthcare Providers REMS Letter

- The Letter for Healthcare Providers will be emailed prior to being sent through traditional mail. Include an email version of the letter with subject heading as it would appear as an email and link to PDF of Factsheet.
- We have provided additional content to better align with the Boxed Warning. See tracked changes version of the REMS Letter for Healthcare Providers.

Letter for Professional Society REMS Letter

- We have provided additional content to better align with the Boxed Warning. See tracked changes version of the REMS Letter for Professional Societies.

Factsheet

- We have provided additional content to better align the Factsheet with the Boxed Warning and REMS Document. See tracked changes version of Factsheet.

Prescriber Training Program

- We have provided additional content to better align the Training with the Prescribing Information. We added a slide to call out prescriber counseling.

Adverse Event Management Guide

- We have updated language in the guide based on currently revised labeling. See tracked changes version of the Adverse Event Management Guide attached.

Prescriber Enrollment Form

- We have simplified the content in the Instructions section.
- The PDF version of Prescriber Enrollment Form has the second page with the green shading across the top similar to the pharmacy enrollment form. Please fix color coding to blue to match first page.
- We recommend putting the contact information that appears below the header on the PDF version, at the bottom of the page. The contact information is contained within the instructions. This would move the more important information up on the first page.
- All contact information is already included above. We recommend putting this information at the bottom of the form.
- See tracked changes version of Prescriber Enrollment Form.

Knowledge Assessment

- The paragraph on the first page is text heavy. Skip a line after the second and fourth sentences to improve readability.

Pharmacy and Healthcare Setting Training Program

- We have made revisions throughout to better align content with revisions to label and REMS Document. See edited version of Pharmacy and Healthcare Setting Training Program.

Pharmacy and Healthcare Setting Enrollment Form

- We have simplified the content in the Instructions section.
- We recommend putting the contact information that appears below the header on the PDF version, at the bottom of the page. The contact information is contained within the instructions. This would create more space for readability or other content.
- All contact information is already included above. We recommend putting this information at the bottom of the form.
- See tracked changes version of Pharmacy and Healthcare Setting Enrollment Form.

Patient Wallet Card

- We have made edits to the wallet card that focus on the symptoms of CRS and neurotoxicity. See tracked changes version of the wallet card.

REMS Website

- We have made edits to the screenshots to reduce content and make the pages more user friendly. The landing page focuses on risk information, the purpose of the REMS and links for users to find the information they need.

- We have also reordered the content on the landing page to focus on the most important information. We have also cleaned up some of the links to streamline usability so that users do not start clicking and get lost within the website.
- We recommend putting the section concerning reporting adverse events at the bottom of the landing page, instead of scrolling way down the right margin. Other REMS websites have information on reporting adverse events as part of the running footer.
- See tracked changes version of REMS Website.

The Agency requests you accept all tracked changes to the Word documents provided. If you make additional revisions, submit a track changed Word version of the revised document(s) to the Agency for review in addition to the formats outlined in the table below. The Agency requests you submit the REMS documents as shown below **by September 12, 2022**:

	Materials	**Required Formats**
1.	REMS Document	Clean Word
2.	REMS Supporting Document	Clean Word
3.	DHCP REMS Letter	Clean Word & Clean PDF
4.	Professional Society REMS Letter	Clean Word & Clean PDF
5.	REMS Fact Sheet	Clean Word & Clean PDF
6.	Prescriber Enrollment Form	Clean Word & Clean PDF
7.	Pharmacy Enrollment Form	Clean Word & Clean PDF
8.	Patient Wallet Card	Clean Word & Clean PDF
9.	Prescriber Training Program	Clean MS PowerPoint & Clean PDF
10.	Pharmacy and Healthcare Setting Training Program	Clean MS PowerPoint & Clean PDF
11.	Prescriber Knowledge Assessment	Clean Word & Clean PDF
12.	Adverse Reaction Management Guide	Clean Word & Clean PDF
13.	Website	Clean MS Word & Clean PDF
14.	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	Clean PDF

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CELESTE A KARPOW
09/08/2022 04:08:38 PM

LAURA A ZENDEL on behalf of KATE H OSWELL
09/08/2022 04:22:12 PM

NAOMI S BOSTON
09/08/2022 04:46:53 PM

LAURA A ZENDEL
09/08/2022 04:50:06 PM

Office of Prescription Drug Promotion

Internal Consult

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

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

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

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer, OPDP

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP
Frances Fahnbulleh, PharmD, Safety Regulatory Project Manager, OSE
Naomi Boston, Team Leader, DRM
Celeste Karpow, PharmD, MPH, Risk Management Analyst, DRM
Michael Wade, OPDP
CDER-OPDP-RPM

Date: August 26, 2022

Re: BLA 761291
TECVAYLI™ (teclistamab-cqyv) injection, for subcutaneous use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

---

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for TECVAYLI:

- Healthcare Provider (HCP) REMS Materials:
  - TECVAYLI REMS Letter for HCPs
  - TECVAYLI REMS Letter for Professional Societies
  - TECVAYLI REMS Factsheet
  - TECVAYLI REMS Prescriber Training
  - TECVAYLI REMS Prescriber Knowledge Assessment
  - TECVAYLI REMS Adverse Reaction Management Guide
  - TECVAYLI REMS Prescriber Enrollment Form
  - TECVAYLI REMS Pharmacy and Healthcare Setting Training
  - TECVAYLI REMS Pharmacy and Healthcare Setting Enrollment Form

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

- TECVAYLI REMS Website

The version of the draft REMS materials used in this review were sent from DRM by Kate Oswell via email on August 10, 2022. The draft REMS materials are attached to the end of this review memorandum.

