CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761152Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEWS

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	761152
PDUFA Goal Date	December 26, 2025
Nexus TTT #	2025-13873
Reviewer Name	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Laura Zendel, PharmD
Review Completion Date	December 22, 2025
Subject	Evaluation of Need for a REMS
Proper Name	Narsoplimab
Trade Name	Yartemlea
Name of Applicant	Omeros Corporation
Therapeutic Class	Monoclonal antibody: Mannan-binding lectin-associated serine protease 2 inhibitor (Lectin pathway complement inhibitor)
Dosage Form	185 mg/mL solution for intravenous (IV) injection
Dosing Regimen	Greater than or equal to 50 kg: 370 mg once weekly as an IV infusion Less than 50 kg: 4 mg/kg once weekly as an IV infusion

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 Yartemlea (narsoplimab-wuug) is necessary to ensure the benefits outweigh its risks. Omeros Corporation resubmitted Biologics License Application (BLA) 761152 for narsoplimab-wuug on March 26, 2024, with the proposed indication for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) in response to a Complete Response letter issued on October 15, 2021, due to clinical and statistical deficiencies. The March 26, 2024, resubmission (the subject of this review) included additional data from the global expanded access program. This application is under review in the Division of Nonmalignant Hematology (DNH). The Applicant did not submit a REMS or risk management plan with this application.

DRM and DNH have determined that a REMS is not needed to ensure the benefits of narsoplimab outweigh its risks. The review team concluded that the benefit of narsoplimab was demonstrated based on the TMA-response rates from the 28 high-risk subjects in the pivotal trial and based on data from 19 high-risk patients in the expanded use program. During the course of the review, the Agency revised the indication to the following: for the treatment of adult and pediatric patients two years of age and older with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA).

Narsoplimab is a complement inhibitor; therefore, the risk under consideration for a REMS was serious infections. Risk mitigation approaches vary across the approved complement inhibitors. In the United States, there are several complement inhibitors approved with REMS that include elements to assure safe use to mitigate the risk of meningococcal infections (complement C5 inhibitors) or to mitigate the risk of serious infections caused by encapsulated bacteria (complement C3 inhibitor, complement Factor B inhibitor, and complement Factor D inhibitor). However, narsoplimab has a different mechanism of action than other approved agents in this class. Narsoplimab inhibits the lectin pathway while leaving the classical and alternative pathways intact. Due to its mechanism of action, the risk of serious infections appears to be less than the risk associated with other complement inhibitors that require a REMS. In addition, TA-TMA is a rare, acute, and serious condition associated with hematopoietic stem cell transplants. Patients who undergo hematopoietic stem cell transplant are immunosuppressed and at high risk for serious and severe infections. The standard of care includes close monitoring for infections. Labeling is sufficient to mitigate the risk of serious infections in this population and this risk will be conveyed as a Warning and Precaution. We do not anticipate additional mitigation strategies are necessary beyond labeling to ensure prescribers are monitoring and managing serious infections in the indicated population.

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) Yartemlea (narsoplimab-wuug) is necessary to ensure the benefits outweigh its risks. Omeros Corporation (hereafter referred to as the Applicant) submitted a Biologics License Application (BLA) 761152 for narsoplimab-wuug with the

proposed indication for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA). The Agency issued a Complete Response letter on October 15, 2021, due to clinical and statistical deficiencies.[a] The Agency concluded that there was insufficient confirmatory evidence to provide substantial evidence of effectiveness.

A class 2 resubmission was submitted on March 26, 2025, which is the subject of this review. The submission included additional data from the global expanded access program. This application is under review in the Division of Nonmalignant Hematology (DNH). The Applicant did not submit a REMS or risk management plan with this application.

2. Background

2.1. Product Information

Yartemlea (narsoplimab-wuug [hereafter referred to as narsoplimab]), a new molecular entity[b], is proposed for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy. During the course of the review, the Agency revised the indication to the following: for the treatment of adult and pediatric patients two years of age and older with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA).

