CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761324Orig1s000

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	761324
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Review Completion Date	May 12, 2023
Subject	Evaluation of the need for a REMS
Established Name	Epcoritamab-bysp
Trade Name	Epkinly
Name of Applicant	Genmab US, Inc.
Therapeutic Class	Bispecific CD20 directed CD3 T cell engager
Formulation(s)	4 mg/0.8 mL and 48 mg/0.8 mL injections in a single-dose vials
Dosing Regimen	Administer subcutaneously according to the step-up schedule in 28-day cycles

Table of Contents

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Epkinly (epcoritamab-bysp) is necessary to ensure the benefits outweigh its risks. Genmab US, Inc. submitted a Biologic Licensing Application (BLA) 761324 for epcoritamab-bysp with the proposed indication (b) (4) The serious risks associated with the use of epcoritamab-bysp are cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), infections, cytopenias, and embryo-fetal toxicity. The Applicant did not submit a REMS but proposed voluntary risk management activities that includes an education materials package (EMP) focused on the risks of CRS and ICANS, which consists of letters for healthcare providers and professional societies.

The Division of Risk Management (DRM) and the Division of Hematology Malignancies 2 (DHM2) have determined that a REMS is not necessary to ensure the benefits of epcoritamab-bysp outweigh its risks. Based on the efficacy and safety information currently available, the clinical reviewer stated that epcoritamab-bysp shows clinically meaningful benefit and recommends approval of epcoritamab-bysp as a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy. The risks of CRS and ICANS will also be communicated in a Boxed Warning to alert healthcare providers of the serious and potentially life-threatening risk. The overall incidence of CRS and ICANS at the recommended dose of epcoritamab-bysp is low, the incidence of Grade ≥3 CRS is very low, and there were no deaths associated with CRS in the epcoritamab-bysp clinical trial. Due to the low rate and low severity of CRS and ICANS seen in the clinical development program, the review team concluded that at this time these risks did not rise to the level of a REMS. Prescribers and healthcare providers administering epcoritamab-bysp in a healthcare setting are expected to have experience in monitoring for, identifying and managing CRS and ICANS, having gained experience with products such as Blincyto, chimeric antigen receptor (CAR) T-cell therapy and Tecvayli. If approved, Boxed Warning for the risks of CRS and ICANS, and Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with epcoritamab-bysp, as well as information to be included in Patient Counseling Information, and a Medication Guide as part of labeling to inform patients regarding the potential risks.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for Epkinly (epcoritamab-bysp) is necessary to ensure the benefits outweigh its risks. Genmab US, Inc. submitted a Biologic Licensing Application (BLA) 761324 for epcoritamab-bysp with the proposed indication (b) (4) [1] This application is under review in the Division of Hematology Malignancies 2 (DHM2). The Applicant did not submit a REMS but proposed voluntary risk management activities that includes an education materials package (EMP) focused on the risks of CRS and ICANS, which consists of letters for healthcare providers and professional societies.

2 Background

2.1 PRODUCT INFORMATION

Epcoritamab-bysp is a new molecular entity (NME) BLA type 351(a) pathway application.[a] This product is a T-cell engaging bispecific antibody that binds to the CD3 receptor expressed on the surface of T-cells and CD20 expressed on the surface of lymphoma cells and healthy B-lineage cells. In vitro, epcoritamab-bysp activated T-cells, caused the release of proinflammatory cytokines, and induced lysis of B-cells.[1] Epcoritamab-bysp is proposed to be supplied as 4 mg/0.8 mL and 48 mg/0.8 mL injections in a single-dose vials. The recommended dosage of epcoritamab-bysp administer subcutaneously according to the step-up schedule in 28-day cycles as follows: [b,1]

Cycle of treatment	Days of treatment	Dose of EPKINLY
Cycle 1	1	0.16 mg (Step-up dose 1)
	8	0.8 mg (Step-up dose 2)
	15	48 mg (First full dose)
	22	48 mg
Cycles 2 and 3	1, 8, 15 and 22	48 mg
Cycles 4 to 9	1 and 15	48 mg
Cycle 10 and beyond	1	48 mg

Epcoritamab-bysp is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for epcoritamab-bysp (BLA 761324) relevant to this review:

- 02/27/2018 Investigation New Drug (IND) 135659 submission for epcoritamab-bysp received.
- 06/28/2022: The Agency informed the Applicant at the Pre-BLA Type B meeting that the primary safety issues with epcoritamab-bysp include CRS, neurotoxicity, infections, neutropenia, and injection site reactions. The appropriate risk mitigation will be determined during the BLA review and will consider whether a REMS is warranted to ensure the safe and effective use of epcoritamab-bysp in the intended population.
- 09/21/2022: BLA 761324 submission for epcoritamab-bysp with the proposed indication (b) (4) received.
- 01/06/2023: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Post Mid-cycle meeting that based on the currently available data, a determination on whether a boxed warning will be included in

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

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

labeling is ongoing, and also considering whether a REMS is warranted to ensure the safety of epcoritamab-bysp in patients with LBCL.

- 03/30/2023: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Late-cycle meeting that based on the currently available data, a REMS is not currently being considered.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Lymphomas are solid tumors of the immune system. Hodgkin's lymphoma accounts for about 10% of all lymphomas, and the remaining 90% are referred to as non-Hodgkin lymphoma (NHL).[2] Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL worldwide, representing approximately 30-40%.[3] NHL represents approximately 4% of all cancer diagnoses and is the seventh most common cancer. The expected number of new cases of NHL in the United States in 2022 is 80,470, with 20,250 expected deaths due to the disease.[4, c] Five-year survival for patients diagnosed with NHL is approximately 72.7%.[5] DLBCL is an aggressive NHL that affects B-lymphocytes, and primarily develops in the lymph nodes, though the disease can spread to extranodal sites such as the gastrointestinal tract, testes, thyroid, skin, breast, bone, brain, or essentially any organ of the body. The incidence of DLBCL in the United States is approximately 7 cases per 100,000 person-years, with a male predominance.[d] Incidence increases with age, with a median age of presentation of 64 years. DLBCL can occur de novo as well as through the transformation of many different types of low-grade B-cell lymphomas.[6]

