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RESEARCH**

APPLICATION NUMBER:

761152Orig1s000

OTHER REVIEWS

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Real-World Evidence (RWE)

Date: December 15, 2025

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Subject: Review of RWE Submitted by Applicant to Support Efficacy for
BLA 761152 YARTEMLEA (narsoplimab-wuug) Resubmission

Drug Name: Yartemlea (narsoplimab)

Application Type/Number: BLA 761152

Submission Number: 79

Applicant/sponsor: Omeros Corporation

TTT #: [2025-13875](#)

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EXECUTIVE SUMMARY

On March 26, 2025, the Division of Non-Malignant Hematology (DNH) requested the Division of Epidemiology-I (DEPI-I) review real-world evidence (RWE) submitted by Omeros Corporation in support of a resubmission for Biologics License Application (BLA) 761152, for Yartemlea (narsoplimab) for treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA). The submission included two study reports intended as confirmatory evidence of effectiveness: an external control study (OMS-TMA-ECC) comparing overall survival (OS) in the single-arm pivotal trial (OMS721-TMA-001) to patients in the Kyoto Stem Cell Transplantation Group (KSCTG) registry in Japan, and a supplemental report incorporating Expanded Access Program (EAP) data. This review provides DEPI-I's assessment of the adequacy of the submitted RWE to serve as confirmatory evidence of effectiveness for the proposed indication.

TA-TMA is a rare, severe complication of hematopoietic stem cell transplantation (HSCT) with high mortality and no FDA-approved therapies, representing a significant unmet medical need. Narsoplimab is a MASP-2 inhibitor intended to block inflammatory and prothrombotic responses. The initial BLA for narsoplimab received a Complete Response in October 2021 for failing to provide substantial evidence of effectiveness.

The current primary RWE submission, Study OMS-TMA-ECC, is a retrospective cohort study that compared OS of 28 high-risk TA-TMA patients from the pivotal trial to an external control cohort of 108 patients from the KSCTG registry. The primary analysis utilized Cox proportional hazards models with propensity score-based inverse probability of treatment weighting (IPTW) to balance baseline covariates and multiple imputation to adjust for immortal time bias. The results indicated a statistically significant 68% reduction in mortality risk for the narsoplimab group (Hazard Ratio [HR]=0.32; 95% CI: 0.23-0.44). The estimated 1-year survival rate was 41% for narsoplimab patients compared to 14% for KSCTG controls. The supplemental study included three analyses incorporating 49 EAP patients, showing consistent survival benefits with mortality risk reductions ranging from 49-63% (HRs ranging from 0.37 to 0.51).

Strengths of the external control study and its supplement include use of advanced statistical methods such as propensity score-based IPTW to balance baseline covariates, appropriate methods to account for immortal time bias, and extensive pre-specified sensitivity analyses that consistently supported primary results. Additionally, the KSCTG registry serves as a reliable external control source, demonstrating data relevance and reliability through standardized TA-TMA diagnostic criteria consistent with international consensus guidelines and rigorous quality control processes that ensure data accuracy, completeness, and traceability.

However, DEPI-I identified significant limitations that compromise the internal and external validity of the findings. Major concerns include a lack of patient comparability

between the treatment and control cohorts due to temporal disparities, geographic differences, and differing selection criteria, which introduced a high potential for confounding and selection bias that could systematically favor the narsoplimab arm. Furthermore, the analysis did not adjust for several key prognostic factors and potential confounders – including patient baseline performance status, HLA mismatch, stem cell source, and calendar year – suggesting the treatment effect are likely overestimated. Finally, the poor overlap in propensity score distributions indicates that the cohorts had fundamentally different baseline characteristics, which can lead to unstable effect estimates and limits the generalizability of the findings. Given these limitations, the submitted studies do not meet rigorous methodological standards required for robust RWE, and their utility for informing regulatory decision-making is limited.

In conclusion, the findings from the external control study and its supplement should be interpreted with considerable caution, as the magnitude of treatment effect is likely overestimated due to systematic biases and unmeasured confounding inherent in the non-randomized study design. In the context of a rare disease with a high unmet medical need, DEPI-I defers to the clinical review team to determine the utility of this evidence, weighing the identified methodological limitations against the overall benefit-risk profile and other data submitted in the application as part of the totality of evidence.

1 INTRODUCTION

On March 26, 2025, the Division of Non-Malignant Hematology (DNH) requested the Division of Epidemiology-I (DEPI-I) review real-world evidence (RWE) submitted by Omeros Corporation as part of biologics license application (BLA) 761152 resubmission for Yartemlea (narsoplimab) for treatment of hematopoietic stem cell transplant - associated thrombotic microangiopathy (TA-TMA or HSCT-TMA). The submission included two study reports intended as confirmatory evidence of effectiveness: (1) an external control study report (OMS-TMA-ECC) titled “Comparison of Survival Following TA-TMA in Study OMS721-TMA-001 to Survival of Patients Diagnosed with TA-TMA in the Kyoto Stem Cell Transplantation Group (KSCTG) Registry,” and (2) a supplemental report to OMS-TMA-ECC titled “Comparison of Survival Following TA-TMA in Narsoplimab-Treated Patients from Study OMS721-TMA-001 and the Expanded Access Program to Survival of Patients Diagnosed With TA-TMA In the KSCTG Registry – Supplement to the External Control Report”. This review provides DEPI-I’s assessment of the adequacy of the submitted RWE to serve as confirmatory evidence of effectiveness for the proposed indication.

1.1 BACKGROUND

TA-TMA is a rare, severe, and potentially life-threatening complication following hematopoietic stem cell transplant (HSCT). This condition results from endothelial injury and is characterized by microvascular occlusive disorder that leads to thrombocytopenia, hemolytic anemia, and end-organ damage, particularly affecting the kidneys, lungs, and gastrointestinal tract.¹ The reported cumulative incidence of TA-TMA during the early post-HSCT period ranges from 3% to 39%.² TA-TMA carries a poor prognosis, with mortality rate as high as 50% to 60%.^{3,4} The prognosis is particularly unfavorable for patients with high-risk profiles, including those with graft-versus-host disease (GVHD), significant infections, and multi-organ involvement.^{1,5} Current first-line treatment for TA-TMA focuses on identifying and removing the triggering cause and providing supportive care. No FDA-approved therapies currently exist for TA-TMA, representing a significant unmet medical need.

¹ Jodele S, Laskin BL, Dandoy CE, Myers KC, El-Bietar J, Davies SM, Goebel J, Dixon BP. A new paradigm: diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. *Blood reviews*. 2015 May 1;29(3):191-204.

² Van Benschoten V, Roy C, Gupta R, Ouellette L, Hingorani S, Li A. Incidence and risk factors of transplantation-associated thrombotic microangiopathy: a systematic review and meta-analysis. *Transplantation and Cellular Therapy*. 2022 May 1;28(5):266-e1.

³ Martinez MT, Bucher CH, Stussi G, Heim D, Buser A, Tsakiris DA, Tichelli A, Gratwohl A, Passweg JR. Transplant-associated microangiopathy (TAM) in recipients of allogeneic hematopoietic stem cell transplants. *Bone marrow transplantation*. 2005 Dec;36(11):993-1000.

⁴ Daly AS, Hasegawa WS, Lipton JH, Messner HA, Kiss TL. Transplantation-associated thrombotic microangiopathy is associated with transplantation from unrelated donors, acute graft-versus-host disease and venoocclusive disease of the liver. *Transfusion and Apheresis Science*. 2002 Aug 1;27(1):3-12.

⁵ Elsallabi O, Bhatt VR, Dhakal P, Foster KW, Tendulkar KK. Hematopoietic stem cell transplant-associated thrombotic microangiopathy. *Clinical and Applied Thrombosis/Hemostasis*. 2016 Jan;22(1):12-20.

Narsoplimab is a monoclonal antibody that inhibits mannan-binding lectin-associated serine protease 2 (MASP-2), the effector enzyme of the lectin pathway of complement. By targeting MASP-2, narsoplimab inhibits the inflammatory and prothrombotic responses to endothelial injury. Omeros is proposing narsoplimab for the treatment of TA-TMA with a recommended dosing regimen of 4 mg/kg administered as a 30-minute intravenous infusion (maximum 370 mg per infusion) once or twice weekly.

1.2 REGULATORY HISTORY

Omeros initially submitted BLA 761152 on November 17, 2020, for narsoplimab based on results from the phase 2, single-arm, pivotal trial OMS721-TMA-001, which utilized response rate as the primary endpoint. FDA issued a Complete Response Letter (CRL) on October 15, 2021, stating the application failed to establish substantial evidence of effectiveness. Following subsequent discussions, Omeros proposed external control studies comparing OS in narsoplimab-treated patients with the KSCTG registry cohort and submitted these study results as confirmatory evidence of effectiveness for the proposed indication. Table 1 summarizes the relevant regulatory history for this review.

Table 1. Relevant Regulatory History for BLA761105 of Narsoplimab

Date	Event
November 17, 2020	BLA 761152 initial submission
October 15, 2021	FDA issued Complete Response Letter (CRL)
June 15, 2022	Omeros submitted a formal dispute resolution request (FDRR) in response to CRL
November 3, 2022	FDA issued a Formal Dispute Resolution Appeal Denied letter, and outlined several paths forward
May 11, 2023	Type B meeting to discuss the proposed paths forward
November 6, 2023	Omeros submitted the initial protocol and SAP for an external control study, titled “ <i>Comparison of Survival Following HSCT-TMA in Study OMS721-TMA-001 to Survival of Patients Diagnosed with HSCT-TMA in the Kyoto Stem Cell Transplantation Group (KSCTG) Registry</i> ” (SN 0069)
January 4, 2024	Type B WRO regarding comparison of OS from KSCTG registry to TMA-001 trial along with Expanded Access Program (EAP)
January 24, 2024	Omeros submitted the revised protocol and SAP for the proposed external control study, titled “ <i>Comparison of Survival Following HSCT-TMA in Study OMS721-TMA-001 to Survival of Patients Diagnosed with HSCT-TMA in the KSCTG Registry</i> ” (SN 0072).
September 5, 2024	Type B Meeting to discuss proposal for resubmission using KSCTG as external control and using survival data from EAP as confirmatory evidence

Date	Event
September 16, 2024	Omeros submitted the updated protocol (dated September 16, 2024) and SAP (dated September 12, 2024) for the proposed external control study, titled “ <i>Comparison of Survival Following HSCT-TMA in Study OMS721-TMA-001 to Survival of Patients Diagnosed with HSCT-TMA in the KSCTG Registry</i> ”. (SN 0075)
November 15, 2024	The general advice letter sent to Omeros (DARRTS #: 5479754).
January 31, 2025	Omeros submitted the patient-level dataset in excel format for study OMS721-TMA-001 and KSCTG registry, and the final updated SAP titled “ <i>Comparison of Survival Following HSCT-TMA in Study OMS721-TMA-001 to Survival of Patients Diagnosed with HSCT-TMA in the KSCTG Registry</i> ”, dated December 3, 2024. (SN 0077)
February 6, 2025	FDA sent information request (IR) regarding the dataset for the proposed external control study
March 26, 2025	Omeros submitted excel datasets for 2,425 patients included the KSCTG registry. (SN 0079)
March 26, 2025	BLA 761152 resubmission
April 28, 2025	FDA sent IRs regarding raw/source data for the KSCTG registry patients
May 20, 2025	Omeros submitted the responses to FDA’s IRs dated April 28, 2025 (SN 0082)
July 1, 2025	FDA sent IRs regarding the KSCTG registry datasets and literature review/meta-analysis to evaluate natural history and OS of TA-TMA patients.
July 8, 2025	Omeros submitted the responses to FDA’s IRs (#1-3) dated July 1, 2025, regarding datasets for KSCTG registry. (SN 0087)
July 16, 2025	Omeros submitted the responses to FDA’s IRs (#4-6) dated July 1, 2025, regarding literature review/meta-analyses to evaluate natural history and OS of TA-TMA patients. (SN 0088)
August 8, 2025	FDA sent IRs (recommended by DEPI-I) regarding the primary external control study (OMS-TMA-ECC) and the supplement study
August 22, 2025	Omeros submitted the responses to FDA’s IRs dated August 8, 2025. (SN 0094)

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS TO BE REVIEWED

DEPI-I has conducted a comprehensive review of the following submissions:

- 1) External Control Study Report (OMS-TMA-ECC)** titled “Comparison of Survival Following Hematopoietic Stem Cell Transplant-Associated Thrombotic

- Microangiopathy (TA-TMA) in Study OMS721-TMA-001 to Survival of Patients Diagnosed with TA-TMA in the Kyoto Stem Cell Transplantation Group (KSCTG) Registry” (Submitted on March 26, 2025), along with:
- **External Control Comparison Protocol** (dated December 3, 2024, submitted on March 26, 2025)
 - **Statistical Analysis Plan (SAP)** (dated December 3, 2024, submitted on January 31, 2025)
- 2) **Supplemental report to OMS-TMA-ECC**, titled “Comparison of Survival Following Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy (TA-TMA) in Narsoplimab-Treated Patients from Study OMS721-TMA-001 and the Expanded Access Program to Survival of Patients Diagnosed With TA-TMA In the Kyoto Stem Cell Transplantation Group Registry – Supplement to the External Control Report” (Submitted to FDA on March 26, 2025), along with
- **Supplemental SAP** (dated December 9, 2024, submitted on March 26, 2025)
- 3) **Omeros’s Response to FDA Information Request dated April 28, 2025**, regarding source data for external control in KSCTG registry (submitted on May 20, 2025)
- 4) **Omeros’s Response to FDA Information Request dated July 1, 2025**, regarding KSCTG registry datasets and literature review/meta-analysis to evaluate natural history and OS of TA-TMA patients (submitted on July 8 and July 15, 2025)
- 5) **Omeros’s Response to FDA Information Request dated August 8, 2025**, regarding the primary external control study (OMS-TMA-ECC) and the supplement study (submitted on August 22, 2025)

We also referenced the following documents for additional information regarding study OMS-TMA-001 and the EAP as well as the regulatory context:

- **Clinical Overview** (submitted on March 26, 2025)
- **Summary of Clinical Efficacy** (submitted on March 26, 2025)
- **Expanded Access Program report (OMS-TMA-EAP)**, titled “Study Report Summarizing Survival in Narsoplimab Expanded Access Program” (submitted on March 26, 2025)
- **Interim Clinical Study Report for OMS721-TMA-001**, titled “A Phase 2, uncontrolled, three-stage, dose-escalation cohort study to evaluate the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and clinical activity of OMS721 in Adults with Thrombotic Microangiopathies” (submitted on November 17, 2020), along with:
 - **Clinical Protocol for OMS721-TMA-001** (Amendment 11.1, dated June 1, 2020, submitted on November 17, 2020)

2.2 CRITERIA APPLIED TO REVIEW

DEPI-I evaluated the requested study reports in accordance with the following FDA guidance documents:

- Draft Guidance for Industry: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. Feb 2023. Silver Spring (MD): Food and Drug Administration.
- Guidance for Industry: Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision Making for Drug and Biological Products. Aug 2023. Silver Spring (MD): Food and Drug Administration.
- Guidance for Industry: Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products. Dec 2023. Silver Spring (MD): Food and Drug Administration.
- Draft Guidance for Industry: Rare Diseases: Natural History Studies for Drug Development. March 2019. Silver Spring (MD): Food and Drug Administration.
- Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials. May 2001. Silver Spring (MD): Food and Drug Administration.
- Draft Guidance for Industry Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Dec 2019. Silver Spring (MD): Food and Drug Administration.
- Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence. Sep 2023. Silver Spring (MD): Food and Drug Administration.