Narsoplimab is a human monoclonal antibody that inhibits mannan-binding lectin-associated serine protease 2 (MASP-2). MASP-2 is a key enzyme involved in activation of the complement lectin pathway. When activated, MASP-2 cleaves complement proteins C4 and C2 leading to the formation of C3 convertase and further activation of the complement cascade. Inhibition of MASP-2 by narsoplimab prevents complement activation via the lectin pathway. Narsoplimab does not affect the classical and alternative pathways. In the setting of TA-TMA, this mechanism is hypothesized to reduce inflammation, endothelial cell activation, and tissue injury.

Narsoplimab is proposed to be supplied as a 370 mg/2 mL single-dose vial that must be diluted prior to administration. The preparation and administration instructions depend on the patient's weight. The proposed dosage is 4 mg/kg (up to a maximum 370 mg) as an intravenous infusion once or twice a week. During the course of the review, the dosage regimen was revised as below:

[a] Yanoff, L, October 15, 2021, Complete Response Letter for Yartemlea (narsoplimab), BLA 761152.

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

Table 1. Recommended Dosage[c]

Weight (kg)	Recommended Dosage
Greater than or equal to 50 kg	370 mg given as an intravenous infusion over 30 minutes once weekly. Increase frequency to twice weekly if there is inadequate improvement in TA-TMA signs and symptoms.
Less than 50 kg	4 mg/kg given as an intravenous infusion over 30 minutes once weekly. Increase frequency to twice weekly if there is inadequate improvement in TA-TMA signs and symptoms

Given the severity of the proposed indication, narsoplimab will likely be administered in an inpatient setting. Inpatient settings are experienced with providing intravenous infusions and can provide close monitoring of the patient. Narsoplimab is intended to be used to treat an acute complication (TMA) and not intended as a chronic therapy.[d] Narsoplimab is not currently approved in any jurisdiction.

If approved, narsoplimab would be the first complement inhibitor that targets the lectin pathway. There are several complement inhibitors approved in the United States and the risk mitigation approaches vary. Several complement inhibitors are approved with REMS that include elements to assure safe use; however, for some complement inhibitors labeling was determined to be sufficient (Refer to Section 7 for additional discussion).

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761152 relevant to this review:

- **04/26/2018**: Breakthrough Therapy Designation granted for IND 120524 for the treatment of patients with hematopoietic stem-cell transplant associated thrombotic microangiopathy (TA-TMA) who have persistent TMA despite modification of immunosuppressive therapy.
- **10/22/2018**: Orphan Drug Designation granted for TA-TMA.
- **11/17/2020:** BLA 761152 submission for the treatment of patients with TA-TMA received.
- **10/15/2021:** The Agency issued a Complete Response (CR) letter to the Applicant due to clinical and statistical deficiencies. The Agency concluded that there was insufficient confirmatory evidence to provide substantial evidence of effectiveness. This conclusion was based on the lack of at least one "adequate and well controlled" trial and insufficient mechanistic evidence that narsoplimab will have the purported effect. DRM deferred a REMS determination at this time.
- **03/26/2025:** Class 2 resubmission for BLA 761152 received.

[c] Omeros Corporation. DRAFT Prescribing Information for Yartemlea (narsoplimab), BLA 761152. Agency edits as of December 12, 2025

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

- **07/10/2025:** The Agency issued a Major Amendment Acknowledgement Letter to the Applicant extending the PDUFA goal date by 3 months to review responses to clinical information requests and to complete the efficacy analysis.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hematopoietic stem cell transplantation-associated thrombotic microangiopathy (TA-TMA) is a severe multisystem complication associated with significant morbidity and mortality. The pathophysiology is complex and multifactorial. TA-TMA is hypothesized to be the result of multiple "hits" that increase the risk for or cause endothelial injury leading to a proinflammatory, prothrombotic state (Khosla et al. 2018; Mahmoudjafari et al. 2023). Research suggests complement overactivation is also involved in the pathogenesis (Mahmoudjafari et al. 2023; Meri et al. 2022). Risk factors for TA-TMA include unrelated donor, human leukocyte antigen mismatch, high-dose chemotherapy, radiation therapy, immunosuppression agents, advanced age, female sex, graft-versus-host disease (GVHD) and infections (Kim et al. 2015).