3.2 Description of Current Treatment Options

The standard therapy for patients with DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Using this regimen, approximately 60–70% of patients with DLBCL are cured of disease. However, about 30–40% of patients will relapse or, in a small patient's subset, be refractory to R-CHOP therapy.[3] Patients with chemosensitive disease proceeding to autologous stem cell transplantation (ASCT) achieve long-term remission in 60% of cases. Patients with primary progressive DLBCL are less chemosensitive to conventional salvage chemotherapy and investigational strategies are recommended in this population to increase the likelihood of proceeding to transplant.[7] Patients with disease that has relapsed or is refractory to R-CHOP have a poor prognosis with short survival times, ranging 6-12 months, with only a small number of patients achieving long-term disease-free survival.[8,9,10] Despite overall improvements in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of morbidity and mortality. Salvage chemotherapy followed by ASCT is the standard second-line treatment for relapsed and refractory DLBCL. Ongoing efforts include exploring novel conditioning regimens and maintenance approaches, but these will have limited impact on the population of relapsed/refractory DLBCL, because only a minority of patients proceed to this treatment. [11] Recently, new therapies have been approved for DLBCL patients

[c] 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.*

[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.*

who have progressed after second-line therapy. These comprise chimeric antigen receptor (CAR) T-cell therapies (CAR-T therapies), axicabtagene ciloleucel (Yescarta; approved October, 2017)[12], tisagenlecleucel (Kymriah; approved May, 2018)[13], lisocabtagene maraleucel (Breyanzi; approved February, 2021)[14], the antibody-drug conjugate polatuzumab vedotin (Polivy; approved June, 2019)[15], in combination with bendamustine and rituximab (Pola + BR), selinexor (Xpovio; approved June 2020)[16], tafasitamab-cxix (Monjuvi; approved July 2020)[17] in combination with lenalidomide, and as well as loncastuximab tesirine (Zynlonta; approved April, 2021)[18]. Please refer DHM2's Assessment Aid (draft) for epcoritamab-bysp for a detailed clinical review on treatment armamentarium relevant to the proposed indication.[22] The CAR-T cell therapies may produce durable complete response (CRs), but their use has limitations because of the toxicity profile, which requires rigorous selection criteria and inpatient administration, and restricted availability in tertiary care facilities. All of these products are approved with REMS with ETASU to mitigate the risk of CRS and neurologic toxicities. Additionally, the waiting period associated with CAR-T manufacture may be prohibitive in patients with symptomatic or rapidly progressing disease.[19,20] Overall, DLBCL patients who progress or do not respond after two lines of treatment are unlikely to respond to further treatment with standard chemotherapy and have a dismal prognosis.[21] There is a clear need for therapeutic strategies that encompass multiple modes of action.

4 Benefit Assessment

The efficacy of epcoritamab-bysp was evaluated in 157 patients with relapsed or refractory LBCL after two or more lines of systemic therapy in study EPCORE NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multi-cohort, multicenter, single-arm trial. Patients received epcoritamab-bysp monotherapy as a subcutaneous injection according to the step-up schedule in 28-day cycles as described in Section 2.1. The study excluded patients with CNS involvement of lymphoma, allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplant, ongoing active infection, and any patients with known impaired T-cell immunity. The efficacy population includes 148 patients with DLBCL not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma. The median age was 64.5 years (range 22 to 83), 61% male, 97% had an ECOG performance status of 0 or 1, and 3% had an ECOG performance status of 2. Race was reported in 125 (84%) patients; of these patients, 61% were White, 20% were Asian, and 0.7% were Native Hawaiian or Other Pacific Islander. There were no Black or African American or Hispanic or Latino patients treated in the clinical trial as reported. The diagnosis was DLBCL NOS in 86%, including 28% with DLBCL transformed from indolent lymphoma, and high-grade B-cell lymphoma in 14%. The median number of prior therapies was 3 (range: 2 to 11), with 29% receiving 2 prior therapies, 32% receiving 3 prior therapies, and 39% receiving 4 or more prior therapies. Eighteen percent had prior autologous HSCT, and 39% had prior chimeric antigen receptor (CAR) T-cell therapy. Eighty-two percent of patients had disease refractory to last therapy and 29% of patients were refractory to CAR T-cell therapy. Efficacy was established based on overall response rate (ORR) determined by Lugano 2014 criteria as assessed by Independent Review Committee (IRC) and duration of response. The efficacy results are summarized in Table 1.[1,22,e]

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

Table 1: Efficacy Results in EPCORE NHL-1 in Patients with LBCL[1,22,e]

Endpoint[a]	**TRADENAME (N=148)**
ORR, n (%)	90 (61)
(95% CI)	(52.5, 68.7)
CR, n (%)	56 (38)
(95% CI)	(30.0, 46.2)
PR, n (%)	34 (23%)
(95% CI)	(16.5, 30.6)
DOR	
Median (95% CI), months	15.6 (9.7, NR)
9-month estimate % (95% CI)	63 (51.5, 72.4)

ORR = overall response rate; CI = confidence interval; CR = complete response; PR = partial response; DOR = duration of response; NR = not reached.

[a] determined by Lugano criteria (2014) as assessed by independent review committee (IRC).

The clinical reviewer stated that the IRC-assessed ORR was 61% (95% CI: 52.5, 68.7), with 38% achieving a complete response, was clinically meaningful, with median time to response of 1.4 months (range 1 to 8.4 months).[1,22,e] Among responders, with a median follow-up for DOR 9.8 months (range 0.0 to 17.3 months), the estimated median DOR was 15.6 months (95% CI: 9.7, not reached).[1] The clinical reviewer also stated that the overall response with associated durability for epcoritamab-bysp provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell in the 3rd line setting and beyond.