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

Study OMS-TMA-ECC is a retrospective cohort study designed to provide confirmatory evidence of effectiveness by comparing OS of 28 high-risk TA-TMA patients from the single-arm pivotal trial OMS721-TMA-001 to a matched external control group of 108 high-risk patients from the Japanese KSCTG registry. Using a Cox proportional hazards (CPH) model with propensity score-based inverse probability of treatment weighting (IPTW) for confounding control and multiple imputation for immortal time bias adjustment, the results demonstrated a statistically significant 68% reduction in mortality risk (hazard ratio [HR]=0.32; 95% confidence interval [CI]: 0.23–0.44). The estimated 1-year survival rate following TA-TMA diagnosis was 41% (95%CI: 26%, 66%) for narsoplimab group compared to 14% (95%CI: 9%, 22%) for the KSCTG group. Appendix 7.1 summarizes the key aspects of the study design, statistical analysis, and major findings from this external control study.

The supplemental study included three OS comparative analyses using CPH model:

- **Analysis 1** compared OS in 49 adult, high-risk TA-TMA patients treated with narsoplimab through the Omeros-sponsored EAP to an external control group of 121 high-risk TA-TMA patients from the KSCTG registry, showing a 49% mortality reduction (HR=0.51; 95% CI: 0.37-0.71).
- **Analysis 2** compared all 77 narsoplimab-treated patients (28 from the single-arm trial OMS721-TMA-001 and 49 from the EAP) to the 121 KSCTG controls, demonstrating a 63% mortality reduction (HR=0.37; 95% CI: 0.28-0.48).
- **Analysis 3** was a sensitivity analysis based on all 77 narsoplimab-treated patients versus 121 KSCTG controls using an alternative propensity score modeling and weighting approach to test the robustness of Analysis 2 results, which showed a 58% mortality reduction (HR=0.42; 95% CI: 0.32-0.54).

All analyses employed consistent statistical methodologies for confounding control and immortal time bias adjustment. The results were supported by multiple sensitivity analyses, with E-values ranging from 4.2 to 7.6, indicating robust evidence for narsoplimab's survival benefit in high-risk TA-TMA patients.

3.2 STUDY OBJECTIVES

- **Study OMS-TMA-ECC:** to compare OS in patients with TA-TMA treated with narsoplimab in the pivotal trial OMS721-TMA-001 to a well-matched external control group.
- **Supplement study to OMS-TMA-ECC:** to compare OS of patients treated with narsoplimab in the EAP combined with patients in the pivotal trial OMS721-TMA-001 to OS in a well-matched external control group.

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

Both the primary OMS-TMA-ECC study and the supplement study are retrospective cohort studies.

3.3.1.2 Population Periods

The study population are high-risk TA-TMA adult patients.

Study OMS-TMA-ECC consisted of high-risk TA-TMA patients from two data sources: the OMS721-TMA-001 trial and KSCTG registry.

- (1) OMS721-TMA-001 (treatment group): Adult patients (≥ 18 years) who were enrolled in the TA-TMA cohort of the single-arm trial OMS721-TMA-001 between August 2015 and October 2019, all of whom had received at least 1 dose of narsoplimab and had multiple (2 or more) risk factors for poor outcome.
- (2) KSCTG registry (External Control Group): TA-TMA patients (≥ 16 years) identified by the KSCTG from the Japanese KSCTG registry who underwent HSCT between January 2000 and September 2016 and had ≥ 2 risk factors for poor outcome.

The supplemental study consisted of high-risk TA-TMA patients from three different data sources: the OMS721-TMA-001 trial, Omeros-sponsored EAP, and KSCTG registry.

(1) Treatment Group:

- Analysis 1: Adult (≥ 16 years) patients who received ≥ 1 dose of narsoplimab through Omeros-sponsored EAP, had ≥ 1 risk factor(s) for poor outcome, and had no prior TA-TMA treatment with eculizumab, ravulizumab, pegcetacoplan, or defibrotider.
- Analysis 2 and 3: Adult patients receiving narsoplimab from the single-arm trial OMS721-TMA-001 and the EAP.

(2) External Control Group:

- For all three analyses: TA-TMA patients (≥ 16 years) identified by the KSCTG from the KSCTG registry who underwent HSCT between January 2000 and September 2016 and had ≥ 1 risk factor(s) for poor outcome.

3.3.1.3 Data Source for External Control Group

The KSCTG registry contains stem cell transplant data from 17 institutions across Japan, including Kyoto University and affiliated hospitals. Data are obtained through the Japanese Transplant Registry Unified Management Program (TRUMP), a national registry sponsored by the Japanese Society for Transplantation and Cellular Therapy. Reporting of all stem cell transplantation procedures and associated information is mandatory across KSCTG sites, with standardized data collection undergoing rigorous quality control processes.⁶

To compile the KSCTG TA-TMA patient database, the investigators performed a retrospective chart review of registry patients to identify those with TA-TMA, document

⁶ Atsuta Y. Introduction of Transplant Registry Unified Management Program 2 (TRUMP2): scripts for TRUMP data analyses, part I (variables other than HLA-related data). International journal of hematology. 2016 Jan;103(1):3-10.

risk factors, evaluate therapeutic strategies, and determine outcomes. The final cohort included 2,425 allogeneic HSCT patients, of whom 134 were identified by their treating physicians in the TRUMP registry as having “TMA”. Of these, 121 patients met diagnostic criteria and were confirmed as having TA-TMA - all had at least one risk factors for poor outcomes (Appendix 7.2).⁷ Among the confirmed TA-TMA patients, 111 had at least two risk factors for poor outcomes and comprise the comparator control group for the external control study.

Omeros explained that KSCTG registry was selected as the fit-for-purpose external control data source because it uniquely combines several critical elements: standardized TA-TMA diagnostic criteria consistent with international consensus guidelines, comprehensive patient-level data with minimal missing information, and rigorous quality control processes that meet both FDA and EMA regulatory requirements for external control studies, including data accuracy, completeness, provenance, and traceability.

Unlike other major registries such as CIBMTR and EBMT, which lack mandatory or uniform TA-TMA data collection and rely on subjective physician diagnosis with varying criteria across institutions, KSCTG employed protocol-specified diagnostic criteria verified by HSCT experts and captured detailed risk factor information necessary for high-risk patient identification and propensity matching. The registry's mandatory reporting system covers >99% of Japanese transplantation centers and has been validated by international HSCT experts as highly reliable for TA-TMA research, while extensive evaluation of alternative data sources—including literature reviews, electronic health records, and other registries—revealed critical limitations in diagnostic consistency, data completeness, or regulatory compliance that rendered them unsuitable for supporting FDA approval.

3.3.1.4 Selection, Inclusion and Exclusion Criteria

(1) **Single-arm trial OMS721-TMA-001:**

Key inclusion criteria:

- Age $\geq$ 18 years at screening (visit 1)
- Signed information consent
- Had a diagnosis of TA-TMA in accordance with the diagnostic criteria described in Table 1.

Key Exclusion Criteria:

- Had eculizumab therapy within 3 months prior to screening;
- Have an active systemic bacterial or fungal infection requiring antimicrobial therapy;

⁷ Matsui H, Arai Y, Imoto H, Mitsuyoshi T, Tamura N, Kondo T, Kanda J, Ishikawa T, Imada K, Ueda Y, Toda Y. Risk factors and appropriate therapeutic strategies for thrombotic microangiopathy after allogeneic HSCT. *Blood Advances*. 2020 Jul 14;4(13):3169-79.

- Poor prognosis with a life expectancy less than 3 months;
- Abnormal cardiac, vascular, or liver function;
- Are pregnant or lactating
- Have received treatment with an investigational drug or device within 4 weeks prior to screening.
- Had missing data on survival (survival status or index date)

(2) KSCTG Registry:

Key inclusion criteria:

- Age $\geq$ 16 years with hematological diseases who received allogeneic HSCT between 1 January 2000 and 30 September 2016
- Met the prespecified criteria for TA-TMA diagnosis as determined by the KSCTG (Table 1)
- Had $\geq$ 2 risk factors for poor outcomes as defined by the international consensus criteria for high-risk TA-TMA⁹
 - Elevated LDH $\geq$ 2x ULN
 - Organ dysfunction (i.e., renal, pulmonary, gastrointestinal, and/or neurological dysfunction)
 - Acute GvHD grade II-IV
 - Systemic infection

Key Exclusion Criteria:

- Received double-unit cord blood transplantation (CBT) and unrelated peripheral blood stem cell transplantation (PBSCT)
- Patients who were followed for less than 30 days or for whom data on donor source, mismatch in HLA, GVHD prophylaxis, date of last follow-up, and number of HSCT were lacking
- Unavailable medical records
- Had any off-label potential therapeutic agent(s) drawn from eculizumab, ravulizumab, defibrotide, and pegcetacoplan
- Had missing data on survival (survival status or index date)

(3) EAP group:

Key inclusion criteria:

- TA-TMA patients $\geq$ 16 years in the narsoplimab EAP
- Had received at least one dose of narsoplimab
- Had $\geq$ 1 risk factor(s) for poor outcomes as defined by the international consensus criteria for high-risk TA-TMA
 - Elevated LDH $\geq$ 2x ULN
 - Organ dysfunction (i.e., renal, pulmonary, gastrointestinal, and/or neurological dysfunction)
 - Acute GvHD grade II-IV
 - Systemic infection

Key Exclusion Criteria:

- Had received, prior to treatment with narsoplimab, any off-label potential therapeutic agent(s) drawn from eculizumab, ravulizumab, defibrotide, and pegcetacoplan
- Had missing data on survival (survival status or index date)

Table 1. Diagnostic Criteria for TA-TMA - KSCTG Registry, Single-arm Trial OMS721-TMA-001, and the Published Consensus Panel

KSCTG Registry	Trial OMS721-TMA-001	Published Consensus ⁸
Presence of 2 of the following 5 diagnostic criteria: • Presence of erythrocyte fragmentation and schistocytes • Increased serum LDH levels above institutional baseline • <i>De novo</i> prolonged or progressive thrombocytopenia or anemia • Concurrent renal dysfunction and/or neurological dysfunction^a without other causes • Negative direct and indirect Coombs test results or a decrease in serum haptoglobin concentration^b	All of the following at least 2 weeks following modification or discontinuation of calcineurin inhibitor treatment or at least 30 days after the transplant: • Platelet count < 150,000/μL^c • Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > ULN, or haptoglobin < LLN) • Renal dysfunction (doubling of serum creatinine from pre-transplant)^d • Thrombocytopenia or anemia with no apparent alternative explanation	Presence of ≥ 4 of the following 7 criteria within 14 days at 2 consecutive time points: • Anemia • Thrombocytopenia • Elevated LDH (> ULN for age) • Schistocytes (present) • Hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) • Elevated sC5b-9 ($\geq$ ULN) • Proteinuria (≥ 1 mg/mg rUPCR)

^a OMS721-TMA-001 diagnostic criteria did not include neurological dysfunction while KSCTG did include it.

^b Negative direct and indirect Coombs test results were not part of the OMS721-TMA-001 diagnostic criteria; however, the study has an exclusion criterion of a positive direct Coombs test.

^c In the KSCTG study, thrombocytopenia was defined as platelet count <50,000/ μ L or a $\geq 50\%$ decrease from previous counts.

^d Six patients in OMS721-TMA-001 received a waiver for not meeting the inclusion criterion of renal dysfunction.

3.3.2 Exposure & Outcome

The exposure of interest was narsoplimab per protocol specifications: 4 mg/kg weekly in OMS721-TMA-001 trial and flexible dosing in the EAP.

The primary endpoint was overall survival (OS), measured in days from the index date to death or last known alive status.

⁸ Schoettler ML, Carreras E, Cho B, Dandoy CE, Ho VT, Jodele S, Moissev I, Sanchez-Ortega I, Srivastava A, Atsuta Y, Carpenter P. 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. *Transplantation and cellular therapy*. 2023 Mar 1;29(3):151-63.

The index date was defined as the first day of narsoplimab treatment for treated patients. For KSCTG control patients, the index date represented as “latent treatment day” calculated by adding a multiple imputed time interval to each patient's TA-TMA diagnosis date. These imputed intervals were sampled with replacement from the observed diagnosis-to-treatment intervals in the narsoplimab-treated cohorts, controlling for immortal time bias through 1,000 iterations of multiple imputation.

3.3.3 Covariates

The primary analyses included the following eight covariates which further were utilized in the propensity score model to control for potential confounding.

- Two demographic variables: age and sex
- Six risk factors for poor outcomes in TA-TMA, as defined by an international expert consensus panel:
 - 1) Acute graft-versus-host disease (GvHD) grade II-IV
 - 2) Systemic infection
 - 3) Neurological dysfunction
 - 4) Pulmonary dysfunction
 - 5) Renal dysfunction
 - 6) Elevated lactate dehydrogenase (LDH) ≥ 2 times the upper limit of normal

3.3.4 Sample Size/Power

The sample size analyzed for each study:

- The primary OMS-TMA-ECC study: 28 treated patients in OMS721-TMA-001 trial and 108 untreated patients in the KSCTG control group.
- Supplemental Analysis 1: 49 patients in the narsoplimab EAP group and 121 patients in the KSCTG control group.
- Supplemental Analyses 2 and 3: 77 patients in the combined narsoplimab group (28 from TMA-001 + 49 from EAP) and 121 patients in the KSCTG control group.

3.3.5 Statistical Analyses

The primary analyses for both OMS-TMA-ECC and its supplement studies utilized a Cox Proportional Hazard (CPH) model with propensity score-based IPTW to estimate HR and 95%CI for OS, comparing the narsoplimab group to the KSCTG control group. The propensity score model include eight key covariates (age, sex, acute GvHD grade II-IV, infection, neurological dysfunction, pulmonary dysfunction, renal dysfunction, and LDH ≥ 2 times ULN) for potential confounding control. A multiple imputation approach was employed to address immortal time bias by imputing the “latent treatment day” for the KSCTG control patients. Kaplan-Meier (KM) curve and the 100-day, 6-month, 1-year, and 2-year absolute survival differences were summarized for the primary analysis.

A set of 14 sensitivity analyses were performed to assess the robustness of the primary results, summarized as below:

- Alternative Statistical Approaches (1-3)
 - 1) CPH model with treatment exposure only (no covariates, no weighting)
 - 2) CPH model with treatment exposure only plus IPTW weighting
 - 3) Augmented inverse probability weighting (AIPW) in primary CPH model (not conducted due to methodological limitations)
- Propensity Score Method Validation (4-5)
 - 4) CPH model using propensity score stratification (quintiles)
 - 5) Propensity score matching (1:1 and 1:2) with CPH models run with and without covariates
- Immortal Time Bias Robustness (6, 10-11)
 - 6) Multiple imputation using shortest, median, and longest diagnosis-to-treatment intervals
 - 10) Model-based imputation using linear regression of baseline covariates predicting time delay
 - 11) CPH model within narsoplimab-treated patients testing if treatment delay affects survival
- Proportional Hazards Assumption Testing (7)
 - 7) Sequential CPH models truncating follow-up at 100 days, 6 months, 1 year, and 2 years
- Missing Data and Censoring Sensitivity (8-9)
 - 8) Binary analysis of OS, weighted by IPTW (patients with a last known status of alive were considered “survival”)
 - 9) Three analyses converting 10% of shortest-exposed censored patients to deaths (both groups, KSCTG only, narsoplimab-treated only)
- Clinical and Temporal Factors (12-14)
 - 12) Stratified analysis by early (<100 days) vs. late ($\geq$ 100 days) TMA diagnosis timing
 - 13) CPH model including baseline demographics and transplant characteristics without propensity weighting
 - 14) One-year survival estimates from transplant date and TMA diagnosis date

In addition, E-values were also calculated for the primary and sensitivity analyses to assess the robustness of the findings by quantifying the minimum strength of association an unmeasured confounder would need to have with both the treatment and the survival outcome to fully negate the observed survival benefit.