Around 24,000 stem cell transplants are performed in the United States each year (Phelan et al. 2022). The reported incidence of TA-TMA in adults ranges from 4 to 68% (Khosla et al. 2018; Mahmoudjafari et al. 2023).[e,f] The diagnosis is challenging as the clinical presentation overlaps with other complications such as graft-versus-host disease and calcineurin-induced hypertension or renal injury (Khosla et al. 2018; Mahmoudjafari et al. 2023). TA-TMA is characterized by thrombocytopenia, hemolysis, presence of schistocytes, hypertension, and microvascular thrombosis leading to renal injury and other end-organ damage (including central nervous system, cardiovascular, pulmonary, and gastrointestinal). TA-TMA is typically an early complication with the majority of cases diagnosed between 20 to 100 days following the transplant; however, late cases diagnosed >100 days after hematopoietic stem cell transplantation (HSCT) have been reported (Heybeli et al. 2020; Schoettler et al. 2023). Milder forms of TA-TMA can result in an increased risk of long-term complications such as chronic kidney disease, whereas severe forms with multiorgan involvement are associated with mortality rates of 60 to 90% (Jodele et al. 2015).[g]

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

[f] The wide ranges in reported incidence are due to a historic lack of consensus on diagnostic criteria. Consensus diagnostic criteria by an international panel of experts were published in 2023 to assist with recognition and differentiation from other HSCT complications. However, these criteria were published after the clinical trial was initiated.

[g] 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

There are no FDA-approved therapies for TA-TMA. The first-line management is supportive care including management of hypertension and treatment of underlying GVHD or infections (Java and Brennan 2025; Mahmoudjafari et al. 2023). Dose modifications or withdrawal of calcineurin inhibitors may be considered as initial management; however, more recent data suggest this approach does not impact HSCT outcomes and may cause or exacerbate GVHD (Khosla et al. 2018). Therapeutic plasma exchange (TPE) has not demonstrated a reduction in the risk of chronic organ damage in TA-TMA; however, it may still be used in some scenarios, such as early TA-TMA or when complement-targeted therapy is not available (Khosla et al. 2018; Mahmoudjafari et al. 2023).

Off-label treatments utilized in severe or refractory TA-TMA include complement inhibitors (including C5 and C3 inhibitors), rituximab, and defibrotide (Mahmoudjafari et al. 2023). Evidence for these agents is limited and based on small, mostly observational or open-label studies (Java and Brennan 2025). These options are also limited by their adverse event profiles including serious infections (complement inhibitors, see section 2.1), bleeding (defibrotide[h]), and infusion reactions, peripheral edema, hypertension, and less common but serious reactions including reactivation of hepatitis B virus and progressive multifocal leukoencephalopathy (rituximab[i]). There is an unmet need for safe and effective therapies for TA-TMA.

4. Benefit Assessment

The benefit of narsoplimab for the treatment of TA-TMA was demonstrated in a phase 2, single-arm, open-label study (OMS721-TMA-001 [NCT02222545]; hereafter referred to as Study TMA-001). Study TMA-001 enrolled 28 adult subjects with TA-TMA who were at high risk for poor outcomes. Twenty-four subjects received narsoplimab 4 mg/kg IV once weekly and 4 subjects received narsoplimab 370 mg IV once weekly. The efficacy was based on TMA-response defined as improvement in 1) laboratory TMA markers (LDH levels and platelet counts) and 2) at least one of two clinical findings, specifically organ function and freedom from transfusion. In total, 17 of 28 subjects with TA-TMA (61%, 95% CI: 40.6, 78.5) in Study TMA-001 responded to narsoplimab treatment. The review team noted that the magnitude of the response is clinically meaningful for patients with TA-TMA. The subjects in this study were high-risk; therefore, based on the natural history of disease, a spontaneous recovery would be unexpected. The review team commented that a response rate of 61% would be unexpected without an effective TA-TMA directed therapy.[j]

[h] See DEFITELIO (defibrotide) at http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208114

[i] See RITUXAN (rituximab) at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103705

[j] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Nonmalignant Hematology. Clinical, Statistical, and Clinical Pharmacology Join Review for Narsoplimab, BLA 761152 (Resubmission after Complete Response). Draft as of December 15, 2025.