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for epcoritamab-bysp. The safety of epcoritamab-bysp was evaluated in the EPCORE NHL-1. A total of 157 patients received epcoritamab-bysp via subcutaneous injection until disease progression or unacceptable toxicities according to the step-up schedule in 28-day cycles as described in Section 2.1. (see Section 4: Benefit Assessment). The median duration of exposure for patients receiving epcoritamab-bysp was 5 cycles (range: 1 to 20 cycles).[1]

The most common (≥ 20%) adverse reactions are cytokine release syndrome (CRS) (50%), injection site reactions (28%), fatigue (23%), musculoskeletal pain (28%), pyrexia (24%), abdominal pain (23%), nausea (20%), and diarrhea (20%). The most common Grade 3 to 4 laboratory abnormalities (≥10%) are decreased lymphocyte count (77%), decreased neutrophil count (32%), decreased white blood cell count (22%), decreased hemoglobin (12%), and decreased platelets (12%).[1]

Deaths

In the Safety Pool 01 LBCL group (n=167), fatal treatment-emergent adverse events (TEAEs) were reported for 12 (7.2%) subjects. One fatal TEAE of immune effector cell-associated neurotoxicity syndrome (ICANS) was considered related to epcoritamab-bysp by the investigator; all other TEAEs were not considered related to epcoritamab-bysp by the investigator or Applicant. Fatal TEAEs attributed to disease progression (6 subjects), included general physical health deterioration (2 subjects), loss of consciousness due to cerebral hemorrhage, pulmonary embolism, hepatotoxicity, and malignant neoplasm progression. Fatal TEAEs related to COVID-19 infection (3 subjects), included COVID-19 (2 subjects) and COVID 19 pneumonia. Fatal TEAEs attributed to existing comorbidities/impact of prior therapies (2 subjects) included myocardial infarction (1 subject, existing cardiac disease) and PML (1 subject, attributed to prior rituximab exposure). Eleven of the 12 fatal TEAEs were on treatment events with onset during the first 2 cycles of treatment, except for the event of loss of consciousness due to cerebral hemorrhage (in the setting of progressive disease), which occurred beyond first 2 cycles.[22]

A fatal episode of ICANS in a 72-year-old patient with DLBCL was considered related to epcoritamab-bysp by the investigator. Lymphoma involvement at screening included target lesions in spleen, pancreas, and para-aortic lymph node. The patient's relevant medical history included hyperlipidemia (grade 1), type 2 diabetes mellitus (grade 2), hypertension (grade 1), and paresthesia (grade 1). Relevant medication history included pregabalin, insulin human injection, metformin/saxagliptin, pancreatin/simethicone/ ursodeoxycholic acid, sulfamethoxazole, and trimethoprim. A diagnosis of grade 3 pancreatitis was made on Day 10. ICANS was an on-treatment event with onset on Day 12, 5 days after the subject's second (and last) dose of epcoritamab-bysp (0.8 mg intermediate dose), and treatment with dexamethasone was initiated. An EEG showed non-convulsive status epilepticus, and antiepileptics were added. A brain MRI revealed multifocal cerebrovascular ischemia (grade 1, unrelated to epcoritamab-bysp). On Day 17, ICANS worsened to grade 4, and the subject developed hypertension, along with fever, diagnosed as grade 1 CRS, and tocilizumab was administered. Methylprednisolone and phenobarbital were also administered. On Day 18, the subject became comatose and was transferred to the ICU, where another dose of tocilizumab was administered. CRS was reported to resolve 4 days later and repeat CT scan showed possible improvement in pancreatitis but also showed a new splenic infarction in the setting of platelet count decreased (grade 3). The subject's mental status continued to deteriorate, and the patient died on Day 25. Per Lugano criteria, the subject had progressive disease (PD) evaluated by the IRC (Days 6 to 24). Even though the ICANS event was considered related to epcoritamab-bysp by the investigator, the patient had several confounding conditions including disease progression.[23]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 41% of patients who received epcoritamab-bysp. Serious adverse reactions in ≥2% patients included CRS, infections (including sepsis, COVID-19, and pneumonia, and upper respiratory tract infections), pleural effusion, febrile neutropenia, fever, and ICANS. Permanent discontinuation of epcoritamab-bysp due to an adverse reaction occurred in 3.8% of patients. Adverse reactions which resulted in permanent discontinuation of epcoritamab-bysp included COVID-19, CRS, ICANS, pleural effusion, and fatigue. Dosage interruptions of epcoritamab-bysp due to an adverse reaction occurred in 22% of patients who received epcoritamab-bysp. Adverse reactions which required dosage interruption in ≥3% of patients included CRS, neutropenia, and thrombocytopenia.[1]

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

5.1 CYTOKINE RELEASE SYNDROME

In the pivotal clinical trial, CRS was reported in 51% of patients receiving epcoritamab-bysp, with Grade 1 CRS occurring in 37%, Grade 2 in 17%, and Grade 3 in 2.5% of patients. There were no Grade 4 or 5 CRS events. In patients who experienced CRS, the signs and symptoms included pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. Concurrent neurological adverse reactions associated with CRS occurred in 2.5% of patients and included headache, confusional state, tremors, dizziness, and ataxia. Recurrent CRS occurred in 16% of patients. Of all the CRS events, most (92%) occurred during Cycle 1. In Cycle 1, CRS events occurred in 9% after the 0.16 mg dose on Cycle 1 Day 1, 16% after the 0.8 mg dose on Cycle 1 Day 8, 61% after the 48 mg dose on Cycle 1 Day 15, and 6% after the 48 mg dose on Cycle 1 Day 22. The median time to onset of CRS from the most recent administered epcoritamab-bysp dose across all doses was 24 hours (range: 0 to 10 days). The median time to onset after the first full 48 mg dose was 21 hours (range: 0 to 7 days). CRS resolved in 98% of patients and the median duration of CRS events was 2 days (range: 1 to 27 days).[1]

Labeling instructs healthcare providers to administer pretreatment medications to reduce the risk of CRS and monitor patients for potential CRS following epcoritamab-bysp accordingly, and patients should be hospitalized for 24 hours after administration of the Cycle 1 Day 15 dosage of 48 mg. At the first signs or symptoms of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care as appropriate. Management of CRS may require either temporary delay or discontinuation of epcoritamab-bysp based on the severity of CRS. Patients who experience CRS (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.[1]

The risk of CRS will be included in the label as a Boxed Warning to inform healthcare providers of this serious risk. Management of CRS, recommendations for premedication with a corticosteroid, antihistamine, and antipyretic, will be included in the Dosage and Administration section of the label to increase the prominence of this information and promote mitigation of CRS.[1]