3.4 STUDY RESULTS

3.4.1 Results of Study OMS-TMS-ECC

3.4.1.1 Baseline Characteristics of the Study Patients

The final analysis set includes 28 TA-TMA patients in the OMS721-TMA-001 trial and 108 TA-TMA patients from the KSCTG registry.⁹ Overall, the narsoplimab group included more male (71% vs 59%) and relatively younger (median age 48 vs 52 years) patients than KSCTG control group (Appendix 7.3). The primary underlying disease for both cohorts was most commonly leukemia. Before propensity score weighting, the narsoplimab group appeared to be more severely ill, with a higher proportion of patients having risk factors such as Grade II-IV GvHD (68% vs. 58%), infection (86% vs. 74%), and elevated LDH $\geq 2x$ ULN (71% vs. 59%). The KSCTG group had a substantially higher rate of umbilical cord blood (UCB) transplants (42% vs. 7%) (Appendix 7.3). After applying the IPTW based on propensity scores, the covariate balance was significantly improved (Table 2).

Table 2. Summary of all covariates included in the propensity score model, weighted by IPTW¹⁰

	Unweighted		Weighted by IPTW	
	KSCTG n (%)	narsoplimab n (%)	KSCTG n (%)	narsoplimab n (%)
N	108	28	108	28
Age (mean, years)	49.7	48.0	49.31	47.39
GvHD	63 (58.3)	19 (67.9)	0.60	0.56
Infection	80 (74.1)	24 (85.7)	0.76	0.80
LDH $\geq 2*ULN$	64 (59.3)	20 (71.4)	0.62	0.65
Neurological Dysfunction	46 (42.6)	16 (57.1)	0.45	0.43
Pulmonary Dysfunction	19 (17.6)	5 (17.9)	0.18	0.17
Renal Dysfunction	83 (76.9)	21 (75.0)	0.77	0.83
Sex: Male	64 (59.3)	20 (71.4)	0.62	0.60

3.4.1.2 Key Efficacy Analysis Results

The primary efficacy analysis demonstrated a statistically significant and clinically meaningful survival benefit for narsoplimab: HR of 0.32 (95% CI: 0.23–0.44; $p < 0.00001$), indicating a 68% reduction in the risk of death for patients treated with

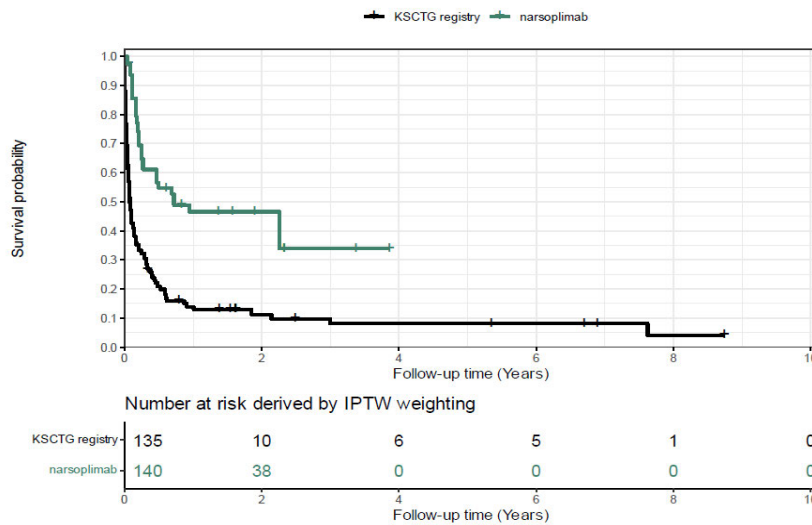
⁹ The analysis to control for immortal time bias required excluding control patients whose survival was shorter than the minimum time-to-treatment in the narsoplimab group (4 days). Therefore, 3 KSCTG patients who survived for less than this period were removed, reducing the control group to 108 patients.

¹⁰ Source: Table 3 (page 17), 3.1 (page 31), and B1 (page 55) in the OMS-TMA-ECC study report

narsoplimab compared to the external control group. E-value was 5.7, suggesting that a hypothetical unmeasured confounder would need to be very strongly associated with both treatment and survival -much more so than any known risk factor - to nullify the observed treatment effect.

The Kaplan-Meier (KM) curves for OS weighted by propensity score-based IPTW indicated that the narsoplimab group remained consistently above the curve for the KSCTG group throughout the follow-up period. The KSCTG curve showed a very steep initial drop, with survival probability falling below 20% within the first year, visually representing the poor prognosis and high early mortality in this untreated high-risk population (Figure 1).

Figure 1. Study OMS-TMA-ECC: Kaplan-Meier Curve for Overall Survival from Date of First Treatment, Weighted by IPTW*



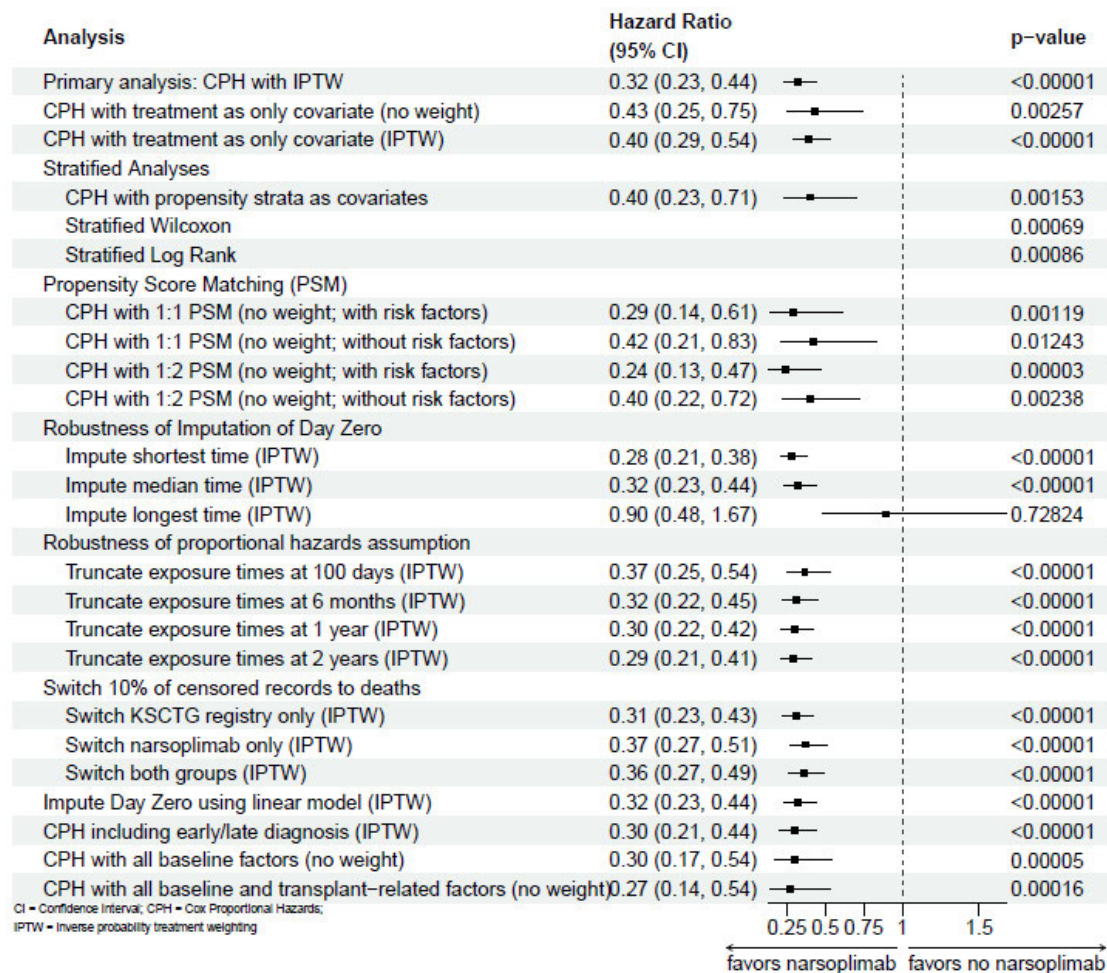
* The survival times for KSCTG registry patients are represented as the average time over 1000 imputed observations.

The estimated OS rate following 1 year from TA-TMA diagnosis was 41% (95%CI: 26%, 66%) for the narsoplimab group compared to 14% (95%CI: 9%, 22%) for the KSCTG group.

3.4.1.3 Sensitivity Analyses Results

Figure 2 summarized the results of different sensitivity analyses in a forest plot. Overall, these analyses appeared to be consistent with primary analysis, with most producing HRs between 0.24 and 0.43 and all remaining highly statistically significant. In addition, the binary survival analysis weighted by IPTW showed an overall survival rate of 43.5% in the narsoplimab group compared to 9.9% in the KSCTG group, with a difference in survival rate of 33.6% (95%CI: 16.9%, 51.4%).

Figure 2. Forest Plot for the Estimated Hazard Ratios and 95% CIs from the Primary and Sensitivity Analyses



3.4.2 Results of the Supplement Study

3.4.2.1 Baseline Characteristics of the Study Patients

The final analysis sets included 121 high-risk TA-TMA patients in KSCTG control group for all three analyses; for narsoplimab group, Analysis 1 included 49 high-risk TA-TMA patients from the EAP, and both Analyses 2 and 3 included 77 high-risk TA-TMA patients pooled from OMS721-TMA-001 trial and the EAP.

Significant baseline imbalances were observed between the narsoplimab group and KSCTG controls: the EAP patients were notably younger than the KSCTG controls (mean age 39.3 vs. 49.3 years) and had substantially lower rates of systemic infection (33% vs. 72%), renal dysfunction (61% vs. 74%), and neurological dysfunction (22% vs. 40%). When the EAP and the single-arm trial patients were combined, this pooled group also remained younger and had lower rates of infection and renal dysfunction compared

to the KSCTG controls (Appendix 7.4). These baseline differences appeared to be balanced after the application of IPTW based on propensity scores (Appendix 7.5).

3.4.2.2 Primary Analyses and Sensitivity Analyses

The three supplemental analyses consistently demonstrated a significant and robust survival benefit for narsoplimab-treated patients compared to the KSCTG external control group. The primary CPH model for Analysis 1 (EAP vs. KSCTG) yielded a hazard ratio (HR) of 0.51 (95% CI: 0.37–0.71). The Kaplan-Meier Curve for OS comparing EAP to the KSCTG group consistently showed a survival advantage for narsoplimab treatment (Figure 3).

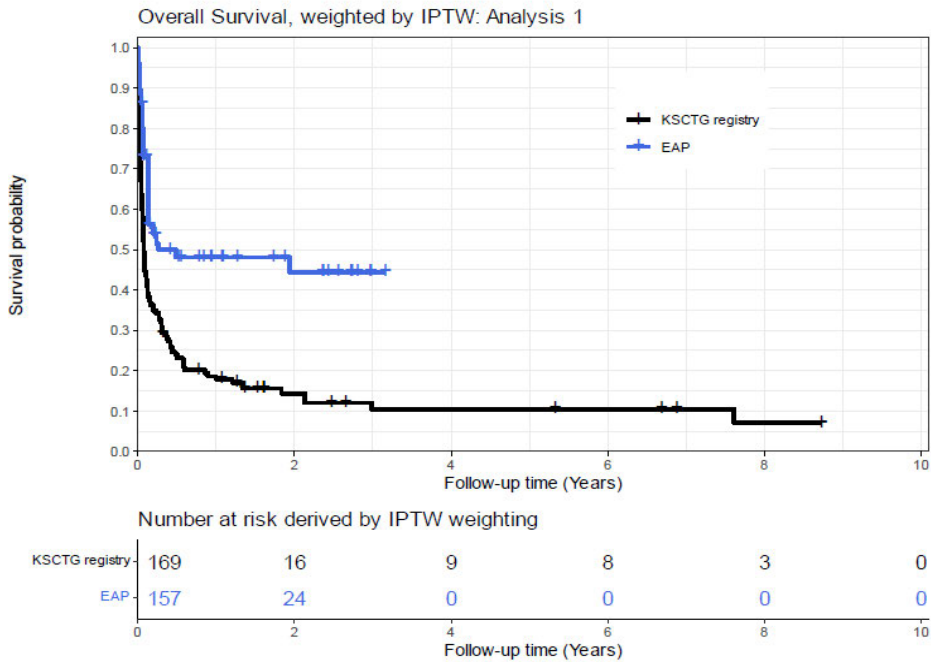
The pooled population in Analysis 2 (Combined vs. KSCTG) showed an HR of 0.37 (95% CI: 0.28–0.48), while the weighted pooled population in Analysis 3 resulted in an HR of 0.42 (95% CI: 0.32–0.54). All primary analyses were statistically significant ($p \leq 0.00005$), with corresponding E-values of 3.3, 4.9, and 4.2, respectively (Table 3). Across the three analyses, the measured baseline covariates have estimated hazard ratios all less than 2.96, suggesting the results are unlikely to be explained away by unmeasured confounding.

Additionally, these findings were consistently supported by the corresponding sensitivity analyses that showed a positive treatment effect across all scenarios (Appendix 7.6).

Table 3. Hazard Ratio Estimates from OMS-TMA-ECC and Supplemental studies (Primary Analysis)

	OMS-TMA-ECC	Supplement Study		
		Analysis 1	Analysis 2	Analysis 3
Comparison	OMS-TMA-001 vs KSCTG (28 vs 108)	EAP vs KSCTG (49 vs 121)	Trial+EAP Combined vs KSCTG (77 vs 121)	Combined-weighted vs KSCTG (77 vs 121)
HR (95% CI)	0.32 (0.23-0.44)	0.51 (0.37-0.71)	0.37 (0.28-0.48)	0.42 (0.32-0.54)
p-value	<0.00001	0.00005	<0.00001	<0.00001
E-value	5.7	3.3	4.9	4.2

Figure 3. Supplemental Analysis I: Kaplan-Meier Curve for Overall Survival from Date of First Treatment, Weighted by IPTW*



* The survival times for KSCTG registry patients are represented as the average time over 1000 imputed observations.

3.5 STUDY CONCLUSIONS

Based on the two reports from study OMS-TMA-ECC and its supplement analyses, Omeros concluded that the primary external control study provides clear and robust evidence that narsoplimab significantly improves overall survival in patients with high-risk TA-TMA. This finding was consistently confirmed by the supplemental analyses, which incorporated real-world data from the EAP. Collectively, all of these analyses, together with the corresponding sensitivity analyses, present convincing evidence of superior survival of narsoplimab in the treatment of TA-TMA.

3.6 OMEROS'S RESPONSES TO FDA'S IRS POST-RESUBMISSION



4 DISCUSSION

The applicant has submitted external control study OMS-TMA-ECC and its supplement to provide confirmatory evidence for the efficacy of narsoplimab in treating TA-TMA. These analyses compare OS in narsoplimab-treated patients from a pivotal single-arm trial (OMS721-TMA-001) or/and an EAP against a historical control cohort from the Japanese KSCTG registry. The results demonstrated statistically significant 68% reduction in mortality risk (HR=0.32; 95% CI: 0.23–0.44) comparing the single-arm, OMS721-TMA-001 trial patients to KSCTG controls, and a significant 49% mortality reduction (HR=0.51; 95% CI: 0.37-0.71) comparing real-world narsoplimab-treated patients in the EAP program to KSCTG controls.

4.1 STUDY STRENGTHS

In the context of a rare and severe disease like TA-TMA, where RCT is not feasible or is challenging to conduct, a non-randomized, externally controlled study design may be a reasonable approach. The submitted external control studies demonstrate several notable strengths.

From a methodological perspective, the major strength is the employment of advanced statistical methods to mitigate potential biases. These include the use of IPTW based on propensity scores to address confounding and a multiple imputation strategy to account

for immortal time bias, a critical step for ensuring the validity of comparisons in this context. Additionally, the robustness of the findings was extensively tested through a wide range of pre-specified sensitivity analyses, which consistently supported the primary analysis results.