Additional data from an expanded access program (EAP) included 19 TA-TMA patients (13 adult and 6 pediatric) with available efficacy data were used to support approval.[k] In total, 13 of 19 patients with TA-TMA (68.4%, 95% CI: 43.4, 87.4) in the EAP responded to narsoplimab treatment, including 9 of 13 adult patients (69.2%, 95% CI: 38.6, 90.9) and 4 of 6 pediatric patients (66.7%, 95% CI: 22.3, 95.7). The clinical reviewer noted that these data provided supportive evidence of efficacy as the patients were comparable and the response rates were similar to subjects in TMA-001.[l] Pediatric patients were included in the EAP; therefore, the Agency revised the indication to include pediatric patients 2 years of age and older.

The review team concluded that substantial evidence of effectiveness was established based on one adequate and well-controlled trial (Study TMA-001) and confirmatory evidence (EAP patients with evaluable efficacy data).[m,n]

5. Risk Assessment & Safe-Use Conditions

The primary safety population for narsoplimab consists of all 28 subjects in the open-label, phase 2, pivotal trial, Study TMA-001.[o] The median duration of treatment was 8 weeks (range 2 to 16.4 weeks).

The most common adverse reactions (≥20%) were viral infections, sepsis, hemorrhage, diarrhea, vomiting, nausea, neutropenia, pyrexia, fatigue, and hypokalemia.

During the adverse event evaluation period[p], 17 subjects (60.7%) experienced a serious adverse event (SAE). The most common SAEs included infections (including sepsis), GVHD, acute kidney injury, neutropenia, and confusional state. There were 4 deaths in the adverse event evaluation period and 12 deaths after this period. The clinical reviewer noted that the high incidence of SAEs is not unexpected as the enrolled subjects were acutely ill and had multiple comorbidities.[q] GVHD was not considered related to treatment by the review team with narsoplimab as it commonly occurs in the post-transplant setting.

---

[k] Efficacy data comparable to TA-TMA Study were available for 19 of 221 patients included in the Expanded Access Program.

[l] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Nonmalignant Hematology. Clinical, Statistical, and Clinical Pharmacology Join Review for Narsoplimab, BLA 761152 (Resubmission after Complete Response). Draft as of December 15, 2025.

[m] 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.*

[n] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Nonmalignant Hematology. Clinical, Statistical, and Clinical Pharmacology Join Review for Narsoplimab, BLA 761152 (Resubmission after Complete Response). Draft as of December 15, 2025.

[o] The clinical reviewer in the integrated review noted that since the safety database was composed of only uncontrolled data, all adverse events were assumed to be drug-related adverse reactions.

[p] The AE evaluation period was defined from the time of informed consent to 37 days after the last narsoplimab dose.

[q] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Nonmalignant Hematology. Integrated Review: Yartemlea (narsoplimab-wuug), BLA 761152. October 15, 2021.

The main risk that required REMS consideration was serious infections (refer to Section 5.1 for additional discussion).

Supportive data included the additional 221 adult and pediatric patients with TA-TMA who were treated in the EAP. The most common serious adverse reaction were in the system organ class, infections and infestations. The clinical reviewer concluded that the safety profile in the EAP appears similar to the pivotal trial.[r]

5.1. Serious Infections

Infections were identified as a pre-specified adverse event of special interest. During the pivotal Study TMA 001, infections occurred in 21 subjects (75%) with serious infections occurring in 10 subjects (36%). The infections included sepsis, bacterial infections, viral infections, and pneumonia. In total, 7% of the TA-TMA patients died due to infections. There were no serious infections caused by encapsulated bacteria (*Neisseria meningitidis*, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*) reported in the adverse event (AE) evaluation period. There was one case of pneumococcal pneumonia in the post-AE evaluation period. There was no comparator arm in Study TMA-001 so it is challenging to interpret whether the infection rates are increased compared to a control population. The safety profile for patients treated with narsoplimab in the EAP did not differ from that seen in the overall clinical development program for narsoplimab.