5.2 IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)

In the clinical trial, ICANS was reported in 6.4% of patients receiving epcoritamab-bysp, with Grade 1 ICANS in 4.5% and Grade 2 ICANS in 1.3% of patients. Clinical manifestations of ICANS included, but were not limited to, confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. There was one (0.6%) fatal ICANS occurrence (see above Section – "Deaths"). The majority of ICANS cases (90%) occurred within Cycle 1 of epcoritamab-bysp treatment, with a median time to onset of 16.5 days (range: 8 to 141 days) from the start of treatment. Relative to the most recent administration of epcoritamab-bysp, the median time to onset of ICANS was 3 days (range: 1 to 13 days). The median duration of ICANS was 4 days (range: 0-8 days) with ICANS resolving in 90% of patients with supportive care.[1]

Labeling instructs healthcare providers to monitor patients for potential ICANS following epcoritamab-bysp. At the first signs or symptoms of ICANS, healthcare providers should immediately evaluate the patient and provide supportive therapy based on severity. The label advises healthcare providers to delay or discontinue epcoritamab-bysp per recommendations in the Dosage and Administration section of the label and consider further management per current practice guidelines. Labeling also

recommends that patients who experience signs or symptoms of ICANS or any other adverse reactions that impair cognition or consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution. Monitoring and dosage modifications for toxicities to address the safety issues with epcoritamab-bysp will be included in the Dosage and Administration section of the label.[1]

5.3 INFECTIONS

In the clinical trial, serious infections, including opportunistic infections, were reported in 15% of patients treated with epcoritamab-bysp at the recommended dose with Grade 3 or 4 infections in 14% and fatal infections in 1.3%. The most common Grade 3 or greater infections were sepsis, COVID-19, urinary tract infection, pneumonia, and upper respiratory tract infection.[1] Fatal infections related to COVID-19 infection (3 patients) included COVID-19 (2 patients) and COVID 19 pneumonia.[22] Labeling instructs healthcare providers to monitor patients for signs and symptoms of infection prior to and during treatment with epcoritamab-bysp and treat appropriately, and also avoid administration of epcoritamab-bysp in patients with active infections. Labeling also instructs healthcare providers to provide PJP prophylaxis prior to initiating treatment with epcoritamab-bysp; consider initiating prophylaxis against herpes virus prior to starting epcoritamab-bysp, and withhold or consider permanent discontinuation of epcoritamab-bysp based on severity.[1]

5.4 CYTOPENIAS

Epcoritamab-bysp can cause serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia. In the clinical trial, among patients who received the recommended dosage, Grade 3 or 4 decreased neutrophils occurred in 32%, decreased hemoglobin in 12%, and decreased platelets in 12% of patients. Febrile neutropenia occurred in 2.5%. Labeling instructs healthcare providers to monitor complete blood counts throughout treatment, and based on the severity of cytopenias, temporarily withhold or permanently discontinue epcoritamab-bysp. Labeling recommends considering prophylactic granulocyte colony-stimulating factor administration as applicable.[1]

5.5 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, epcoritamab-bysp can cause fetal harm when administered to a pregnant woman. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception during treatment with epcoritamab-bysp and for 4 months after the last dose will be communicated in the Use in Specific Populations section of the label.[1]

6 Expected Postmarket Use

If approved, epcoritamab-bysp 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. The expected prescribers include oncologists and hematologists , who likely have experience with monitoring, diagnosing, and managing toxicities such as CRS, ICANS, infections, cytopenias, and embryo-fetal toxicity. The expected prescribers of epcoritamab-bysp and healthcare providers likely have experience

with therapies that have a risk of CRS and ICANS, such as Blincyto (blinatumomab) (approved 12/2014), Kymriah (tisagenlecleucel) (approved 08/2017), Yescarta (approved axicabtagene ciloleucel) and Tecartus (brexucabtagene autoleucel) (approved 10/2017), Breyanzi (lisocabtagene maraleucel)(approved 02/2021), Abecma (Idecabtagene vicleucel)(approved 03/2021), Kimmtrak (tebentafusp-tebn) (approved 01/2022), Carvykti (ciltacabtagene autoleucel) (approved 02/2022), Tecvayli (teclistamab)(approved10/2022), and Lunsumio (mosunetuzumab-axgb) (approved 12/2022.

The CRS and ICANS incidence and severity in the post-market setting may vary from that in the controlled clinical trial program of epcoritamab-bysp. The overall incidence of CRS and ICANS seen in the clinical program was low and mostly Grades 1 and 2, however, it is unknown how this may change in the postmarket setting with a more diverse patient and prescriber population.

There are differences in how the risk was managed in the clinical trial compared to how the risk may be addressed in the post-market setting. Tocilizumab was protocolized and utilized in the epcoritamab-bysp clinical program to treat grade 3 or 4 CRS as well as grade 1 and 2 CRS in an older subject or subject with extensive comorbidities, but tocilizumab is only approved for CRS related to CAR-T cell therapies. Providers in the post-market setting will be expected to utilize other CRS management strategies, such as supportive care, hospitalization, and adherence to premedication protocols for CRS management and mitigation. Furthermore, since CRS onset occurred over a wide range of time (0 to 10 days) in the clinical trial, prescribers in the post market setting will be expected to educate patients on signs and symptoms of CRS and to contact their healthcare provider immediately if they experience these symptoms. CRS associated with epcoritamab-bysp presents with a fever in 229 of the 230 patients in clinical trial, and we expect patients who are eligible to receive epcoritamab-bysp 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

The Applicant did not submit a REMS but proposed voluntary risk management activities such as educational materials and a dissemination plan of these educational materials.[36]

7.1 Other Proposed Risk Management Activities

The applicant has proposed voluntary risk management activities that includes an education materials package (EMP) focused on the risks of CRS and ICANS. These voluntary risk management activities include[36]:

- Epcoritamab Physician Information Sheet
- Dear Healthcare Provider (HCP) / Professional Society Letter
- Grading and Assessment of CRS and ICANS Slide Deck
- Management of CRS and ICANS Associated with Epcoritamab Slide Deck
- HCP CRS Pocket Guide
- HCP ICANS Pocket Guide
- Patient Wallet Card