From a real-world data fitness perspective, the selected KSCTG registry serves as a reasonably appropriate external control despite some limitations. The registry demonstrates data relevance through its use of standardized TA-TMA diagnostic criteria consistent with international consensus guidelines and the availability of comprehensive patient-level data. Data reliability is ensured by rigorous quality control processes that maintain data accuracy, completeness, and traceability.

4.2 STUDY LIMITATIONS

Despite the noted strengths, our assessment has identified significant limitations that compromise both the internal and external validity of these studies. The primary concerns relate to a fundamental lack of patient comparability, unmeasured confounding and selection bias, and additional methodological issues that undermine the reliability of the findings.

Lack of Patient Comparability

One of the major concerns for the external control study is the lack of comparability between the single-arm trial and external control populations, which introduces confounding, selection, and survival bias that may compromise the internal validity of the results.

- **Temporal and Geographic Disparities:** A significant temporal gap exists between the treatment and external control groups, with the KSCTG control data spanning 2000–2016 while the narsoplimab-treated patients were enrolled from 2015 onward (Appendix 7.9). This temporal disparity is clinically significant because transplant outcomes have improved substantially over this period due to advances in supportive care and infection management. This secular trend is evident within the applicant’s external control data, which demonstrated that the proportion of patients surviving beyond one year increased from 15% (7/48) of KSCTG registry patients in the 2000–2009 period to 25% (18/73) in the 2010–2016 period. This temporal improvement represents a major uncontrolled confounder that biases the results in favor of the narsoplimab group.
 - The Applicant provided the results of temporal analyses in response to FDA’s IR dated August 8, 2025 (Appendix 7.8). However, the temporal bias concern was not adequately addressed. The fundamental data source limitations remain that the registry only extend to 2016, creating a 3-7 year gap relative to the pivotal trial period (2015-2019) and the EAP study period (2015-2023).

Geographic differences further challenge comparability, as the control group is exclusively Japanese, while the treated population in both OMS-721-001 and the EAP represents a global cohort with no patients from Japan (Appendix 7.9).

- **Selection Bias and Survival Bias:** The single-arm trial’s eligibility criteria created a left-truncation effect by requiring patients to survive at least 21-30 days post-transplant to meet diagnostic criteria. This requirement introduced survival bias by systematically excluding patients with early-onset, rapidly progressive disease who would typically be included in a real-world registry.

Furthermore, the trial-excluded patients with a life expectancy of less than three months or with certain cardiovascular or hepatic dysfunctions, thereby selecting for a healthier patient population compared to the unselected registry cohort. These selection criteria collectively bias the effect estimate away from the null and in favor of the narsoplimab group.

Substantial Unmeasured and Residual Confounding

The applicant utilized a propensity score model to account for potential confounding. However, several important prognostic factors that showed baseline imbalance between the narsoplimab-treated patients and KSCTG controls were excluded from the model. This exclusion led to significant unmeasured confounding that was likely to bias the results in favor of narsoplimab.

- **HLA Mismatch:** The proportion of HLA mismatched patients was substantially higher in the KSCTG registry (77%, 93/121) as compared to the trial patients (29%, 8/28) (Appendix 7.3). Our analysis of the KSCTG data revealed that a much lower proportion of HLA-mismatched patients survived beyond one year (17%, 16/93) compared to matched patients (32%, 9/28).
- **Time from Transplant to TMA Diagnosis:** Earlier onset of TMA, which is associated with worse prognosis,¹¹ was more prevalent in the KSCTG registry (Appendix 7.10). The trial excluded patients who developed TMA within three weeks following HSCT, while the KSCTG registry include such patients. In the KSCTG registry, 26% (32/121) of patients experienced TMA onset within three weeks of transplantation, with only 6% (2/32) surviving beyond one year. This contrasts with 26% (23/89) among patients with TMA onset occurring more than three weeks post-transplantation. Similarly, in the EAP, 20% (1/5) of patients diagnosed within three weeks survived beyond one year, compared to 68% (28/41) diagnosed later (Appendix 7.10).

¹¹ Van Benschoten V, Roy C, Gupta R, Ouellette L, Hingorani S, Li A. Incidence and risk factors of transplantation-associated thrombotic microangiopathy: a systematic review and meta-analysis. *Transplantation and Cellular Therapy*. 2022 May 1;28(5):266-e1

- **Stem Cell Source:** The use of umbilical cord blood (UCB), which is associated with poorer outcomes,^{12,13} was far more common in the KSCTG registry (39%, 47/121) than in the narsoplimab groups (2-7%. Appendix 7.4).
- **Performance Status:** In the KSCTG registry, 24% (29/121) of patients had a poor performance score (≥ 2). and none (0%) survived beyond one year, compared to 29% (25/85) of patients with better performance status who survived beyond one year.
 - The applicant partially addressed FDA’s comments regarding covariate adjustments in their responses to FDA’s IR dated August 8, 2025. However, the exclusion of key covariates such as performance status, calendar year, and HLA mismatch represented a significant limitation and created risk of residual confounding (Appendix 7.8). Further, combined with the observed poor propensity score overlaps between comparison groups (Appendix 7.11), the incomplete covariate adjustment undermines the reliability of the analysis results in the external control studies.

Additional Methodological and Analytical Concerns

Several technical aspects of the analysis further impact the study’s validity and may introduce additional uncertainty.

- **Multiple Imputation of Index Date:** The study applied simple random sampling approach to impute the index date for KSCTG patients based on the distribution of time interval between HSCT and TMA onset in narsoplimab-treated patients. This indeed assumes that the “latent treatment day” for KSCTG registry patients are “missing” completely at random. This assumption is unlikely to hold given the systematic differences in disease severity, clinical presentation, and healthcare settings between the trial, the EAP, and the registry, where differences in disease severity, patient demographics, healthcare access, clinical presentation may impact treatment timing.
 - In the Applicant’s responses to FDA’s IR dated August 8, 2025, the primary analysis was rerun with multiple imputation based on patients within same propensity scores strata, resulting in a significant treatment effect (HR=0.25, 95%CI: 0.18, 0.36) comparing OS between OMS721-TMA-001 patients to KSCTG registry patients.
- **Propensity Score Methodology:** In the original submission, the applicant failed to provide adequate documentation of the propensity score model diagnostics,

¹² Lim YJ, Arbiv OA, Kalbfleisch ME, Klaassen RJ, Fernandez C, Rayar M, Steele M, Lipton JH, Cuvelier G, Pastore YD, Silva M. Poor outcome after hematopoietic stem cell transplantation of patients with unclassified inherited bone marrow failure syndromes. *European Journal of Haematology*. 2022 Apr;108(4):278-87.

¹³ Lim YJ, Arbiv OA, Kalbfleisch ME, Klaassen RJ, Fernandez C, Rayar M, Steele M, Lipton JH, Cuvelier G, Pastore YD, Silva M. Poor outcome after hematopoietic stem cell transplantation of patients with unclassified inherited bone marrow failure syndromes. *European Journal of Haematology*. 2022 Apr;108(4):278-87.

including assessments of model fit, weight distributions, and covariate overlap. The effectiveness of weight truncation in such a small sample size is also uncertain.

- In responses to FDA’s IR dated August 8, 2025, the Applicant provided propensity score distributions by comparison groups for the primary analysis, Analysis 1, and Analysis 2 (Appendix 7.11). However, the histograms demonstrated poor overlap between both the trial and EAP groups compared to KSCTG controls, indicating fundamentally different baseline characteristics between the treatment and control populations. This poor overlap may result in unstable weights, unreliable effect estimates, and limited generalizability. The results should be interpreted with caution given the poor overlap, as these estimates may not reflect true treatment effects in a more balanced population (Appendix 7.8).
- **Integration of Heterogeneous Treatment Data:** Analysis 2 and 3 of the supplemental study integrated narsoplimab treatment data from all 28 patients in the pivotal trial and all 49 patients in the EAP. However, pooling data from these significantly different sources - a clinical trial versus a real-world setting - without first evaluating for heterogeneity is methodologically inappropriate. This approach risks obscuring the distinct characteristics and outcomes of each patient population.
 - In responses to FDA’s IR dated August 8, 2025, the Applicant explained that Analysis 3 was designed to address the concern of data heterogeneity. The Applicant’s method involved calculating propensity of being in the pivotal trial and weighting EAP patients accordingly. However, this analysis contains a fundamental methodological flaw: it estimates the propensity of being in the trial cohort rather than the propensity of receiving treatment. Consequently, the IPTW approach is invalid, as such weights fail to balance covariates between treated and untreated populations.

External Validity and Generalizability

The external validity of these findings is questionable. Due to the fundamental differences in patient characteristics, donor types (e.g., UCB), and treatment practices between the Japan-only KSCTG registry and the intended global, primarily U.S., patient population, it is uncertain whether the results from this external control study are generalizable.

5 CONCLUSION

The external control study and its supplement demonstrated a statistically significant 68% reduction in mortality risk (HR=0.32; 95% CI: 0.23–0.44) when comparing single-arm OMS721-TMA-001 trial patients to Japanese KSCTG controls, and a significant 49% mortality reduction (HR=0.51; 95% CI: 0.37-0.71) when comparing real-world narsoplimab-treated patients in the EAP to KSCTG controls.

However, the study presents significant methodological limitations that compromise both the internal and external validity of the findings. Major concerns include a lack of comparability between the treatment and control cohorts due to temporal disparities, geographic differences, and differing selection criteria, which introduce a high potential for confounding and selection bias that could systematically favor the narsoplimab arm. Furthermore, the analyses did not adjust for several key prognostic factors and potential confounders - including patient performance status, HLA mismatch, stem cell source, and calendar year of transplant - suggesting the treatment effect estimates are likely overestimated. Finally, the poor overlap in propensity score distributions indicates that the cohorts had fundamentally different baseline characteristics, which can lead to unstable effect estimates and limits the generalizability of the findings.

Given these limitations, the submitted studies do not meet the rigorous methodological standards required for robust RWE, and their utility for informing regulatory decision-making is limited.

6 RECOMMENDATIONS

6.1 RECOMMENDATIONS TO DNH

The findings from the external control study and its supplement should be interpreted with considerable caution, as the magnitude of treatment effect is likely overestimated due to systematic biases and unmeasured confounding in the non-randomized study design. In the context of a rare disease with a high unmet medical need, DEPI-I defers to the clinical review team to determine the utility of this evidence, weighing the identified methodological limitations against the overall benefit-risk profile and other data submitted in the application as part of the totality of evidence.

6.2 RECOMMENDATIONS TO APPLICANT

DEPI-I recommended IRs for the Applicant, which are summarized in Appendix 7.8. These IRs were sent on August 8, 2025, and the Applicant provided responses on August 22, 2025. Upon review of these responses, DEPI-I has no additional recommendations for the Applicant at this time.

7 APPENDICES

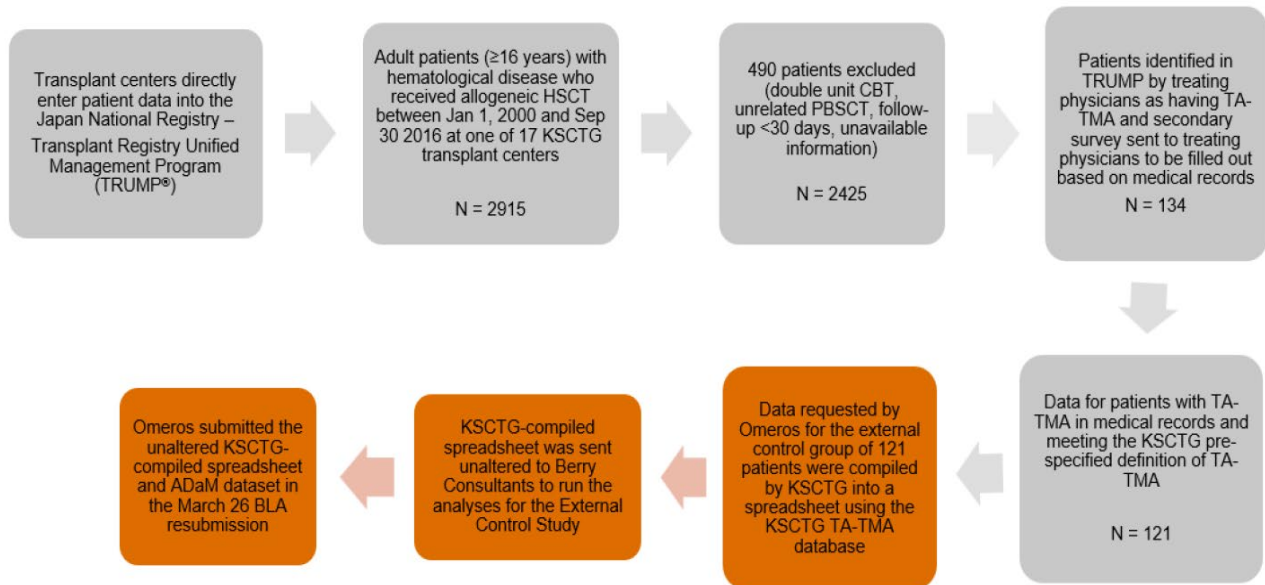
7.1 STUDY SYNOPSIS FOR EXTERNAL CONTROL STUDY OMS-TMA-ECC

Product, therapeutic area, indication	• BLA 761152/Narsoplimab (resubmission) • Treatment of hematopoietic stem cell transplant associated thrombotic microangiopathy (TA-TMA)	
Regulatory purpose	RWE was submitted as part of BLA 761152 to serve as confirmatory evidence of effectiveness for a new indication approval. • The regulatory purpose was to demonstrate the effectiveness of narsoplimab for the proposed indication by leveraging comparisons between single-arm phase 2 trial data, incorporating narsoplimab EAP data, against an external RWD control derived from the KSCTG registry. • This approach allowed the applicant to provide additional supportive evidence for effectiveness in the absence of a traditional randomized controlled trial design.	
Existing evidence from other sources	The original BLA 761152 (submitted on 11/17/2020) included a phase 2, single-arm open-label pivotal trial OMS721-TMA-001 (n=28) supporting the application, with primary endpoint, response rate 61% (17/28, 95% CI, 41% to 79%), whereas FDA reviewer's analysis of response rate 43% (95%CI 24% to 63%). FDA issued CRL on 10/15/2021 stating that the applicant failed to establish substantial evidence of effectiveness.	
Regulatory need and gap	• Efficacy claim	
Study objective	To compare OS in patients with TA-TMA treated with narsoplimab in the pivotal trial OMS721-TMA-001 to a well-matched external control group.	
Study design	Single Arm Trial (OMS721-TMA-001)	External RWD Control (KSCTG Registry)
Studied period	Aug 2015 – Oct 2019	1/1/2000 to 9/30/2016
Type of design	Prospective, phase 2, single-arm, open-label trial	Retrospective cohort study
Data source(s)	OMS721-TMA-001 clinical trial database	Multi-center Japanese transplant registry (KSCTG)
Study population	Adult (≥ 18 years) TA-TMA patients who were enrolled in trial OMS721-TMA-001, all of whom had received at least 1 dose of narsoplimab and had multiple (2 or more) risk factors for poor outcomes. Key Inclusion Criteria • HSCT-TMA persisted at least 2 weeks following modification <u>or</u> discontinuation of calcineurin inhibitor treatment <u>or</u> at least 30 days after transplant with: – Platelet count $< 150,000/\mu\text{L}$ – Evidence of microangiopathic hemolysis (presence of	Adult (≥ 16 years) patients identified by the KSCTG from the KSCTG registry who had met the prespecified criteria for TA-TMA diagnosis and had at least 2 risk factors for poor outcomes. Key Inclusion Criteria: • Age ≥ 16 years with hematological diseases who received allogenic-HSCT between 1 January 2000 and 30 September 2016 • Met the prespecified criteria for TA-TMA diagnosis as determined by the KSCTG • Had ≥ 2 risk factors for poor outcomes as defined by the international consensus criteria for high-risk TA-TMA ▪ Elevated LDH $\geq 2x$ ULN