In the context of the proposed indication, patients are already at high risk for infections in the post-transplant setting as the immune system requires time to recover. While products in the complement inhibitor drug class may increase the risk of serious infections because the complement system is involved in innate and adaptive immune responses, the risk varies based on the targets within the complement system. Narsoplimab targets the lectin pathway while the classical and alternative pathways of the complement system remain intact and allow generation of downstream complement proteins, including C3 and MAC. As such, the risk of serious infections caused by encapsulated bacteria appears less than products that prevent the formation of MAC (C5 inhibitors and C3 inhibitors). This assessment is supported by case series data of patients with inherited MASP-2 deficiency. Not all patients with inherited MASP-2 deficiency experience chronic serious infections; therefore, MASP-2 deficiency may not be an independent risk factor for serious infections caused by encapsulated bacteria (García-Laorden et al. 2020).

The review team concluded that the risk of serious infections should be communicated in labeling.[s] The risk of serious infections will be conveyed in Section 5: Warnings and Precautions. Draft labeling

[r] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Nonmalignant Hematology. Clinical, Statistical, and Clinical Pharmacology Join Review for Narsoplimab, BLA 761152 (Resubmission after Complete Response). Draft as of December 15, 2025.

[s] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Nonmalignant Hematology. Integrated Review: Yartemlea (narsoplimab-wuug), BLA 761152. October 15, 2021.

recommends to monitor patients with active infections closely for signs and symptoms of worsening infections and treat promptly.[t]

6. Expected Postmarket Use

Labeling for narsoplimab is sufficient to communicate the risk of serious infections and ensure safe use conditions are followed in the postmarket setting for the proposed indication. Patients who undergo a HSCT are managed closely by a multidisciplinary team with hematology/oncology and transplant specialists. Post-HSCT, patients are monitored closely for infections as part of the standard of care (Tomblyn et al. 2009). TA-TMA is usually an early and serious complication of HSCT that is often diagnosed and treated in the inpatient setting. If approved, narsoplimab would be administered as an IV infusion, likely in the inpatient setting, due to the severe nature of the disease state. We anticipate patients will receive close monitoring by healthcare providers during treatment for signs and symptoms of infections. We do not anticipate additional mitigation strategies would be necessary beyond labeling to ensure prescribers are monitoring and managing infections.

The anticipated patient population for narsoplimab is expected to be knowledgeable about the risk of infections. Patient selection and pre-and post-transplant education is already part of the standard of care (ASTCT 2025). It is expected that patients/caregivers would be counseled on the risk of infections, monitoring, and when to seek medical care. Early identification of infections and seeking medical care is critical as the immune system takes time to recover. In the setting of TA-TMA, patients are likely to already be hospitalized and undergoing comprehensive monitoring for infections.

7. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of narsoplimab outweigh the risks. Labeling is sufficient to mitigate the risk of serious infections and this risk will be conveyed as a Warning and Precaution.

The review team concluded that the benefit of narsoplimab was demonstrated based on the TMA-response rates from the 28 high-risk subjects in the pivotal trial and on data from 19 high-risk patients in the expanded use program.

Narsoplimab is a complement inhibitor; therefore, the risk under consideration for a REMS was serious infections. Risk mitigation approaches vary across the approved complement inhibitors. In the United States, there are several complement inhibitors approved with REMS that include ETASU to mitigate the risk of meningococcal infections (complement C5 inhibitors) or to mitigate the risk of serious infections caused by encapsulated bacteria (complement C3 inhibitor, complement Factor B inhibitor, and complement Factor D inhibitor). Other complement inhibitors approved without a REMS include the following:

[t] Omeros Corporation. DRAFT Prescribing Information for Yartemlea (narsoplimab), BLA 761152. Agency edits as of December 12, 2025.

- Enjaymo[u] (sutimlimab-jome), complement C1s inhibitor
- Veopoz[v] (pozelimab-bbfg), complement C5 inhibitor
- Tavneos[w] (avacopan), complement C5a inhibitor
- Syfovre [x](pegcetacoplan injection, for intravitreal use), complement C3 inhibitor

The decision to not require a REMS for these products was based on a review of the statutory factors which included, differences in the infection risk based on the product's target pathway in the complement system, the estimated size of the patient population for proposed indications, and the systemic exposure of the product.