The voluntary comprehensive EMP by the Applicant will leverage the information contained in epcoritamab-bysp label to provide information to the HCPs on the safe and appropriate use of epcoritamab-bysp. The educational materials to be directed at HCPs are intended to inform on the proper use of epcoritamab-bysp, including detailed information on monitoring and management of adverse reactions such as CRS and ICANS.[36]

Additional educational materials were provided as part of the EMP to help patients understand signs and symptoms of potential adverse reactions associated with epcoritamab-bysp. The Applicant proposes to include a patient wallet card that includes guidance for patients to contact their healthcare team should they experience an adverse reaction (specifically, CRS or ICANS). These patient education materials can be provided through the HCPs.[36]

Dissemination Plan

The EMP is proposed by the Applicant to educate healthcare professionals who have been identified at appropriate sites of care (see Table 2). Healthcare professionals in focus for the EMP include oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology pharmacists, and oncology nurses who are likely to prescribe epcoritamab-bysp and/or care for patients treated with epcoritamab-bysp. The EMP may help HCPs who are considering using epcoritamab-bysp for their patients to be aware of the safety profile, healthcare facility recommendations, and measures to be considered should additional care be required.

The Applicant is developing a plan to identify the educational needs at different sites of care (see Table 2). The Applicant will engage the healthcare professionals at these sites either through awareness notifications and/or by offering educational materials important to safely administer treatment and care for patients receiving epcoritamab-bysp according to the label and current guidelines (see Table 2).[36]

Table 2: Educating Points of Care on How to Utilize T-cell Engagers / Bispecific Antibodies[36]

Site of Care		**Plan for Engagement**
bsAb-enabled:	Healthcare facilities and sites where patients are currently being treated with T-cell engaging therapies (eg, CAR T, teclistamab, mosunetuzumab, etc) and that have the infrastructure to administer the therapy as well as manage adverse reactions associated with these classes of drugs (eg, CRS and ICANS).	The Applicant proposes to provide educational materials to these sites so the appropriate personnel can be informed on the safe and appropriate use of epcoritamab.
bsAb capable:	Healthcare facilities and sites with specialized oncologists/hematologists and extensive support staff, including trained oncology nurses, nurse practitioners/physician assistants, patient navigators/patient financial counselors, case workers, pharmacists, etc, and with the infrastructure to support administration of IV and SC oncolytics. The center should have the capabilities to manage CRS (eg, trained staff, established protocols, access to inpatient use of tocilizumab and/or other IL-6 agents), with inpatient hospital capabilities (eg, ICU) within close proximity.	The goal is to provide educational materials to these sites and their HCPs to support safe and appropriate use of epcoritamab. The Applicant proposes to provide education on adverse reactions of interest for T-cell engaging therapies and what would be required to support safe and appropriate use. This includes educating on the biology involved in the manifestation of CRS and ICANS as well as current grading and guidelines.

bsAb referral:	Healthcare facilities and sites where patients are not currently being treated with T-cell engaging therapies (eg, CAR T, teclistamab, mosunetuzumab, etc) and do not have the infrastructure to administer therapy as well as manage adverse reactions associated with these classes of drugs (eg, CRS and ICANS).	The goal is to ensure that these sites are educated on the capabilities needed to treat CRS and ICANS. The Applicant proposes to provide education on adverse reactions of interest for T-cell engaging therapies and what is required to support safe and appropriate use. This includes educating on the biology involved in the manifestation of CRS and ICANS as well as current grading and guidelines.
Abbreviations: bsAb = bispecific antibody; CAR T = chimeric antigen receptor T cell; CRS = cytokine release syndrome; HCP = healthcare provider; ICANS = immune effector cell-associated neurotoxicity syndrome; ICU = intensive care unit; IV = intravenous; SC = subcutaneous.		

The Applicant plans to disseminate the EMP across the lymphoma community[36]:

- The Applicant proposes to send letters to HCPs and professional societies informing the approval of epcoritamab-bysp and its indication. In addition, the communication will notify healthcare professionals of the availability of educational materials on the product website for HCPs to support the safe and appropriate use of epcoritamab-bysp.
    - Professional societies being considered are: American Society of Clinical Oncology (ASCO); American Society of Hematology (ASH); Advanced Practitioner Society for Hematology and Oncology (APSHO); Oncology Nursing Society (ONS); National Comprehensive Cancer Network (NCCN); Society of Hematologic Oncology (SOHO); Hematology Oncology Pharmacy Association (HOPA); American Pharmacists Association (APhA); American Society of Health-System Pharmacists (ASHP). Additional professional societies are under consideration.
- The Applicant proposes additional activities including outreach by the Applicant to the bsAb-enabled and capable centers (see Table 2) to offer educational materials to support the safe and appropriate use of epcoritamab-bysp.
    - The Applicant proposes to develop EMP materials based on the approved USPI and medication guide, to help healthcare providers who prescribe epcoritamab-bysp or manage patients being treated with epcoritamab-bysp to be informed on potential risks and management of patients who may experience CRS or ICANS.
    - The Applicant proposes to include patient counseling recommendations for healthcare providers to EMP materials to support healthcare providers when counseling their patients to support informed decisions. These recommendations are currently under development.
    - The Applicant plans to engage patient advocacy organizations to discuss approaches to appropriately educate patients on the safe and appropriate use of epcoritamab-bysp with a focus on self-monitoring for CRS and ICANS. The Applicant proposes to provide the USPI, medication guide, and the patient wallet card to the organizations to inform them as they often develop their own resources and activities for their members.
    - The Applicant proposes to develop a plan to operationalize a comprehensive patient support services program which may include a spectrum of services (e.g., triage call center, nurse educators, adverse event management tools and resources) to support

patients and their care teams based on the approved USPI and medication guide.