Study design	Single Arm Trial (OMS721-TMA-001)	External RWD Control (KSCTG Registry)
	schistocytes, serum lactate dehydrogenase [LDH] > upper limit of normal [ULN], <u>or</u> haptoglobin < lower limit of normal [LLN]) - Renal dysfunction (doubling of serum creatinine from pre-transplant) Key Exclusion Criteria • Had Shiga toxin-producing Escherichia coli-induced hemolytic uremic syndrome (HUS) • Had a positive direct Coombs test • Had an active systemic bacterial or fungal infection requiring antimicrobial therapy • Had malignant hypertension	▪ Organ dysfunction (i.e., renal, pulmonary, gastrointestinal, and/or neurological dysfunction) ▪ Acute GvHD grade II-IV ▪ Systemic infection Key Exclusion Criteria: • Received CBT and unrelated PBSCT • Follow-up time less than 30 days • Data on donor source, mismatch in HLA, GVHD prophylaxis, date of last follow-up, and number of HSCT were lacking • Unavailable medical records • Had any off-label potential therapeutic agent(s) drawn from eculizumab, ravulizumab, defibrotide, and pegcetacoplan • Had missing data on survival (survival status or index date)
Exposure/ Comparator definition	Narsoplimab, administered as a weekly intravenous infusion at a dose of 4 mg/kg or 370 mg for 4 to 8 weeks.	No narsoplimab
Outcome definition, ascertainment, and validation	OS, defined as the time from index date to death or right-censoring at last known date alive.	
Key covariates	8 measured covariates: 1) Age (0, 1) where 1 indicates a patient is 50 or older 2) Sex (0, 1) where 1 indicates a patient is male 3) GVHD (0, 1) where 1 indicates the presence of acute GVHD Grade 2-4 4) Infection (0, 1) where 1 indicates the presence of infection 5) Neurological dysfunction (0, 1) where 1 indicates the presence of neurological dysfunction 6) Pulmonary dysfunction (0, 1) where 1 indicates the presence of pulmonary dysfunction 7) Renal dysfunction (0, 1) where 1 indicates the presence of renal dysfunction 8) LDH $\geq$ 2 times ULN (0, 1) where 1 indicates that LDH is $\geq$ 2 times ULN	
Index date	First day of narsoplimab treatment	Imputed "latent treatment day (when a given patient would have received treatment)" to match narsoplimab group's diagnosis-to-treatment delay. • TMA diagnosis date plus an interval that was multiple imputed by sampling with replacement from the 28 patients' intervals between TMA diagnosis and index date observed in the OMS721-TMA-001 trial.
Start and End of Follow-up	From index date to death or last known date alive.	

Study design	Single Arm Trial (OMS721-TMA-001)	External RWD Control (KSCTG Registry)
Statistical methods	Primary Analysis: • Cox Proportional Hazard model with propensity score-based IPTW to estimate HR and 95%CI for OS, comparing the narsoplimab group to the KSCTG control group. ▪ The propensity score model include eight key covariates (age, sex, acute GvHD grade II-IV, infection, neurological dysfunction, pulmonary dysfunction, renal dysfunction, and LDH $\geq$ 2 times ULN) for potential confounding control. ▪ A multiple imputation approach was employed to address immortal time bias by imputing the “latent treatment day” for the KSCTG control patients. ▪ Kaplan-Meier (KM) plot of OS and the 100-day, 6-month, 1-year, and 2-year absolute survival differences were summarized for the primary analysis. Sensitivity Analyses: testing the robust of primary analysis results • Alternative confounding control or propensity score approaches (matching, stratification) • Robustness of index date imputation • Robustness of CPH model assumption • Switch 10% censored records to death • Binary analysis of OS	
Sample size analyzed	28	108 (of 121 patients meeting TA-TMA criteria, 111 had $\geq$ 2 risk factors, excluding 3 for immortal time bias adjustment (latent treatment date <4 days).
Methods to handle confounding, if applicable	• IPTW using propensity scores based on 8 covariates in primary analysis • Sensitivity Analyses with alternative methods including propensity score matching, stratification, multivariate model • E-value assessment of unmeasured confounding	
Methods to handle immortal time bias	Multiple imputation (1000x) of a "latent treatment day" for KSCTG patients by sampling from the 28 observed diagnosis-to-treatment intervals in TMA-001. Multiple imputation (1000x) of a "latent treatment day" for KSCTG patients by sampling from the 28 observed diagnosis-to-treatment intervals in TMA-001.	
Methods to handle missing data, if applicable	• Patients with missing survival data excluded. (0 for both groups) • Sensitivity analyses assuming 10% of the shortest exposed patients right-censored in each or both groups are considered to have an event at the time of right-censoring.	
Key Results	<u>Primary Efficacy Results:</u> • HR 0.32 (95% CI: 0.23–0.44), p-value: < 0.00001 • OS rate after 1 year following TA-TMA diagnosis was 41% (95%CI: 26%, 66%) for the narsoplimab group vs. 14% (95%CI: 9%, 22%) for the KSCTG group. <u>Sensitivity Analysis Results:</u> • HRs between 0.24 and 0.43 and all remaining statistically significant. • The binary survival analysis weighted by IPTW showed an overall survival rate of 43.5% in the narsoplimab patients vs 9.9% in the KSCTG patients, with a difference of 33.6% I(95%CI: 16.9%, 51.4%).	

7.2 DATA FLOW FOR EXTERNAL CONTROL PATIENTS FROM THE SOURCE DATA, TRUMP REGISTRY¹⁴



¹⁴ Source: Figure 1 on page 4 in Omeros’s Response to FDA Information Request Dated April 28, 2025 (Submitted to FDA on May 20, 2025)

7.3 BASELINE CHARACTERISTICS OF THE TA-TMA PATIENTS INCLUDED IN STUDY OMS-TMA-ECC ¹⁵

	KSCTG Control n (%)	OMS721-TMA-001 n (%)
N	108	28
Age (yr)		
Mean (SD)	49.7 (13.6)	48.0 (13.3)
Median (Min, Max)	52 (17, 74)	48 (22, 68)
Sex		
Male	64 (59.3)	20 (71.4)
Female	44 (40.7)	8 (28.6)
Risk Factors for Poor Outcome		
Elevated LDH $\geq$ 2x ULN	64 (59.3)	20 (71.4)
Acute Grade II-IV GvHD	63 (58.3)	19 (67.9)
Organ dysfunction		
Neurological dysfunction	46 (42.6)	16 (57.1)
Pulmonary dysfunction	19 (17.6)	5 (17.9)
Renal dysfunction	83 (76.9)	21 (75.0)
Infection	80 (74.1)	24 (85.7)
Time from HSCT to TMA Diagnosis (days)		
Mean (SD)	52.9 (59.1)	121 (108.8)
Median (Min, Max)	37 (3, 410)	73.5 (21, 436)
HLA Mismatched Donor¹⁶		
Yes	87 (80.6)	8 (28.6)
No	21 (19.4)	20 (71.4)
Related Donor		
Yes	26 (24.1)	12 (42.9)
No	82 (75.9)	16 (57.1)
Cell Source		
Related bone marrow	10 (9.3)	2 (7.1)
Unrelated bone marrow	37 (34.3)	4 (14.3)
Related peripheral blood stem cells	16 (14.8)	10 (35.7)
Unrelated peripheral blood stem cells	0 (0.0)	10 (35.7)
Umbilical cord blood	45 (41.7)	2 (7.1)
Conditioning Regimen		
Reduced Intensity Conditioning	51 (47.2)	15 (53.5)
Myeloablative Conditioning	57 (52.8)	13 (46.4)
Primary Disease Category		
Leukemia	62 (57.4)	18 (64.3)
Mature lymphoproliferative disorder	31 (29)	6 (21)
Myelodysplastic syndrome and myelofibrosis/other MPD	14 (13)	4 (14)

¹⁵ Source: Table 2-5 in OMS-TMA-ECC study report (Pages 17-19)

¹⁶ According to the Applicant's IR responses received on 10/7/2025 (SN 0104), there was a data entry error in Table 4 of the OMS-TMA-ECC study report. The verified proportion of HLA-mismatched patients in the OMS721-TMA-001 trial is 8/28 (28.6%).

7.4 BASELINE CHARACTERISTICS OF THE TA-TMA PATIENTS INCLUDED IN THE SUPPLEMENTAL ANALYSES¹⁷

	KSCTG n (%)	OMS721-TMA-001 n (%)	EAP n (%)	EAP + OMS721- TMA-001 n (%)
N	121	28	49	77
Age (yr)				
Mean (SD)	49.3 (13.99)	48.0 (13.32)	39.3 (23.84)	42.5 (20.96)
Median (IQR)	52 (40, 61)	48 (36.5, 58.0)	39.3 (16.8, 63.1)	47.2 (23, 61.6)
Min, max	17, 74	22, 68	16, 71.7	16, 71.7
Sex, n (%)				
Male	73 (60.3)	20 (71.4)	25 (51.0)	43 (55.8)
Female	48 (39.7)	8 (28.6)	24 (49.0)	34 (44.2)
Risk Factor for Poor Outcomes				
Elevated LDH $\geq$ 2x ULN	66 (54.5)	20 (71.4)	29 (59.2)	49 (63.6)
Grade II-IV GvHD	65 (53.7)	19 (67.9)	25 (51.0)	44 (57.1)
Neurological dysfunction	48 (39.7)	16 (57.1)	11 (22.4)	27 (35.1)
Pulmonary dysfunction	20 (16.5)	5 (17.9)	8 (16.3)	13 (16.9)
Renal dysfunction	90 (74.4)	21 (75.0)	30 (61.2)	51 (66.2)
Infection	87 (71.9)	24 (85.7)	16 (32.7)	40 (51.9)
Time from HSCT to TMA Diagnosis (days)*				
Mean (SD)	51.5 (58.67)	145.4 (108.43)	157.8 (174.29)	143.9 (153.80)
Median	35	119	94.5	85
Min, Max	3, 410	33, 444	0, 1042	0, 1042
Related Donor, n (%)				
Yes	33 (27.3)	12 (42.9)	17 (34.7)	29 (37.7)
No	88 (72.7)	16 (57.1)	16 (32.7)	32 (41.6)
Unknown	0	0	16 (32.7)	16 (20.8)
Cell Source, n (%)				
Related bone marrow	12 (9.9)	2 (7.1)	2 (4.1)	4 (5.2)
Unrelated bone marrow	41 (33.9)	4 (14.3)	0	4 (5.2)
Related peripheral blood stem cells	21 (17.4)	10 (35.7)	14 (28.6)	24 (31.2)
Unrelated peripheral blood stem cells	0 (0.0)	10 (35.7)	16 (32.7)	26 (33.8)
Umbilical cord blood	47 (38.8)	2 (7.1)	1 (2.0)	3 (3.9)
Unknown	0	0	16 (32.7)	16 (20.8)
HSCT Conditioning Regimen, n (%)				
Reduced intensity conditioning	59 (48.8)	15 (53.5)	16 (32.7)	28 (36.4)
Myeloablative conditioning	62 (51.2)	13 (46.4)	24 (49.0)	40 (51.9)
Unknown	0	0	9 (18.4)	9 (11.7)

* Date of HSCT is missing for 3 patients in the EAP patient dataset

¹⁷ Source: Table 2-4 in the Supplement Report (page 16-17)

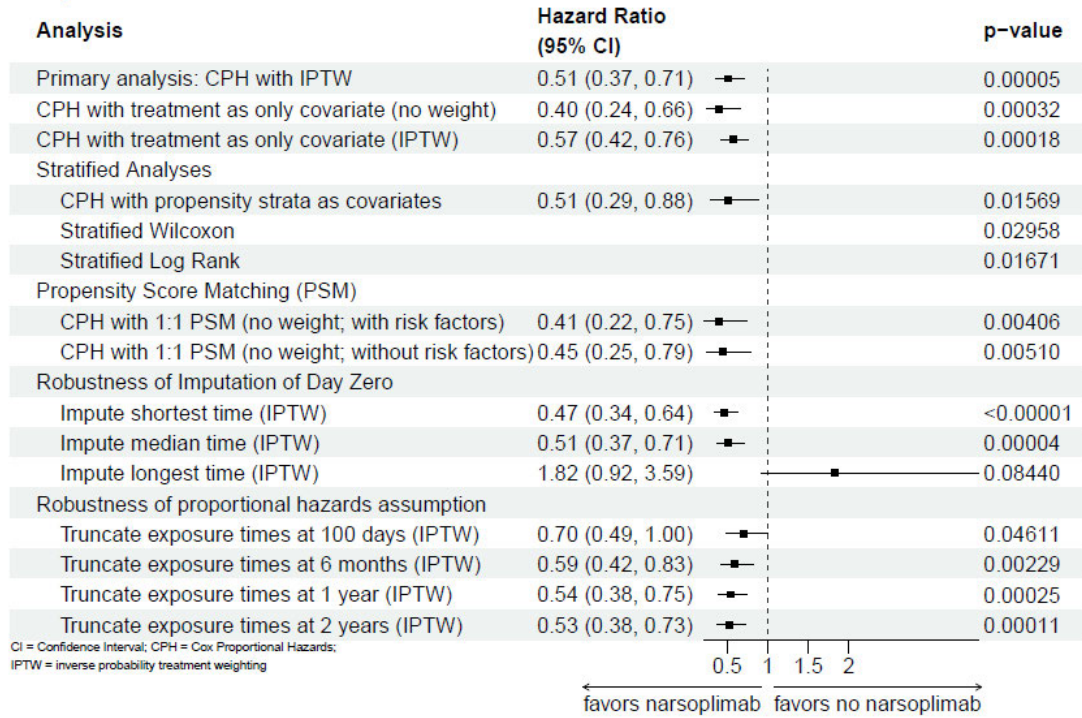
7.5 SUMMARY OF ALL COVARIATES INCLUDED IN THE PROPENSITY SCORE MODEL, WEIGHTED BY IPTW, FOR PATIENTS IN EACH OF SUPPLEMENTAL ANALYSIS POPULATION

	KSCTG registry (N = 121)	EAP (N = 49)	EAP + OMS721-TMA-001 (N = 77)
Analysis 1*			
Age	48.29	46.68	
GvHD	0.56	0.63	
Infection	0.61	0.55	
LDH $\geq$ 2*ULN	0.57	0.63	
Neurological Dysfunction	0.36	0.37	
Pulmonary Dysfunction	0.18	0.27	
Renal Dysfunction	0.71	0.67	
Sex	0.58	0.54	
Analysis 2*			
Age	48.35		47.76
GvHD	0.57		0.58
Infection	0.64		0.62
LDH $\geq$ 2*ULN	0.59		0.61
Neurological Dysfunction	0.38		0.39
Pulmonary Dysfunction	0.18		0.21
Renal Dysfunction	0.71		0.71
Sex	0.60		0.62
Analysis 3*			
Age	49.24		47.68
GvHD	0.55		0.41
Infection	0.75		0.22
LDH $\geq$ 2*ULN	0.57		0.52
Neurological Dysfunction	0.43		0.19
Pulmonary Dysfunction	0.17		0.15
Renal Dysfunction	0.75		0.67
Sex	0.62		0.48