Based on a review of the statutory factors, there were important considerations that support the determination that a REMS is not needed for narsoplimab for the treatment of TA-TMA. Narsoplimab prevents complement activation by inhibiting the lectin pathway and does not affect the classical and alternative pathways. The risk of serious infections caused by encapsulated bacteria associated with narsoplimab is expected to be less than that of complement inhibitors that target the alternative pathway or products that target downstream proteins (e.g., C3 and C5) and prevent the formation of the complement membrane attack complex. TA-TMA is a rare, acute, and potentially life-threatening complication. Patients are likely to be managed in the inpatient setting by a multidisciplinary team including hematology/oncology and transplant specialists. It is not intended as a chronic therapy. The patient population is immunosuppressed and at high risk for serious infections due to the recent HSCT. The standard of care for patients post-HSCT includes close monitoring for infections and prompt evaluation and treatment. Therefore, we do not anticipate that additional mitigation strategies would be necessary beyond labeling to ensure that prescribers are monitoring for and managing serious infections.

7.1. Collaborative Discussions on the Need for a REMS

The REMS Oversight Committee[y] was informed that the review team concluded a REMS is not necessary to ensure the benefits of narsoplimab outweigh the risks. The ROC agreed with the review team's rationale and decision.[z] A ROC member agreed that the decision to not require a REMS for narsoplimab

---

[u] See ENJAYMO (sutimplimab-jome) at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761164

[v] See VEOPOZ (pozelimab-bbfg) at http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=761339

[w] See TAVNEOS (avacopan) at http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=214487

[x] See SYFOVRE (pegcetacoplan injection, for intravitreal use) at http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=217171

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

[z] REMS Oversight Committee (ROC) by Email. Minutes for Yartemlea (narsoplimab), BLA 761152.

was consistent with the approach for other complement inhibitors approved without a REMS, including consideration of the site of action in the complement system, the rarity of the condition, and that the population has well-established protocols for managing the risk of infections. A ROC member inquired whether there were any enhanced pharmacovigilance plans for the risk of serious infections. The review team confirmed that a PMR would be issued for a patient registry to characterize the long-term safety of narsoplimab in patients with transplant-associated thrombotic microangiopathy (TA-TMA). The final study report should include a summary of all safety findings, including serious infections.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for narsoplimab beyond routine pharmacovigilance and labeling.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. Due to its mechanism of action, the risk of serious infections appears to be less than that of other complement inhibitors that require a REMS. We do not anticipate that additional mitigation strategies would be necessary beyond labeling to ensure that prescribers are monitoring and managing serious infections.

Should DNH have any concerns or questions, or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

American Society for Transplantation and Cellular Therapy. Patient Education. Https://Www.Astct.Org/Education/Patient-Education. Accessed December 2025. 2025. [accessed].

García-Laorden, MI, E Hernández-Brito, C Muñoz-Almagro, S Pavlovic-Nesic, I Rúa-Figueroa, ML Briones, O Rajas, L Borderías, A Payeras, L Lorente, J Freixinet, J Ferreres, I Obando, N González-Quevedo, F Rodríguez de Castro, J Solé-Violán, C Rodríguez-Gallego. 2020. Should Masp-2 Deficiency Be Considered a Primary Immunodeficiency? Relevance of the Lectin Pathway. J Clin Immunol. 40(1):203-210.

Heybeli, C, M Sridharan, HB Alkhateeb, JC Villasboas Bisneto, FK Buadi, D Chen, D Dingli, A Dispenzieri, MA Gertz, RS Go, SK Hashmi, SR Hayman, WJ Hogan, DJ Inwards, SS Kenderian, SK Kumar, MR Litzow, LF Porrata, MQ Lacy, IN Micallef, MM Patnaik, MV Shah, N Leung. 2020. Characteristics of Late Transplant-Associated Thrombotic Microangiopathy in Patients Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation. Am J Hematol. 95(10):1170-1179.

Java, A, D Brennan. 2025. Thrombotic Microangiopathy after Kidney Transplantation. In: C Legendre, A Lam, editors. UptoDate. Waltham, MA.

Jodele, S, BL Laskin, CE Dandoy, KC Myers, J El-Bietar, SM Davies, J Goebel, BP Dixon. 2015. A New Paradigm: Diagnosis and Management of Hsct-Associated Thrombotic Microangiopathy as Multi-System Endothelial Injury. Blood Rev. 29(3):191-204.