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

General Comment

Please remind Janssen that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.TECVAYLIREMS.com and toll-free number 1-855-810-8064. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Janssen that the REMS specific website should not be the sole source of approved REMS materials.

The version of the proposed draft Prescribing Information (PI) used in this review, entitled “BLA 761291 teclistamab- USPI-18Aug22,” was obtained from DHM2 (Denise Felluca) on August 18, 2022, and is attached to the end of this review. OPDP’s comments are based on this version of the draft labeling and the REMS materials should be updated, as needed, based on the final approved labeling.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see “Specific Comment[s]” below):

- TECVAYLI REMS Prescriber Knowledge Assessment
- TECVAYLI REMS Pharmacy and Healthcare Setting Enrollment Form

Specific Comment[s]

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

(b) (4)

[redacted]

108 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER W CHEN
08/26/2022 05:12:10 PM

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	761291
PDUFA Goal Date	November 28, 2022
OSE RCM #	2021-2487
Reviewer Names	Celeste Karpow, PharmD, MPH, Risk Management Analyst Kate Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	July 27, 2022
Subject	Evaluation of Need for a REMS
Established Name	teclistamab
Trade Name	Tecvayli
Name of Applicant	Janssen Biotech, Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	Solution for injection
Dosing Regimen	1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule

1. Introduction

This review by the Division of Risk Management (DRM) provides our initial comments on the risk evaluation and mitigation strategy (REMS) submitted on July 8, 2022 for the new molecular entity (NME) Tecvayli (teclistamab). Janssen Biotech, Inc. submitted a Biologic Licensing Application (BLA) 761291 for teclistamab with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior lines, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. This application is under review in the Division of Hematologic Malignancies II (DHMII). 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 teclistamab outweigh the risks of cytokine release syndrome and neurologic toxicity, including ICANS.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for BLA 761291 relevant to this review:

- 12/07/2021: Applicant informed at pre-BLA meeting that there is insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks for teclistamab.
- 11/24/2020: Orphan Drug designation granted.
- 05/26/2021: Breakthrough Therapy designation granted.
- 12/28/2021: BLA 761291 submission for treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody received.
- 04/15/2022: Information request sent to Applicant to clarify the Applicant's anticipated outpatient settings of use for teclistamab.
- 4/19/2022: Response to information request received in which the Applicant proposes teclistamab could be given safely in any outpatient setting without restriction.
- 4/26/2022: Mid-cycle communication sent to the Applicant with information requests regarding the use of tocilizumab in patients with CRS.
- 04/28/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the Agency is strongly considering the need for a REMS to ensure the safe use of teclistamab.
- 05/05/2022: Response to information request received which characterizes the patients who experienced CRS but did not receive tocilizumab.

- 05/27/2022: Information request sent to Applicant to clarify the Applicant's intended distribution model in the postmarket setting for teclistamab.
- 06/02/2022:
    - The Agency held a teleconference with the Applicant to inform the Applicant that a REMS will likely be needed and suggested the Applicant begin working on a REMS for this application.
    - Response to information request received in which the Applicant states teclistamab would not be distributed to outpatient retail pharmacies, specialty, or mail-order pharmacies. The Applicant specified that teclistamab will be distributed to inpatient hospital pharmacy, hospital outpatient pharmacy, community oncology physician offices that administer subcutaneous anti-cancer therapies, and oncology infusion centers that administer SC anti-cancer therapies to enable administration by an health care professional (HCP).
- 06/29/2022: The Agency held a teleconference with the Applicant to formally inform the Applicant that a REMS will be needed with a communication plan, ETASU A, and ETASU B which constitutes a major amendment, moving the PDUFA date from August 28, 2022 to November 28, 2022. Additionally, the Agency asked the Applicant to provide their rationale explaining why ETASU C is not necessary for their proposed REMS program.
- 07/08/2022: The Applicant submitted a proposed REMS consisting of a communication plan, prescriber certification and pharmacy certification. The REMS submission was complete. In addition, the Applicant submitted their rationale why ETASU C is not necessary for this REMS program.
- 07/12/2022: Major amendment acknowledgment letter sent to the Applicant; PDUFA goal date extended by 3 months to November 28, 2022.

3. Comments for the Applicant

The following comments and attached redlined Tecvayli REMS materials are based on our preliminary review of the proposed REMS submitted by Janssen Biotech, Inc. on July 8, 2022. To facilitate our review, please address the following comments and resubmit your REMS as an amendment by August 5, 2022. These comments should not be considered as final edits to the REMS.