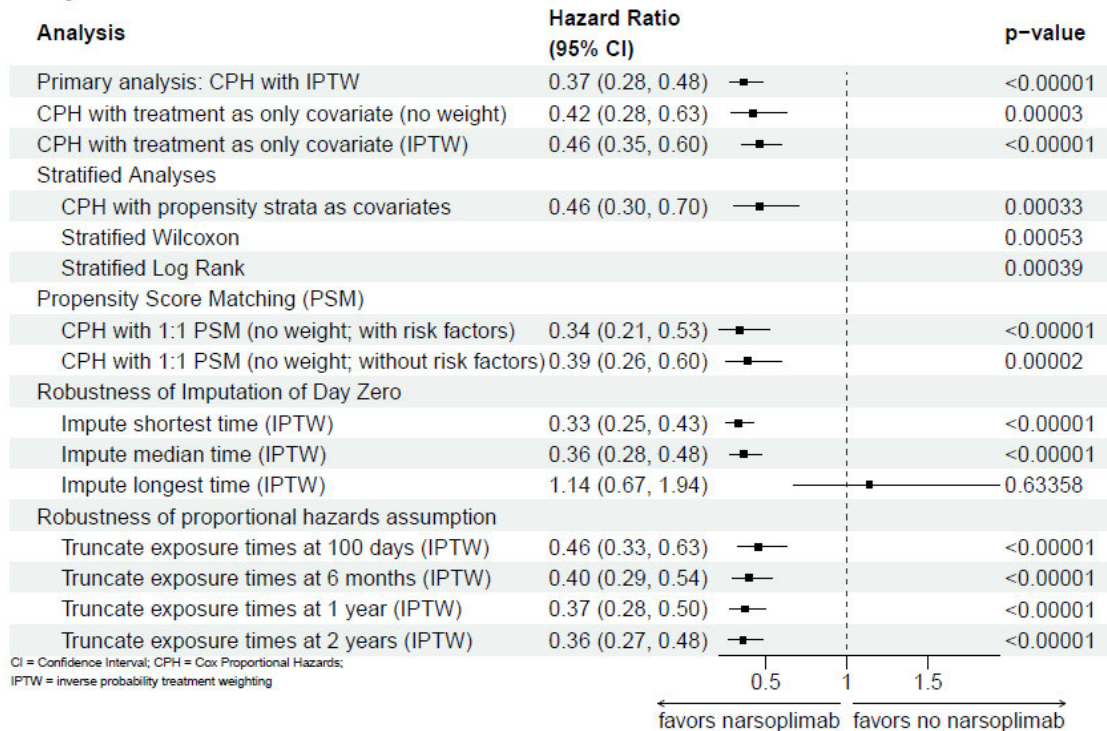
* Values in the table are the average of the covariates

7.6 FOREST PLOT FOR HAZARD RATIO AND 95% CIs ESTIMATED FROM PRIMARY AND SENSITIVITY ANALYSES, SUPPLEMENTAL ANALYSIS 1-3

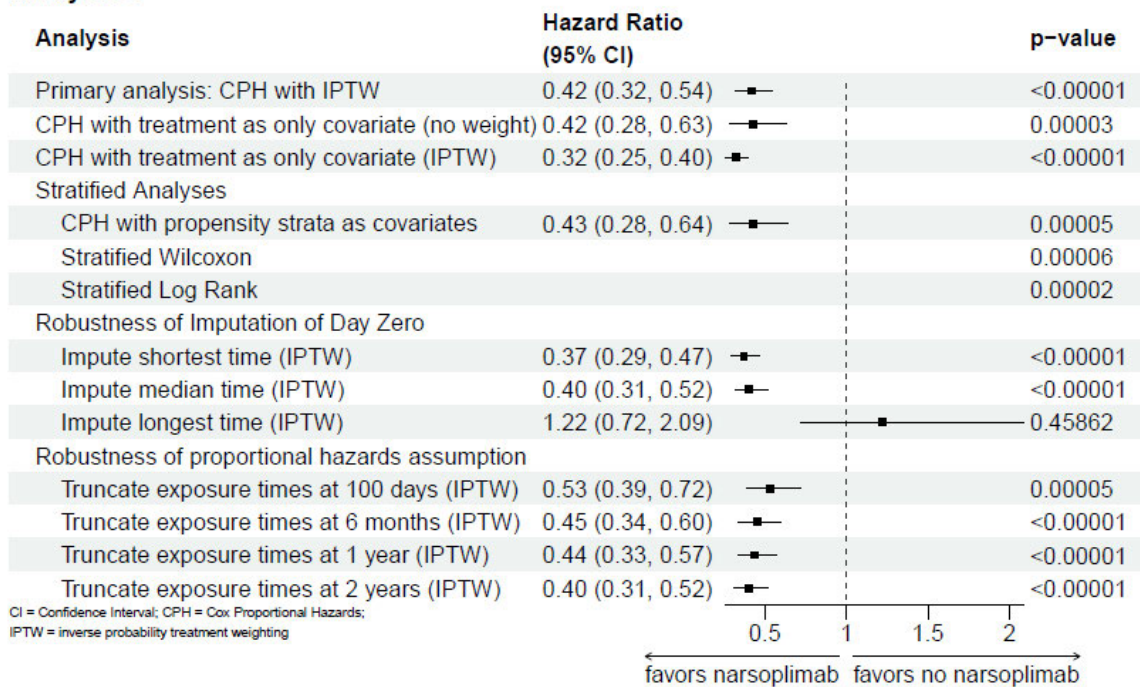
Analysis 1



Analysis 2



Analysis 3



7.7 RESULTS OF COX PROPORTIONAL HAZARDS MODELS COMPARING OVERALL SURVIVAL BETWEEN NARSOPLIMAB-TREATED PATIENTS IN OMS721-TMA-001 AND THE LITERATURE COHORT (N=61)¹⁸

Factor	Hazard Ratio (95% CI)	p-value
Analysis 1a (with treatment-by-region interaction)		
Narsoplimab ^a	0.30 (0.18, 0.50)	<0.00001
Age	1.01 (0.99, 1.02)	0.44776
Graft-versus-host disease Y	1.66 (1.03, 2.68)	0.03826
Region Asia ^b	0.32 (0.15, 0.68)	0.00349
TRT N * Region Asia	2.03 (0.68, 6.06)	0.20281
Analysis 1b (without treatment-by-region interaction)		
Narsoplimab ^a	0.35 (0.23, 0.55)	<0.00001
Age	1.00 (0.99, 1.02)	0.75772
Graft-versus-host disease Y	1.72 (1.07, 2.76)	0.02566
Region Asia ^b	0.45 (0.27, 0.75)	0.00214
Analysis 2a (with treatment by region interaction)		
Narsoplimab ^a	0.23 (0.12, 0.45)	0.00003
Age	1.01 (0.99, 1.02)	0.52292
Graft-versus-host disease Y	1.67 (1.03, 2.69)	0.03681
Region Asia ^c	0.27 (0.12, 0.63)	0.00238
Region Europe ^c	0.74 (0.37, 1.47)	0.38807
TRT N * Region Asia	2.62 (0.79, 8.65)	0.11462
TRT N * Region Europe	1.85 (0.70, 4.93)	0.21514
Analysis 2b (without treatment by region interaction)		
Narsoplimab ^a	0.36 (0.23, 0.56)	<0.00001
Age	1.00 (0.99, 1.02)	0.86113
Graft-versus-host disease Y	1.66 (1.04, 2.64)	0.03384
Region Asia ^c	0.44 (0.25, 0.78)	0.00436
Region Europe ^c	1.04 (0.64, 1.70)	0.87817
Analysis 3 (without treatment by region interaction)		
Narsoplimab ^a	0.09 (0.05, 0.17)	<0.00001
Age	1.00 (0.98, 1.02)	0.94821
Graft-versus-host disease Y	2.26 (1.33, 3.85)	0.00256
Organ Dysfunction Y	6.55 (3.04, 14.08)	<0.00001
Region Asia ^b	0.70 (0.34, 1.42)	0.32116
Analysis 4 (without treatment by region interaction)		
Narsoplimab ^a	0.10 (0.05, 0.19)	<0.00001
Age	0.99 (0.97, 1.01)	0.54594
Graft-versus-host disease Y	2.27 (1.34, 3.83)	0.00226
Organ Dysfunction Y	6.97 (3.10, 15.64)	<0.00001
Region Asia ^c	0.73 (0.34, 1.54)	0.40752
Region Europe ^c	1.47 (0.87, 2.48)	0.15255

^a vs. no narsoplimab treatment

^b vs. rest of the world

^c vs. US/Australia

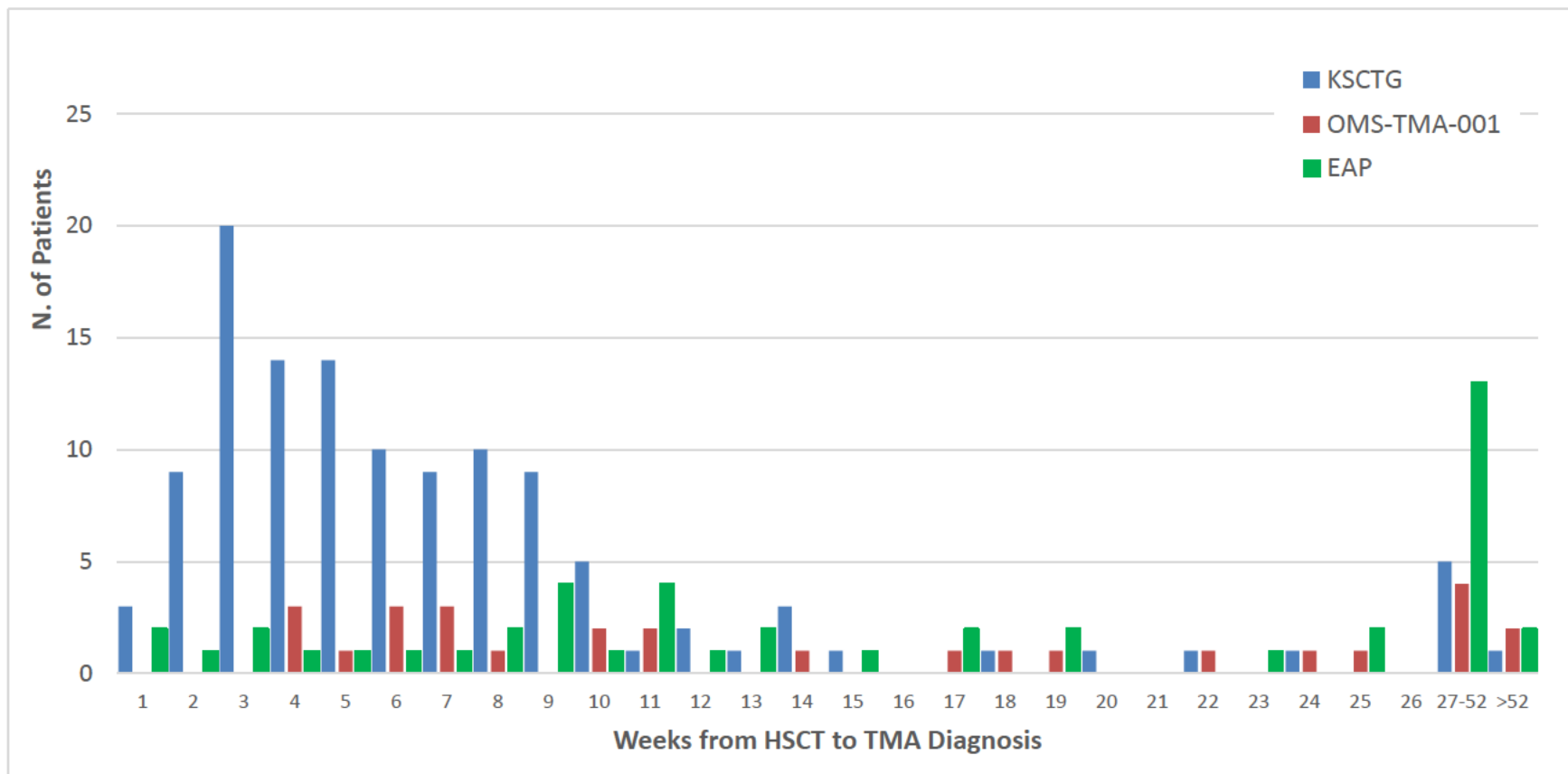
¹⁸ Source: Table 5 of Omeros's Report On TA-TMA Survival-Focused Literature Review And Meta-Analysis (page 16-17), submitted on July 15, 2025.

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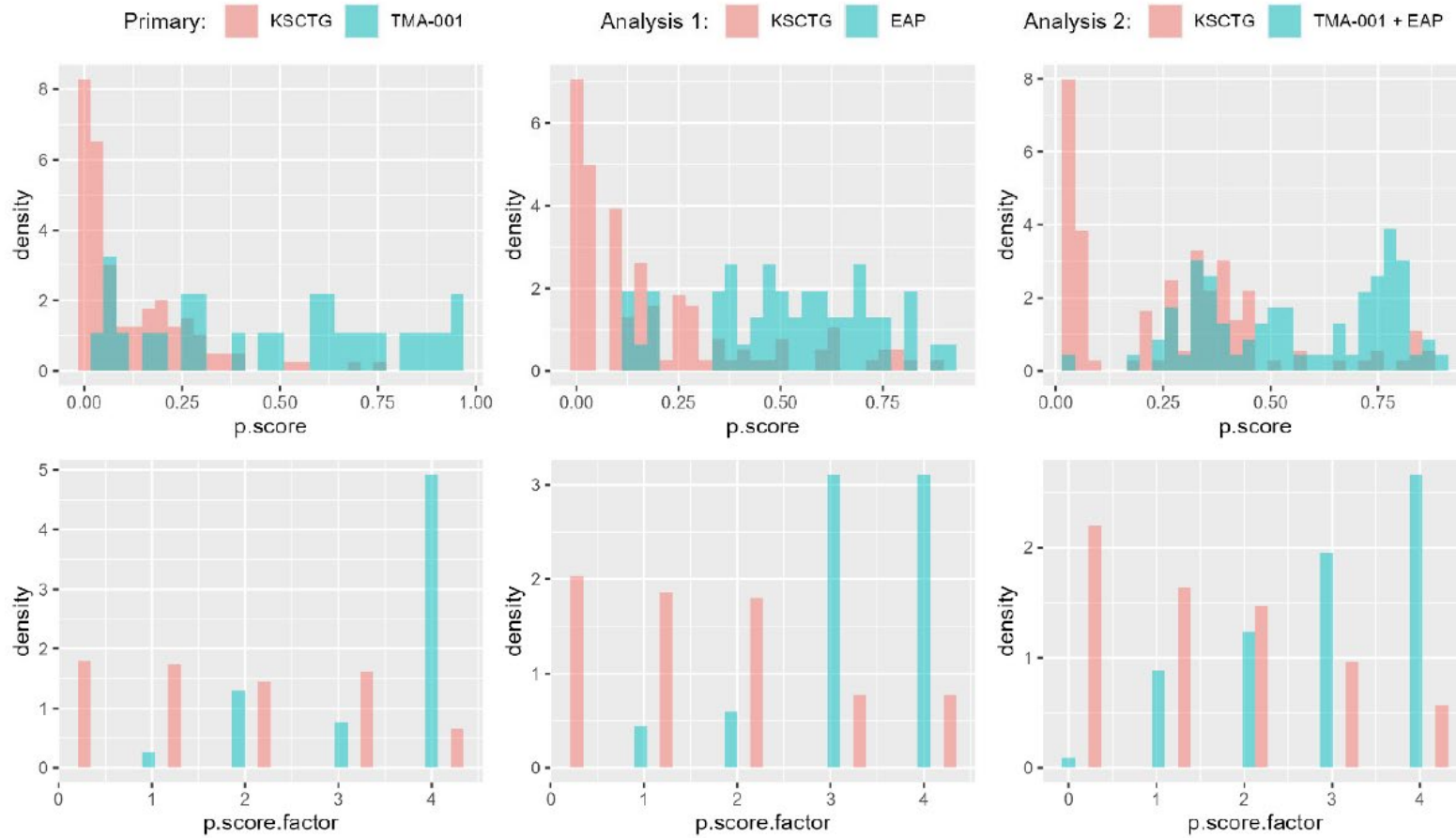
7.9 PATIENT COMPARABILITY BETWEEN NARSOPLIMAB TREATED PATIENTS VERSUS EXTERNAL CONTROL PATIENTS FROM KSCTG REGISTRY