Khosla, J, AC Yeh, TR Spitzer, BR Dey. 2018. Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy: Current Paradigm and Novel Therapies. Bone Marrow Transplant. 53(2):129-137.

Kim, SS, M Patel, K Yum, A Keyzner. 2015. Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy: Review of Pharmacologic Treatment Options. Transfusion. 55(2):452-458.

Mahmoudjafari, Z, MC Alencar, MD Alexander, DJ Johnson, J Yeh, MD Evans. 2023. Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy and the Role of Advanced Practice Providers and Pharmacists. Bone Marrow Transplantation. 58(6):625-634.

Meri, S, D Bunjes, R Cofiell, S Jodele. 2022. The Role of Complement in Hsct-Tma: Basic Science to Clinical Practice. Adv Ther. 39(9):3896-3915.

Phelan, R, M Chen, C Bupp, YT Bolon, L Broglie, J Brunner-Grady, LJ Burns, S Chhabra, D Christianson, R Cusatis, SM Devine, A D'Souza, M Eapen, M Hamadani, M Hengen, SJ Lee, A Moskop, KM Page, M Pasquini, WS Pérez, M Riches, D Rizzo, W Saber, SR Spellman, HE Stefanski, P Steinert, D Weisdorf, M Horowitz, JJ Auletta, BE Shaw, M Arora. 2022. Updated Trends in Hematopoietic Cell Transplantation in the United States with an Additional Focus on Adolescent and Young Adult Transplantation Activity and Outcomes. Transplant Cell Ther. 28(7):409.e401-409.e410.

Schoettler, ML, E Carreras, B Cho, CE Dandoy, VT Ho, S Jodele, I Moissev, I Sanchez-Ortega, A Srivastava, Y Atsuta, P Carpenter, J Koreth, N Kroger, P Ljungman, K Page, U Popat, BE Shaw, A Sureda, R Soiffer, S Vasu. 2023. Harmonizing Definitions for Diagnostic Criteria and Prognostic Assessment of Transplantation-Associated Thrombotic Microangiopathy: A Report on Behalf of the European Society for Blood and Marrow Transplantation, American Society for Transplantation and Cellular Therapy, Asia-Pacific Blood and Marrow Transplantation Group, and Center for International Blood and Marrow Transplant Research. Transplant Cell Ther. 29(3):151-163.

Tomblyn, M, T Chiller, H Einsele, R Gress, K Sepkowitz, J Storek, JR Wingard, J-AH Young, MA Boeckh. 2009. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. Biology of Blood and Marrow Transplantation. 15(10):1143-1238.

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/

LINDSEY W CRIST
12/22/2025 08:37:55 AM

JACQUELINE E SHEPPARD
12/22/2025 10:00:36 AM

LAURA A ZENDEL
12/22/2025 10:04:45 AM

Division of Risk Management (DRISK)
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	761152
PDUFA Goal Date	October 17, 2021
OSE RCM #	2020-2404
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	October 4, 2021
Subject	Deferral Memo due to Complete Response Action
Established Name	Narsoplimab-wuug
Trade Name	Yartemlea
Name of Applicant	Omeros Corporation
Therapeutic Class	Monoclonal antibody: Mannan-binding lectin-associated serine protease 2 inhibitor (Lectin pathway complement inhibitor)
Formulation(s)	185 mg/mL solution for intravenous infusion
Dosing Regimen	4 mg/kg (up to a maximum of 370 mg) once weekly (b) (4)

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) documents deferral for the review to determine whether a REMS is necessary for the new molecular entity Yartemlea (narsoplimab-wuug). Omeros Corporation submitted a Biologics Licensing Application (BLA 761152) for narsoplimab-wuug on November 17, 2020. The application's proposed indication is the treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA), a rare, serious, life-threatening complication of HSCT in which endothelial injury and overactivation of complement results in microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis. This application is under review in the Division of Nonmalignant Hematology (DNH).