In addition, longer follow-up and additional data intended to be practice-informing for managing CRS and ICANS is planned with submissions of abstracts to ONS, Journal of the Advanced Practitioner in Oncology (JADPRO), and HOPA describing the safety profile and management of patients receiving epcoritamab-bysp, and the Applicant proposes that these abstracts will be the basis for corresponding manuscript(s) to similarly focused peer-reviewed journals.[36]

Reviewer's Comments: *These activities voluntarily proposed by the applicant are outside of a required REMS program. We do not oppose the applicant's proposal to communicate with stakeholders, including outreach to the healthcare professionals.*

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for epcoritamab-bysp, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Epcoritamab-bysp is a bispecific CD20-directed CD3 T-cell engager, with the proposed indication (b) (4)

NHL represents approximately 4% of all cancer diagnoses and is the seventh most common cancer. DLBCL is the most common type of NHL worldwide, representing approximately 30-40%. Despite overall improvements in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of morbidity and mortality. Overall, DLBCL patients who progress or do not respond after two lines of treatment are unlikely to respond to further treatment; there is a clear need for therapeutic strategies that encompass multiple modes of action. Based on the efficacy and safety information currently available, the clinical reviewer stated that epcoritamab-bysp shows clinically meaningful benefit and recommends approval of epcoritamab-bysp as a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy.[1,22]

The main safety concerns of epcoritamab-bysp are the risks of CRS and ICANS. CRS is a systemic inflammatory response that can be triggered by a variety of factors such as infections and certain drugs. As T-cells are engaged, subsequent activation of immune cells results in release of cytokines. CRS can present with a variety of symptoms ranging from mild, flu-like symptoms to severe life-threatening manifestations of the overshooting inflammatory response. Mild symptoms of CRS include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by hypotension as well as high fever and can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure. Laboratory abnormalities that are common in patients with CRS include cytopenias, elevated creatinine and liver enzymes, deranged coagulation parameters, and a high C-Reactive protein (CRP).[24] ICANS may present with a diverse range of neurologic symptoms; however, patients often develop a characteristic evolution of neurologic features.[25] ICANS typically manifests as a toxic encephalopathy and starts with word-finding difficulty, confusion, dysphasia, aphasia, impaired fine motor skills and somnolence. In more severe cases, seizures, motor weakness, cerebral edema and coma have been noted. The majority of patients who develop clinical features of ICANS will have had

preceding CRS. CRS can therefore be considered an 'initiating event' or cofactor for ICANS. ICANS generally occurs after the symptoms of CRS have subsided, although, less frequently, concurrent presentation of CRS and ICANS can occur. Similar to CRS, ICANS is reversible in most patients with no permanent neurological deficits.[26] In an effort to harmonize the definitions and grading systems for CRS and neurotoxicity, experts from all aspects of the field met at a meeting (June, 2018) supported by the American Society for Transplantation and Cellular Therapy (ASTCT), and the goal was to provide a uniform consensus grading system for CRS and neurotoxicity associated with immune effector cell therapies, for use across clinical trials and in the postapproval clinical setting.[27]

In the context of approved therapies for relapsed or refractory (r/r) DLBCL, the safety profile of epcoritamab-bysp is more favorable regarding CRS compared to CAR-T therapies such as Yescarta, Kymriah and Breyanzi (see the "Table 3: Comparison of CRS/NT/ICANS and Risk Mitigation strategies with other Therapies" in Appendix). The overall CRS incidence is 51% with Grade 1 CRS occurring in 37%, Grade 2 in 16%, and Grade 3 in 2.5% of patients in the primary safety cohort for epcoritamab-bysp[1] compared to 93%, including ≥ Grade 3 CRS in 9% for Yescarta indicated for indolent NHL.[12] Among patients with LBCL who died after receiving Yescarta, four had ongoing CRS events at the time of death.[12] Neurologic toxicities occurred in 74% of patients with LBCL receiving Yescarta, including ≥ Grade 3 cases in 25%, whereas 6.4% of patients receiving epcoritamab-bysp were reported with ICANS, with Grade 1 ICANS in 4.5% and Grade 2 ICANS in 1.3% of patients and there was one (0.6%) fatal ICANS occurrence. CRS occurred in 74% with 23% ≥ Grade 3 CRS for Kymriah, indicated for r/r DLBCL. Neurologic toxicities occurred in 60% of the patients with r/r DLBCL, including ≥ Grade 3 in 19%.[13] In patients receiving Breyanzi after two or more lines of therapy for LBCL, CRS occurred in 46%, including ≥ Grade 3 CRS in 4.1% of patients. One patient had fatal CRS and 2 had ongoing CRS at time of death. CAR T cell associated neurologic toxicities occurred in 35%, including ≥ Grade 3 cases in 12% of patients for Breyanzi. Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death.[14] Other well-known immunotherapy associated with CRS and neurologic toxicity is the class of CAR-T cell therapy for various hematologic malignancies, which includes Tecartus[28], Abecma[29], and Carvykti[30]. All of these products are approved with REMS with ETASU to mitigate the risk of CRS and neurologic toxicities. Because of the incidence and severity of CRS reported during clinical trials, the REMS for these products include restricting the products 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.

Several other approved bispecific T-cell engagers have risks of CRS and neurologic toxicity including ICANS. Risk mitigation strategies for these products is variable ranging from no REMS, communication plan REMS, to REMS with ETASU depending on the benefit-risk profile for the specific product.

Tecvayli, indicated for multiple myeloma, is a bispecific T-cell engager recently approved in October 2022. Tecvayli had an overall CRS incidence of 72%, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6% in clinical trials.[31] Recurrent CRS occurred in 33% of patients with Tecvayli[31], whereas recurrent CRS occurred in 16% of patients with epcoritamab-bysp[1]. In the clinical program for Tecvayli, tocilizumab was administered for 36% of patients, with 21% of Grade 1 CRS events and 88% of Grade 2 CRS events.[31] Whereas, in the clinical trial program for epcoritamab-bysp, tocilizumab was administered for 23% (n=27/116) events, with 5.1% (n=4/78) of Grade 1 CRS events and 59% (n=19/32) of Grade 2 CRS events, and all 100% (n=4/4) of Grade 3 events.[22] This was generally consistent with the protocol recommendation that tocilizumab be used to treat grade 3 or 4 CRS as well as grade 1 and 2 CRS in an older subject or subject with extensive comorbidities.[23] In the clinical trial, neurologic toxicity occurred in 57% of patients who received Tecvayli, with Grade 3 or 4 neurologic

toxicity occurring in 2.4% of patients. ICANS was reported in 6% of patients who received Tecvayli in the clinical trial; recurrent ICANS occurred in 1.8% of patients.[31] Dosage interruptions of Tecvayli due to an adverse reaction occurred in 73% of patients, whereas the dosage interruptions of epcoritamab-bysp due to an adverse reaction occurred in 22% of patients who received epcoritamab-bysp.[1,31] Although CRS and neurologic toxicity appear to be common in the treatment for relapsed or refractory multiple myeloma (RRMM), Tecvayli is unique due to the high incidence of CRS and neurologic toxicity despite risk mitigation activities employed in the clinical trials; and it was the first subcutaneous bispecific T-cell engager product. The review team was also concerned about the incidence and severity of neurologic toxicity associated with Tecvayli, including ICANS. Tecvayli was approved with a REMS with ETASU with a goal to mitigate CRS and neurologic toxicity including ICANS by educating prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.