	OMS721-TMA-001	Expanded Access Program (EAP)	KSCTG registry (External control)
Design	Prospective, single-arm, Phase 2 trial	Retrospective cohort	Retrospective cohort
Study Period	2015 -2019 (6 years)	2016-2023 (7 years)	2000-2016 (16 years)
Geographics	Global: US, Europe, Asia (China-Hong Kong, Singapore, Malaysia)	Global: US, Europe, Asia (China-Hong Kong, India)	Asia: <i>Japan</i>
Sample Size	28 adults (≥ 18 years), all had ≥ 2 risk factors	49 adults (≥ 16 years) with ≥ 1 risk factors	121 adults (≥ 16 years) with ≥ 1 risk factors; 108 adults with ≥ 2 risk factors
TMA diagnosis	Meet all 4 diagnostic criteria at least 2 weeks following modification or discontinuation of calcineurin inhibitors or at least 30 days after transplant.	Diagnosed by treating physician, defined as thrombocytopenia and evidence of microangiopathic hemolytic anemia.	Diagnosed by treating physician and confirmed through chart review, presenting 2 of the 5 diagnostic criteria.
Key Inclusion Criteria	Informed consent; age ≥ 18 years; diagnosis of TMA;	Documented high-risk HSCT-TMA (≥ 1 risk factors);	documented high-risk HSCT-TMA (≥ 1 or ≥ 2 risk factors);
Key Exclusion Criteria	- Had eculizumab therapy within 3 months prior to screening; - Active systemic bacterial/fungal infection requiring antimicrobial therapy; - Abnormal cardiac, vascular, or liver function; - Poor prognosis with a life expectancy less than 3 months;	had received any off-label potential therapeutic agent(s) drawn from eculizumab, ravulizumab, defibrotide, and pegcetacoplan, prior to treatment with narsoplimab.	had received narsoplimab or any off-label potential therapeutic agent(s) drawn from eculizumab, ravulizumab, defibrotide, and pegcetacoplan

7.10 DISTRIBUTION OF TIME FROM HSCT TO TMA DIAGNOSIS AMONG THE TMA-001 TRIAL, THE EAP, AND THE KSCTG REGISTRY PATIENTS



7.11 HISTOGRAMS OF PROPENSITY SCORES, BY ARM, FOR THE PRIMARY ANALYSIS, ANALYSIS 1, AND ANALYSIS 2¹⁹



¹⁹ Source: Figure 3.1 of Omeros’s Responses to FDA’s IR dated August 8, 2025 (page 16-17), submitted on August 22, 2025.

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/s/

FANG TIAN
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12/15/2025 11:50:25 AM



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
General ARIA Sufficiency Memorandum**

Date 12/8/2025
Product Name Yartemlea (narsoplimab-wuug)
Application Type/Number BLA 761152
Sponsor/Applicant Omeros Corporation
NEXUS Task Tracking Tool ID # 2025-13868
Safety Assessment Meeting Date (virtual) 9/17/2025

Reviewer Kate Gelperin, MD, MPH
Division of Epidemiology I

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Sentinel Program Lead (designee) Sarah Dutcher, PhD
Office of Surveillance and Epidemiology

1. Executive Summary

	Outcome #1: Serious infections	Outcome #2: Autoimmune disorders
Context: Is FDA considering requiring a FDAAA PMR and/or is this a part of a NISS assessment?	<i>FDAAA PMR</i> Yes	<i>FDAAA PMR</i> Yes
	<i>NISS</i> No	<i>NISS</i> No
FDAAA Purpose¹	Assess a known serious risk	Assess signals of a serious risk
NISS	N/A	N/A
Medical product exposure	Yartemlea (narsoplimab-wuug)	Yartemlea (narsoplimab-wuug)
Comparators	N/A	N/A
Outcomes and MedDRA preferred terms (PT)	Serious infections	Autoimmune disorders
	PT 10021789 (“Infection”)	HLGT 10003816 (“Autoimmune disorders”)
Review phase	During review of an original or supplemental NDA or BLA (pre-approval)	During review of an original or supplemental NDA or BLA (pre-approval)
ARIA sufficiency determination	No	No
If ARIA is insufficient, identify epidemiologic area(s) of insufficiency.	☒ Study Population	☒ Study Population
	☒ Exposure	☒ Exposure
	☐ Outcome	☒ Outcome
	☒ Covariates	☒ Covariates
	☐ Analytic Tools	☐ Analytic Tools

2. Background Information

Narsoplimab-wuug is a monoclonal antibody that binds to and blocks mannan-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin pathway of complement, inhibiting the inflammatory and pro-thrombotic responses to endothelial and other tissue injury while leaving the adaptive immune (i.e., the classical pathway) response intact and fully functional. The proposed indication is for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA). The recommended dosing is 4 mg/kg, given as a 30-minute intravenous infusion (up to a maximum of 370 mg per infusion) once or twice weekly.

TA-TMA is a potentially life-threatening complication of transplantation caused by endothelial injury, which activates the lectin pathway of complement. There is currently no approved therapy. TA-TMA is manifest as renal dysfunction and/or unexplained neurologic dysfunction, together with evidence of intravascular hemolysis that typically develops 20 to 100 days after transplantation.² The incidence and risk factors for TA-TMA are poorly defined; reports differ, in part, because of various definitions of the syndrome in assorted studies. The cumulative incidence of TA-TMA three years after allogeneic HCT was 3 percent among 23,665 children and adults in a multinational retrospective, registry-based study by

¹ Per Section 505(o)(3)(B), please ensure that the selected purpose is consistent with the PMR/PMC Development Template. This purpose will also appear in the approval letter.

² Early complications of hematopoietic cell transplantation; UpToDate; Accessed August 28, 2025.

the Center for International Blood and Marrow Transplant Research (CIBMTR).³ High risk TA-TMA is defined based on published consensus criteria.⁴ Patients with any of the following features are at increased risk of nonrelapse mortality and should be stratified as high-risk TA-TMA: elevated sC5b-9, LDH ≥ 2 times the ULN, rUPCR ≥ 1 mg/mg, multiorgan dysfunction, concurrent grade II-IV acute graft-versus-host disease (GVHD), or infection (bacterial or viral).

Narsoplimab was evaluated for safety and efficacy in 28 patients with TA-TMA in a single-arm, open-label study (Study TMA-001) and in 19 pediatric and adult patients with available efficacy data in an expanded access program (EAP). The efficacy was based on TMA-response defined as improvement in (i) two laboratory TMA markers (LDH levels and platelet counts) and (ii) at least one of two clinical findings, specifically organ function and freedom from transfusion. In Study TA-001, response was achieved in 17/28 (61%) patients. In the EAP, TA-TMA response was achieved in 13/19 (68.4%) patients. An additional 221 adult and pediatric patients with TA-TMA were treated with narsoplimab in a global EAP.⁵ Primary safety results included 28 patients from Study TMA-001. The most common adverse reactions ($\geq 15\%$) were infections, hemorrhage, hypotension, diarrhea, vomiting, nausea, abdominal pain, neutropenia, anemia, pyrexia, fatigue, hypokalemia, and back pain. Serious adverse reactions occurred in 61% of patients receiving narsoplimab. Serious adverse reactions in $>5\%$ of patients included acute kidney injury, confusional state, acute respiratory failure, neutropenic sepsis, septic shock, pulmonary edema and vomiting. Serious infections occurred in 10/28 (36%) of patients. Neutropenic sepsis and septic shock occurred in two patients.⁶

2.1 Medical Product

Drug Name(s)	Narsoplimab-wuug (Yartemlea)
Indication – (proposed)	The proposed indication is for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA).
Route of Administration	Intravenous infusion
Dosing Regimen	The recommended dosing is 4 mg/kg, given as a 30-minute intravenous infusion (up to a maximum of 370 mg per infusion) once or twice weekly.
Therapeutic Class	Monoclonal antibody
Mechanism of Action	Mannan-binding lectin-associated serine protease-2 (MASP-2) inhibitor
Current standard of care	Supportive care, identifying and addressing underlying causes, and complement inhibition
Alternative therapeutic options	Anti-complement therapy (e.g., eculizumab, ravulizumab); If anti-complement therapy is not available, plasma exchange
Other product information (relevant to the safety concern)	An important risk associated with narsoplimab is serious infections. In addition, autoimmunity has rarely been associated with MASP-2 deficiency, and since narsoplimab inhibits MASP-2, there is a theoretical risk of autoimmunity.

³ Epperla N, Li A, Logan B, Fretham C, et al. Incidence, Risk Factors for and Outcomes of Transplant-Associated Thrombotic Microangiopathy. *Br J Haematol.* 2020 Jun;189(6):1171-1181. <https://pubmed.ncbi.nlm.nih.gov/32124435/>

⁴ Schoettler ML, Carreras E, Cho B, et al. 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.* 2023 Mar;29(3):151-163. PMID: 36442770.

⁵ Draft Narsoplimab-wuug (Yartemlea) USPI, dated September 26, 2025.

⁶ Draft Narsoplimab BLA 761152 Clinical, Statistical and Clinical Pharmacology Review, dated October 14, 2025.



2.2 Characterization of the Safety Concern

The overall goal of this section is to summarize the context for the safety concern, including characterization of the signal strength and supporting evidence driving the concern. Provide enough clinical detail to understand whether ARIA is sufficient to assess the safety concern.

	Outcome #1: Serious infections	Outcome #2: Autoimmune disorders
Source(s) of safety concern Choose all that apply.	☐ Citizen Petition	☐ Citizen Petition
	☐ Compliance Inspection/Report	☐ Compliance Inspection/Report
	☐ Congressional Inquiry	☐ Congressional Inquiry
	☐ FAERS	☐ FAERS
	☐ Foreign Regulatory Agency	☐ Foreign Regulatory Agency
	☐ Lay Media	☐ Lay Media
	☐ Medical Literature	☐ Medical Literature
	☒ NDA or sNDA/BLA or sBLA ⁷	☒ NDA or sNDA/BLA or sBLA ⁷
	☐ Other Submission (IND)	☐ Other Submission (IND)
	☐ Other Federal Agency	☐ Other Federal Agency
	☐ Periodic Safety Update Report	☐ Periodic Safety Update Report
	☐ PMR/PMC Report	☐ PMR/PMC Report
	☐ Not Applicable	☐ Not Applicable
	☐ Other: <i>Click to enter other source(s).</i>	☐ Other: <i>Click to enter other source(s).</i>
Evidence driving the safety concern⁸ Choose all that apply and describe below.	☐ Meta-analyses	☐ Meta-analyses
	☒ Clinical trials	☒ Clinical trials
	☐ Observational studies	☐ Observational studies
	☐ Pharmacovigilance activities	☐ Pharmacovigilance activities
	☐ Other studies (animal, in vitro)	☐ Other studies (animal, in vitro)
	☒ Expert experience/mechanism of action (class-based risk)	☒ Expert experience/mechanism of action (class-based risk)

⁷ Including animal studies, in vitro studies, imbalance RCT

⁸ Describe safety concern(s), including case characteristics (e.g., is there a clinical pattern of events?), temporal distribution of outcomes (e.g., acute onset vs. variable-onset), assessment of the quality, directness, precision and causal association.



Signal strength⁹	Strong	Strong
Level of clinical concern¹⁰	Strong	Strong
Risk management strategies: Long-term safety will be monitored through a clinical PMR and through routine pharmacovigilance.		
Labeling	W&P is planned for serious infections	N/A
REMS	N/A	N/A
Postmarket study or commitment	A PMR will be issued for a prospective clinical registry evaluating long-term safety including risk for serious infections.	A PMR will be issued for a prospective clinical registry evaluating long-term safety including risk for autoimmune disorders.
Enhanced pharmacovigilance	N/A	N/A
Other strategies	N/A	N/A
Other regulatory background	N/A	N/A
Regulatory gap	The long-term safety of patients who receive treatment with narsoplimab is unknown. The goal of a patient registry PMR is to provide continued follow-up of patients to characterize the long-term safety of narsoplimab in patients with TA-TMA. The FDAAA purpose is to assess a known serious risk related to the use of the drug. An important risk associated with narsoplimab is serious infections. MASP-2 is an effector enzyme in the lectin complement pathway, which plays an important role in innate immunity. In addition, autoimmunity has rarely been associated with MASP-2 deficiency, and since narsoplimab inhibits MASP-2, there is a theoretical risk of autoimmunity. The desired registry would provide safety follow-up data and a summary of the major safety findings for this population, including all serious infections and autoimmune disorders.	

⁹ This is the DEPI reviewer’s subjective qualitative assessment of the “strength” of the signal, as based on the quality of the source of information about the safety concern, as well as the quantity and reliability of data to support the signal.

¹⁰ This is the DEPI reviewer’s subjective qualitative assessment of the “level of clinical concern” (e.g., seriousness of safety concern, magnitude of risk, prevalence of exposure) following discussions with the relevant team members.



2.3 Study Purpose

	Outcome #1: Serious infection	Outcome #2: Autoimmune disorders
FDAAA purpose ^{11,12}	Assess a known serious risk	Assess signals of a serious risk
Regulatory goal ¹³	Signal Evaluation	Signal Refinement

3. Study Population

3.1 Study Population

Age group(s)	Pediatric and adult
Sex	Both male and female
Racial group(s)	All racial groups
Clinical indication	Transplant-associated thrombotic microangiopathy (TA-TMA)
Clinical setting	All care settings
What variables are needed for inclusion and exclusion criteria that will be used to define the cohort?	N/A

3.2 ARIA Sufficiency for Study Population

Is ARIA sufficient to assess the intended population?	No
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	ARIA is not able to identify TA-TMA, which requires clinical information as well as laboratory data for diagnosis. Additionally, TA-TMA is a rare condition, occurring in only 3% of patients within the CIBMTR registry – a multinational working group of more than 500 transplant centers worldwide. ARIA is not expected to capture a sufficient number of patients with this condition. Therefore, ARIA is not sufficient for the population.
If ARIA is insufficient, what is the root cause(s) why ARIA cannot identify the intended population? Check all that apply.	☒ Absence of validated code algorithm
	☐ Identification of clinical concepts with code algorithms not possible or inadequate
	☐ Inability to capture intent of treatment
	☒ Inadequate sample size
	☐ Insufficient capture of information on race
	☐ Insufficient capture of patient medical and/or family history

¹¹ A Serious Risk is a serious adverse drug experience whose definition also includes any failure of expected pharmacologic action, which may include reduced effectiveness.

¹² Per Section 505(o)(3)(B), please ensure that the selected purpose is consistent with the PMR/PMC Development Template. This purpose will also appear in the approval letter.

¹³ **Signal Evaluation:** consists of the implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest. **Signal Refinement:** a process by which an identified potential safety signal is further investigated to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome. **Signal Identification:** the detection of new and unexpected potential medical product safety concerns and may be for pre-specified or unspecified (hypothesis-free) safety concern(s)/health outcome(s). Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. *Pharmacoepidemiol Drug Saf.* 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.