Narsoplimab-wuug is a human monoclonal antibody that interacts with the complement host defense system. There are three major independent but overlapping pathways for the activation of complement, which include the classical pathway, the lectin pathway, and the alternative pathway.[1] Lectins are proteins that recognize and bind to carbohydrate patterns found on the surfaces of pathogenic microorganisms or injured host cells (such as endothelial cells) and target mannan-binding lectin-associated serine protease (MASP) enzymes to the site. Activation of the lectin pathway appears to be involved with the pathophysiologic processes associated with HSCT-TMA.[2] Narsoplimab-wuug binds to and inhibits MASP-2, a key enzyme responsible for activation of the lectin pathway.[3]

A Phase 2, single-arm, open-label study (OMS721-TMA-001 [NCT02222545]) was conducted to assess the safety and efficacy of narsoplimab-wuug in the treatment of HSCT-TMA in 28 adult patients. The draft Integrated Review noted there is a lack of consensus on the diagnostic criteria as well as the definition of response to treatment for HSCT-TMA.[4] The primary efficacy endpoint was defined by the Applicant as a composite response based on the proportion of patients who experienced both an improvement in platelet count and lactate dehydrogenase levels, *and* freedom from platelet transfusion or clinical improvement in organ function (renal, pulmonary, neurologic, or gastrointestinal). Adherence to conduct of the study was problematic in that 11 of the 28 (39%) patients did not meet inclusion/exclusion criteria and were granted enrollment waivers. In addition, not all patients who the Applicant classified as responders met all three components of the primary endpoint definition. Most patients also had other concurrent disease for which they were actively treated as well as various concomitant medications that may have impacted the response to narsoplimab-wuug and confounded interpretation of the results. The Applicant chose a response rate of 15% as evidence of efficacy. The Applicant's analysis concluded that 17 of the 28 patients (61% [95% C.I., 41% to 79%]) enrolled met the definition for primary endpoint response.[3] The Agency's analysis determined that 12 out of 28 patients (43% [95% C.I., 24% to 63%]) were responders. DNH also consulted two subject matter experts who reviewed the cases and separately concluded that 14/28 (50%) and 15/28 (54%) of the patients appeared to have a response to treatment.[4]

During the review cycle, the Applicant submitted a literature review to estimate the response rate of patients with HSCT-TMA treated with the standard of care.[5] The Agency determined this submission constituted a major amendment to the application. There were several limitations with interpretation of the literature review, including unknown validity and accuracy of the data, potential response rate measurement errors across different publications, the timing of treatment visits, likely selection bias, and other limitations. The historical data showed a response rate of 32% (95% C.I., 26% to 40%) for all patients,

and a rate of 23% (95% C.I., 15% to 34%) for a subset of patients who did not receive pharmacological treatment. The review team concluded the literature review could not serve as an external control because of the various limitations in interpreting the results and that the literature did not provide sufficient evidence to support the use of a 15% response rate to define efficacy.

Additionally, the review team concluded the Applicant did not provide sufficient mechanistic evidence to provide confirmatory evidence for the application. There appears to be involvement of lectin pathway activation and MASP-2 in patients with HSCT-TMA based on in vitro models. However, the magnitude of narsoplimab-wuug's effect in limiting complement activation downstream of MASP-2 inhibition and whether this translates into a measurable clinical benefit was unclear, as the data provided were not sufficient.[4]

Due to the lack of an adequate and well-controlled trial and insufficient confirmatory evidence to provide substantial evidence of effectiveness, the review team is recommending a Complete Response. Because the efficacy of the treatment has not been established, DRM is unable to formulate recommendations for risk management, specifically REMS, at this time.

References

[1] Liszewski MK and Atkinson JP. Complement pathways. Schur PH, Marsh R, Feldweg AM (Eds). UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (Accessed on January 20, 2021).
[2] Rambaldi A, et al. Endothelial injury and thrombotic microangiopathy in COVID-19: Treatment with the lectin-pathway inhibitor narsoplimab. Immunobiology 2020; 225(6):152001
[3] Omeros. Clinical Overview for narsoplimab, BLA 761152, November 17, 2020.
[4] Draft Integrated Review Narsoplimab-wuug, BLA 761152, September 30, 2021.
[5] Omeros. Clinical Information Amendment, BLA 761152, April 23, 2021.

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/

ROBERT G PRATT
10/04/2021 10:47:20 AM

DORIS A AUTH on behalf of NAOMI S BOSTON
10/04/2021 10:52:45 AM

DORIS A AUTH
10/04/2021 10:56:43 AM