Blincyto, a bi-specific T-cell engager, was approved in 2014 for the treatment of acute lymphoblastic leukemia (ALL) with a Communication Plan (CP) REMS to mitigate the risks of CRS, neurologic toxicities, and the risk of preparation and administration errors. The release of the Blincyto REMS was approved on December 5, 2022, citing the communication plan requirements have been fulfilled and knowledge surveys of healthcare professionals demonstrate acceptable understanding of the risks of CRS and neurologic toxicities.[32,33] Lunsumio is a bispecific T-cell engager recently approved in December 2022 for the treatment of relapsed or refractory follicular lymphoma with an overall CRS incidence of 39%, including Grade 1 CRS occurring in 28%, Grade 2 in 15%, Grade 3 in 2%, and Grade 4 in 0.5% of patients. Recurrent CRS occurred in 11% of patients. Neurologic toxicity occurred in 39% of patients with Lunsumio in the clinical trial, with Grade 3 neurologic toxicity occurring in 3% of patients.[34] Since the overall incidence of CRS at the recommended dose of Lunsumio is low and the incidence of Grade 3 and Grade 4 CRS is very low, and there were no deaths associated with CRS in the Lunsumio clinical trial, and also, as patients were not required to be hospitalized for administration of the IV infusion in the clinical trial, the review team recommended strengthening labeling for the risk management of CRS associated with Lunsumio.[35] The Lunsumio USPI contains a Boxed Warning for CRS. Labeling also includes recommendations to administer pre-medications, to administer Lunsumio in a healthcare setting, and to utilize practice guidelines for CRS management.[34]

DRM and DHM2 have determined that if approved, a REMS is not necessary to ensure the benefits of epcoritamab-bysp outweigh its risks. Epcoritamab-bysp appeared efficacious in its primary outcome of ORR and secondary outcome of DOR, and its risks can be communicated and managed through labeling.[1,22] The clinical reviewer stated that the IRC-assessed ORR with associated durability for epcoritamab-bysp provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell in the 3rd line setting and beyond.[22] The most concerning adverse reactions observed with the use of epcoritamab-bysp are risks for CRS, ICANS, infections, cytopenias, and embryo-fetal toxicity. The risks of CRS and ICANS will be included in the label as a Boxed Warning. Monitoring and dosage modifications for toxicities to address the safety issues with epcoritamab-bysp will be included in both the Warnings and Precautions and the Dosage and Administration sections of the label, as well as safety information to be included in Patient Counseling Information, and a Medication Guide as part of labeling to inform patients regarding the potential risks. Of note, labeling negotiations are still ongoing with the Applicant. It is expected that oncologists and hematologists, familiar with the management of these toxicities, will be the likely prescribers of epcoritamab-bysp. Rationale for the REMS for Tecvayli included concern that being the first subcutaneous bispecific T-cell engager product and the “off the shelf” nature of the product, the high incidence of CRS and neurologic toxicity despite risk mitigation activities employed in the clinical trials, and the higher usage of tocilizumab in Grade 1 & 2 events, therefore, a required training program to

inform all prescribers of the risks was necessary for safe use of that product. Although epcoritamab-bysp is also available as a subcutaneous injection, the review team did not come to the same conclusion for the following reasons:

- the highest incidence of CRS (40%) and ICANS (5.7%) occurred at or shortly after the Cycle 1 Day 15 dose, the first full dose of 48 mg, where the review team expects most patients to be monitored in a healthcare facility with medical support to manage CRS or overseen by prescribers more familiar with management of CRS and ICANS
- the overall rate and severity of CRS and ICANS that were reported for epcoritamab-bysp were significantly lower
- lesser usage of tocilizumab in the clinical trial as per the protocol recommendation that tocilizumab be used to treat grade 3 or 4 CRS as well as grade 1 and 2 CRS in an older subject or subject with extensive comorbidities
- the occurence of Grade ≥3 CRS rarely occurred in clinical trial
- dosage interruptions in the clinical trial program due to an adverse reactions were low
- the recurrence rate was low and if it occurred was mostly the same grade
- consideration of the familiarity with CRS and management in the prescribing population

The review team recommends strengthening labeling for the risk management of CRS and ICANS associated with epcoritamab-bysp by adding a Boxed Warning for CRS and ICANS. The labeling will also include recommendations to administer pre-medications, recommendations for hospitalization for 24 hours after administration of the Cycle 1 Day 15 dosage of 48mg of epcoritamab-bysp, and to utilize practice guidelines for CRS management. Monitoring and dosage modifications for toxicities to address the safety issues with epcoritamab-bysp will be included in both the Warnings and Precautions and the Dosage and Administration sections of the label, as well as safety information to be included in Patient Counseling Information, and a Medication Guide as part of labeling to inform patients regarding the potential risks. The applicant did not submit a REMS with this application but proposed voluntary risk management activities to further communicate CRS and ICANS with healthcare professionals.[36] Despite the applicant's proposal of the voluntary risk management activities, DRM in concurrence with DHM2 does not find these activities to be necessary for approval or to ensure safe use. We do not oppose the Applicant's proposal to voluntary communicate with stakeholders. REMS Oversight Committee (ROC) was informed that DRM aligned with DHM2 to conclude that a REMS is not necessary to mitigate CRS and ICANS associated with epcoritamab-bysp. The ROC agreed that although products may share the same safety risk (e.g., CRS, ICANS), the appropriate risk management strategy may vary and should be determined on a case-by-case basis, and concur that a REMS is not necessary to ensure the benefits outweigh the risks of epcoritamab-bysp.[f] Additionally, the applicant will be required to conduct a post-marketing required (PMR) study to characterize the rates and types of toxicities occurring with longer term administration of epcoritamab-bysp in the proposed patient population.[37]