A. General Comments

1. Clarify how you intend to ensure that pharmacies only dispense TECVAYLI prescriptions written by certified prescribers. Please include this information in the supporting document.
2. We note that your proposed labeling is currently under review. Ensure all REMS materials and documents are revised to align with labeling.
3. Provide a proposed implementation timeline for the REMS program following approval.
4. Comments and edits on the attestations to use on the enrollment forms will be forthcoming with the REMS Document.
5. Phone numbers used by the Tecvayli REMS may not link to information that is promotional in tone.

B. Training Materials

1. The prescriber and pharmacy training materials are currently presented as one document. This is not efficient and creates a burden for both prescribers and pharmacies reviewing the training materials. We recommend you create two separate training programs, one for prescribers and one for pharmacies that include relevant information for each target audience. Update training based on currently revised labeling.

C. Website

1. All REMS website screenshots must be submitted to the Agency for review. Ensure you submit your web portal outlining each use case with step-by-step screenshots with user instructions. If you choose to have a login on your website, include any screenshots that occur after login as part of the REMS Supporting Document.
2. It is unclear how the prescriber will complete the certification process through your REMS website. Describe and show through the website screenshots how a prescriber would complete the certification process, including reviewing the training materials, and completing and submitting both the Knowledge Assessment and Prescriber Enrollment Form. Explain how the website ensures the prescriber reviews the required materials before submitting the Knowledge Assessment and Enrollment Form.
3. It is unclear why a prescriber needs to logon to complete a one-time certification. Show what happens when a user sets up an account and logs in. In addition, clarify the purpose of a prescriber logon to complete the certification. You may wish to consider renaming the logon button to “Prescriber Certification” to align with the subsequent steps after the prescriber clicks the button.

4. It is unclear how a pharmacy will verify prescriber certification through the website. Create and provide the screenshots showing how a pharmacist would verify prescriber certification before dispensing Tecvayli.
5. The screenshots for the knowledge assessment were not included in the REMS submission received on July 8, 2022. Include these screenshots in your next submission.
6. You provided the pharmacy enrollment form, but you did not include the prescriber enrollment form in your website screenshots. Include the prescriber enrollment form in your next submission.

D. Patient Wallet Card

1. Previous qualitative research on wallet cards has shown that healthcare providers tend to pay more attention to the card if there is red or yellow coloring and a warning symbol that shows importance of the information on the side of the card that is directed to them. We recommend an exclamation point included in a hazard triangle next to the most important information for healthcare providers.

E. Knowledge assessment

1. The knowledge assessment can be improved. Currently, you indicate at least 7 of the 8 questions must be answered correctly. However, REMS programs typically have a requirement to answer all Knowledge Assessment questions correctly to continue to certify and enroll in the REMS. The prescribers may take the assessment multiple times before being locked out. Revise instructions to say that all questions must be answered correctly.
2. The knowledge assessment should focus on ensuring providers understand the risks of CRS and neurotoxicity and how to identify and manage them. If you include a question regarding indication, it should be to ensure providers understand the proper population among patients with multiple myeloma.
3. We recommend you expand the Knowledge Assessment to include questions to adequately assess knowledge of risk and management strategies for both CRS and neurologic toxicity, including ICANS and other neurologic toxicities.
4. In addition to including questions about timing and presentation of CRS, you should include a question that addresses the potential life-threatening complications of CRS (e.g., “Possible complications of CRS include…”) to ensure providers understand that CRS can be fatal if not recognized and treated promptly.
5. Include a question that addresses appropriate management of CRS (e.g., the potential need for hospitalization, IV fluids (IVFs), O2, pressors).
6. Add a question(s) that addresses peripheral neuropathy (including Guillain-Barré syndrome) and motor dysfunction. Also include a question to ensure prescribers understand that neurologic toxicity can occur at any time during treatment.
7. Please see attached word document for more specific feedback.

The Agency requests you submit the REMS documents as shown below **by August 5, 2022**:

	Materials	**Required Formats**
1.	REMS Document	--
2.	REMS Supporting Document	--
3.	DHCP REMS Letter	--
4.	Professional Society REMS Letter	--
5.	REMS Fact Sheet	--
6.	Prescriber Enrollment Form	--
7.	Pharmacy Enrollment Form	--
8.	Patient Wallet Card	Clean MS Word & Clean PDF
9.	Prescriber Training Module	Clean MS PowerPoint
10.	Pharmacy Training Module	Clean MS PowerPoint
11.	Prescriber Knowledge Assessment	Tracked MS Word, Clean Word, & Clean PDF
12.	Adverse Reaction Management Guide	Clean MS Word & Clean PDF
13.	Website	Clean MS Word & Clean PDF
14.	Compiled PDF file that includes the REMS Document and all REMS materials in their final format	--

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CELESTE A KARPOW
07/27/2022 05:13:00 PM

KATE H OSWELL
07/27/2022 09:42:55 PM

NAOMI S BOSTON
07/28/2022 10:05:22 AM

LAURA A ZENDEL
07/28/2022 10:11:13 AM