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks of epcoritamab-bysp for the treatment of adult patients with relapsed or refractory DLBCL not otherwise

[f] Dal Pan G, Bunting J, Helen E to Olickal T. ROC response as E-mail communication from the ROC panel to DRM, dated May 12, 2023.

specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy. The management of the risks associated with epcoritamab-bysp treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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11 Appendices

Table 3: Comparison of CRS/NT/ICANS and Risk Mitigation strategies with other Therapies

	Epkinly (epcoritamab-bysp) %	Yescarta (axicabtagene ciloleucel) %	Kymriah (tisagenlecleucel) %	Breyanzi (lisocabtagene maraleucel) %	Abecma (idecabtagene vicleucel)	Carvykti (ciltacabtagene autoleucel)	Lunsumio (mosunetuzumab-axgb) %	Tecvayli (teclistamab) %	Blincyto (blinatumomab) %	Kimmtrak (tebentafusp-tebn) %
Indication	Bispecific T cell engager for R/R LBCL	CART NHL; LBCL; iNHL	CART ALL; DLBCL; FL	CART LBCL	CART R/R MM	CART R/R MM	Bispecific T cell R/R FL	Bispecific T cell R/R multiple myeloma	Bispecific T cell R/R ALL	Bispecific T-cell uveal melanoma
Major Risk	CRS, ICANS	CRS, NT	CRS, NT	CRS, NT	CRS, NT	CRS, NT	CRS, NT	CRS, NT/ICANS	CRS, NT	CRS
Overall CRS incidence	50	90 (NHL) 93 (LBCL) 84 (iNHL)	77 (ALL) 74 (DLBCL) 53 (FL)	46 (LBCL)	85	95	39	72	15 (r/r ALL) 7 (MRD-pos ALL)	89
Grade 1	37	NR	NR	NR	NR	NR	28	50	NR	12
Grade 2	16	NR	NR	NR	NR	NR	15	21	NR	Grade ≥2 77
Grade 3	2.5	Grade ≥3 9 (NHL) 9 (LBCL) 8 (iNHL)	Grade ≥3 48 (ALL) 23 (DLBCL) 0 (FL)	Grade ≥3 3.1 (DLBCL)	Grade ≥3: 9 Grade 5: 0 8	Grade ≥3: 5 Grade 5: 1 patient	2	0.6	NR	
Grade 4	0						0.5	0	NR	
Grade 5	0						0	0 (1 case of fatal MODS, cannot rule out CRS)	NR	
Median time to onset of CRS	21 hours (0 to 10 days	3 (1-10) days (LBCL) 4 (1-20) days (iNHL)	3 (1-22) days (ALL) 3 (1-51) days (DLBCL) 4 (1-14) days (FL)	5 (1-15) days	1 (1-23) days	7 (1-12) days	Cycle 1 Day 1 -5 hours (1 hour to 3 days); Cycle 1 Day 8 - 28 hours (5 hours to 3 days); Cycle 1 Day 15 - 25 hours (0.1 hours to 16 days); Cycle 2 Day 1 - 46 hours (12 hours to 3 days)	2 (1 to 6) days	NR	Day of the infusion
Mean Duration	1 day (0 to 26 days)	7 (2-43) days (LBCL) 6 (1-27) days (iNHL)	8 (1-36) days (ALL) 7 (2-30) days (DLBCL) 4 (1-13) days (FL)	5 (1-17) days	7 (1-63) days	4 (1-40) days	3 days(1-29)	2 (1 to 9) days	5 (median)	2 (median)
Overall NT/ICANS incidence	6.4 (ICANS)	NT 78 (NHL) 74 (LBCL) 77 (iNHL)	NT 71 (ALL) 60 (DLBCL) 43 (FL)	NT 35	NT 28	ICANS 23	39 (NT) 1 (ICANS	57 (NT) 6 (ICANS)	65 (NT)	NA
Grade	Grade 1: 4.5 Grade 2: 1.3 Grade ≥3: 2.5 Grade 5: 0.6 (1 patient)	Grade ≥3 25 (NHL) 25(LBCL) 21 (iNHL)	Grade ≥3 22 (ALL) 19 (DLBCL) 6 (FL)	Grade ≥3: 12	Grade 3: 4	Grade ≥3: 3 Grade 5: 2	NT Grade ≥3: 3 ICANS Grade 1: 0.5 Grade 2: 0.5	NT Grade ≥3: 2.4	Grade ≥3: 13	
Median time to onset of NT/ICANS	16.5 (8 to 141 days	5 (1 to 133) days (LBCL) 6 (1-79) days (iNHL)	6 (1-301) days (ALL) 5 (1-368) days (DLBCL) 8 (1-345) days (FL)	8 (1-46) days	2 (1-42) days	8 (1-28) days	NR	ICANS 4 (2-8) days	Within first 2 weeks	
Mean Duration	1 day (0 to 26 days)	15 days(LBCL) 16 days (iNHL)	7 days (ALL) 17 days (DLBCL) 5 days (FL)	12 (1-87) days	5 (1-61) days	6 (2-143) days	NR	ICANS 3 (1-20) days	NR	
Risk Mitigation	W&P, Boxed Warning	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning **ETASU REMS**	W&P, Boxed Warning	W&P, Boxed Warning **ETASU REMS**	W&P Boxed Warning Communication Plan REMS; released in Dec 2022	W&P, Boxed Warning

R/R=relapsed or refractory; CART=Chimeric antigen receptor T-cell therapy; NHL= non-Hodgkin lymphoma; iNHL=indolent non-Hodgkin lymphoma LBCL= large B-cell lymphoma; DLBCL=Diffuse large B-cell lymphoma; ALL=acute lymphoblastic leukemia; MM= multiple myeloma; FL= follicular lymphoma; CRS=cytokine release syndrome; ICANS= immune effector cell-associated neurotoxicity syndrome; NT= neurological toxicities; NR= not reported; NA= not applicable

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TILL OLICKAL
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NAOMI S BOSTON
05/12/2023 01:15:56 PM

LAURA A ZENDEL
05/12/2023 01:22:15 PM