	☐ Insufficient clinical and laboratory cancer data that might be in a registry
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)
	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient inpatient data
	☒ Insufficient laboratory data
	☐ Insufficient observation time available
	☐ Insufficient radiology/pathology data
	☐ Insufficient representation of the population of interest
	☐ Unavailable linkage with Risk Evaluation and Mitigation Strategy (REMS) registry
	☐ Other: <i>Click to enter other explanation.</i>
If no, what type of data would be necessary to make the determination sufficient to assess the intended population?	☒ Laboratory and/or imaging data are needed to identify the study population
	☐ Structured electronic health records review to identify the study population
	☐ Chart review (including unstructured data) to identify the study population
	☐ Linkage to disease-based registry <i>Click to enter registry if known.</i>
	☐ Linkage to NDI is needed for data on cause of death
	☒ Primary data collection to identify the study population
	☐ Other: <i>Click to enter other data necessary to assess the population.</i>

4. Exposures

Exposure(s) of interest and comparator(s)

Describe the medical product of interest and any comparators to be included in the study. For fields that do not apply, enter "not applicable".

4.1 Exposure(s) of Interest

Medical product(s)	Yartemlea (narsoplimab-wuug)
Dosing/duration of use	4 mg/kg, given as a 30-minute intravenous infusion (up to a maximum of 370 mg per infusion) once or twice weekly
Clinical setting	Outpatient or inpatient
How will the exposure(s) be identified in the desired study?	Procedure codes
Other aspects of the exposure(s) of interest	N/A

4.2 Comparator Exposures

Medical product(s)	N/A
Dosing/duration of use	N/A
Clinical setting	N/A
How will the comparator(s) be identified in the desired study?	N/A
Other aspects of the comparator(s) of interest	N/A



4.3 ARIA Sufficiency for Exposure of Interest and Comparator(s)

Is ARIA sufficient to assess the exposure of interest?	No
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	ARIA can identify the exposure through procedure codes. However, this PMR requires collection of drug dosage, which is measured in mg/kg. ARIA does not have body mass index for calculation of dosage. Thus, ARIA is not sufficient.
Is ARIA sufficient to assess the comparator of interest?	N/A
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	N/A
If ARIA is insufficient, what is the root cause(s) why ARIA cannot identify the intended exposure or comparator of interest? Check all the apply.	☐ Absence of validated code list algorithm
	☐ Identification of medical products with code algorithms not possible or inadequate
	☐ Inability to capture intent of treatment
	☐ Inability to identify over-the-counter medication use
	☐ Inadequate sample size
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)
	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient inpatient data
	☐ Insufficient observation time available
	☐ Unavailable linkage with Risk Evaluation and Mitigation Strategy (REMS) registry
	☒ Other: PMR requires collection of drug dosage which is measured in mg/kg. ARIA does not have BMI for calculation of dosage.
If no, what type of data would be necessary to make the determination sufficient to assess the exposure/comparator of interest?	☒ Structured electronic health records review to identify the exposure/comparator
	☐ Chart review (including unstructured data) to identify the exposure/comparator
	☐ Linkage to disease-based registry <i>Click to enter registry if known.</i>
	☐ Linkage to NDI is needed for data on cause of death
	☐ Primary data collection to identify the exposure/comparator of interest
	☐ Other: <i>Click to enter other data necessary to assess the exposure/comparator.</i>



5. Outcomes

5.1 Outcomes of Interest

List outcomes as they appear in the approval letter or as stated in a NISS	Outcome #1: Serious infections	Outcome #2: Autoimmune disorders
Clinical case definition(s)	The case definition will be developed by the sponsor with submission of the PMR. Per the PMR language, analyses should include “patient level data on narsoplimab-wuug dosing, serious infections, serious treatment emergent adverse events, laboratory data (i.e., CBC with differential and renal function tests), autoimmune disorders, and concomitant medications.”	
Clinical setting	This study will be conducted in outpatient or inpatient settings and through routine visits with a healthcare provider.	
How will the outcomes be identified in the desired study? (Include any relevant validation studies)	Prospective collection of clinical and laboratory data as part of a prospectively enrolling registry.	
Timing of outcome assessment relative to exposure (i.e., risk-window)	The outcome would be expected to occur during or after an episode of treatment.	
Other aspects of the outcomes of interest	N/A	

5.2 ARIA Sufficiency for the Outcome of Interest

If ARIA is sufficient for the outcome of interest, complete the first two rows below. If ARIA is insufficient, complete all items below and refer to [Appendix B](#) when selecting the reason of insufficiency for this domain.

	Outcome #1: Serious infections	Outcome #2: Autoimmune disorders
Is ARIA sufficient to assess the outcome of interest?	Yes	No
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	An algorithm is available in ARIA to identify serious infections resulting in hospitalization. ARIA is sufficient to identify serious infections occurring during follow-up.	Diagnostic codes are available for many autoimmune diseases. Diagnostic and treatment coding could be combined to identify many of them. Given the large number of autoimmune diseases and insufficiencies noted elsewhere in this memo, a comprehensive review of coding for autoimmune diseases was not conducted. Overall, while some autoimmune diseases have been studied using claims data, ¹⁴ most have not. Although code lists and algorithms are available for a large number of autoimmune diseases, the sensitivity and predictive value for most of these are unknown. Therefore, ARIA is not sufficient for this outcome.

¹⁴ Abend AH, He I, Bahroos N, Christianakis S, et al. Estimation of prevalence of autoimmune diseases in the United States using electronic health record data. J Clin Invest. 2024 Dec 12;135(4):e178722. <https://pubmed.ncbi.nlm.nih.gov/39666393/>



If ARIA is insufficient, what is the root cause(s) why ARIA cannot identify the outcome of interest? Check all that apply.	☐ Absence of validated code algorithm	☒ Absence of validated code algorithm
	☐ Identification of clinical concepts with code algorithms not possible or inadequate	☐ Identification of clinical concepts with code algorithms not possible or inadequate
	☐ Inadequate sample size	☐ Inadequate sample size
	☐ Insufficient clinical and laboratory cancer data that might be in a registry	☐ Insufficient clinical and laboratory cancer data that might be in a registry
	☐ Insufficient data on behavioral and/or lifestyle risk factors	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)
	☐ Insufficient inpatient data	☐ Insufficient inpatient data
	☐ Insufficient laboratory data	☒ Insufficient laboratory data
	☐ Insufficient observation time available	☐ Insufficient observation time available
	☐ Insufficient radiology/pathology data	☐ Insufficient radiology/pathology data
	☐ Limited ability to ascertain cause of death	☐ Limited ability to ascertain cause of death
	☐ No access to patient-reported outcomes or physician-administered assessments	☐ No access to patient-reported outcomes or physician-administered assessments
☐ Other: <i>Click to enter other explanation.</i>	☐ Other: <i>Click to enter other explanation.</i>	
If no, what type of data would be necessary to make the determination sufficient to assess the outcomes of interest?	☐ Laboratory and/or imaging data to identify the outcome	☒ Laboratory and/or imaging data to identify the outcome
	☐ Structured electronic health records review to identify the outcome	☐ Structured electronic health records review to identify the outcome
	☐ Chart review (including unstructured data) to identify the outcome	☐ Chart review (including unstructured data) to identify the outcome
	☐ Linkage to disease-based registry <i>Click to enter registry if known.</i>	☐ Linkage to disease-based registry <i>Click to enter registry if known.</i>
	☐ Linkage to NDI is needed for data on cause of death	☐ Linkage to NDI is needed for data on cause of death
	☐ Primary data collection to identify the outcome	☒ Primary data collection to identify the outcome
	☐ <i>Click to enter other data necessary to assess the outcome.</i>	☐ <i>Click to enter other data necessary to assess the outcome.</i>

6. Covariates

6.1 Covariates of Interest

Covariate	Why is the covariate necessary for the study? Specify which outcome(s) each covariate applies to.	Conduct an a priori QBA to evaluate the potential impact of unmeasured/uncontrolled confounding on study findings (Including identification of plausible values for QBA parameters) Refer to the Draft DEPI QBA framework . (Optional)	Does the a priori QBA indicate that the missing or misclassified covariates likely change the study inference?



Covariate 1: Age	Age may affect risk of serious infections	N/A	Not Applicable
Covariate 2: Baseline comorbidity	Medical comorbidities may affect risk of serious infections	N/A	Not Applicable
Covariate 3: Clinical laboratory data	Abnormalities in clinical laboratory data may affect risk of serious infections	N/A	Not Applicable

6.2 ARIA Sufficiency for Covariates of Interest

If ARIA is sufficient for the covariates of interest, complete the first two rows below. If ARIA is insufficient, complete all items below and refer to [Appendix B](#) when selecting the reason of insufficiency for this domain.

Is ARIA sufficient to assess the covariates?	No
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	This study requires collection of laboratory data during follow-up to characterize the progression of disease (i.e., complete blood count (CBC) with differential and renal function tests). While ARIA has laboratory data on a limited number of patients, ARIA is not sufficient to systematically capture laboratory covariate data at set intervals during follow-up.
If ARIA is insufficient, which covariates are insufficient?	Clinical laboratory data
If ARIA is insufficient, what is the root cause(s) why ARIA cannot identify the covariates of interest? Check all that apply.	☐ Absence of validated code list algorithm
	☐ Identification of clinical concepts with code algorithms not possible or inadequate
	☐ Inability to capture intent of treatment
	☐ Inability to identify over-the-counter medication use
	☐ Information on socioeconomic status unavailable
	☐ Insufficient capture of patient medical and/or family history
	☐ Insufficient capture of information on race
	☐ Insufficient clinical and laboratory cancer data that might be in a registry
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)
	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient inpatient data
	☒ Insufficient laboratory data
	☐ Insufficient observation time available
	☐ Insufficient radiology/pathology data
	☐ No access to patient-reported outcomes or physician-administered assessments
☐ Unavailable data on environmental risk factors	
☐ Other: <i>Click to enter other explanation.</i>	
If no, what type of data	☒ Laboratory and/or imaging data are needed to identify covariates



would be necessary to make the determination sufficient to assess covariates?	☒ Structured electronic health records review to identify covariates
	☐ Chart review (including unstructured data) to identify covariates
	☐ Linkage to disease-based registry <i>Click to enter registry if known.</i>
	☐ Linkage to NDI is needed for data on cause of death
	☐ Primary data collection to identify the covariates
	☐ Other: <i>Click to enter other data necessary to assess covariates.</i>

7. Analytic Tools

Identify the types of analyses required to conduct the postmarket study, including both the final desired analysis and any feasibility assessments that would be needed. For fields that do not apply, enter “not applicable”.¹⁵

7.1 Analytic Tools

Type of analysis desired Check all that apply.	☒ Descriptive: unadjusted incidence rates (L1)
	☐ Inferential: self-controlled risk interval (L2)
	☐ Inferential: propensity score-based method (i.e., matching, stratification or inverse probability of treatment weighting) (L2)
	☐ Interrupted time series (L2)
	☐ Sequential monitoring (L3)
	☐ Signal identification using TreeScan
	☐ Other: <i>Click to enter other analysis.</i>

7.2 ARIA Sufficiency for Analytic Tools

Is ARIA sufficient with regards to the analytic tools available to assess the question of interest?	Yes
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	This study requires descriptive characteristics to summarize the collected data. ARIA is sufficient for the analytic tools.
If ARIA is insufficient, why are the analytic tools a major limiting factor?	☐ Insufficient capabilities in ARIA analytic tool to perform required safety issue analysis
	☐ Other: <i>Click to enter other explanation.</i>
If no, what analytic capabilities would be necessary to make the determination sufficient to answer the question of	☐ Protocol-based assessment with customized programming
	☐ Other: <i>Click to enter other analytic tool(s).</i>

¹⁵ The Sentinel website includes detailed information on ARIA analytic tools. <https://www.sentinelinitiative.org/methods-data-tools/routine-querying-tools>



interest?	

8. Additional Information:

8.1 Other information relevant to the ARIA sufficiency determination

N/A

8.2 Sponsor Postmarketing Requirement (PMR)

If ARIA is deemed sufficient: complete the ARIA Planning Concept Brief within 12 months following approval of the drug product.

If ARIA is deemed insufficient, complete the table below:

Will a sponsor PMR be required?	Yes
If yes, how is FDA ensuring that identified reasons for ARIA insufficiency and the data or information needed to make the determination sufficient are being addressed within the PMR?	☒ PMR language in the approval letter
	☒ PMR study protocol negotiation process with sponsors
	☐ Other: <i>Click or tap here to enter text.</i>
If yes, provide the proposed PMR language	PMR: Establish a registry to characterize the long-term safety of narsoplimab-wuug in at least 50 adult and pediatric patients with transplant-associated thrombotic microangiopathy (TA-TMA), with at least 1 year of follow-up. The final study report should include a summary of the major safety findings for all patients including patient level data on narsoplimab-wuug dosing, serious infections, serious treatment emergent adverse events, laboratory data (i.e., CBC with differential and renal function tests), autoimmune disorders, and concomitant medications.

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/s/

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DAVID G MOENY
12/09/2025 11:54:18 AM

SARAH K DUTCHER
12/09/2025 02:09:52 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 4, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761152
Product Name, Dosage Form, and Strength:	Yartemlea (narsoplimab-wuug) ^a injection, 370 mg/2 mL (185 mg/mL)
Applicant Name:	Omeros Corporation (Omeros)
FDA Received Date:	October 31, 2025
TTT ID #:	2025-13872-2
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

^a The non-proprietary name "narsoplimab-wuug" was found conditionally acceptable for this BLA 761152 on June 9, 2025.

1 PURPOSE OF MEMORANDUM

Omeros Corporation (Omeros) submitted revised carton labeling received on October 31, 2025 for Yartemlea. We reviewed the revised carton labeling for Yartemlea (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

Omeros Corporation (Omeros) implemented all of our recommendations. Omeros confirmed the established name is at least half the size of the proprietary name on the container labels and carton labeling. In addition, we previously requested the wave graphic above the proprietary name to be decreased relative to the prominence of the proprietary name, established name, and strength on the principal display panel (PDP). In response, Omeros reduced the size of the wave graphic and increased the font size of other critical information on the PDP (i.e., dosage form, route, net quantity and discard statements) and relocated the proprietary name upward on the PDP. Lastly, Omeros clarified the green box is a placeholder for a 2D black-and-white barcode representing the carton's part number used by contract packager/labeler to ensure that that Yartemlea commercial presentation is assembled with the correct packaging components. We have no additional recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

^b Black, S. Review of Revised Label and Labeling for Yartemlea (BLA 761152). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 SEP 16. TTT ID: 2025-13872-1.

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11/04/2025 08:14:13 AM

NICOLE F IVERSON
11/04/2025 08:31:10 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: October 10, 2025

To: May Zuwannin, Regulatory Project Manager,
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling,
(DNH)

From: Melissa Khashei, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for YARTEMLEA (narsoplimab-wuug)
injection, for intravenous use

BLA: 761152

Background:

In response to DNH's consult request dated April 15, 2025, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for YARTEMLEA (narsoplimab-wuug) injection, for intravenous use.

PI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 30, 2025, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on March 26, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
10/10/2025 04:47:09 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health PLLR Labeling Review

Date: September 29, 2025 **Date consulted:** August 20, 2025

From: Kerry R. Shaab, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, Division Director
Division of Pediatrics and Maternal Health

To: Division of Nonmalignant Hematology (DNH)

Drug: Yartemlea (narsoplimab)

BLA: 761152

Applicant: Omeros Corporation

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy

Materials Reviewed:

- DPMH consult request, dated 8/20/2025. DARRTS Reference ID: 5646385.
- Applicant's background package and proposed labeling for BLA 761152, Sequence Number (SN) 0001 and 0007, dated 11/17/2020.

- Applicant’s resubmission package and proposed labeling for BLA 761152, Sequence Number (SN) 0079, dated 3/26/2025.
- Applicant’s response to DPMH Information Request (IR) dated 8/28/2025, SN 0099, submitted 9/5/2025.

Consult Question: PLLR Labeling Review - “Request to review section 8 of the PI”

I. INTRODUCTION AND BACKGROUND

On March 26, 2025, the Applicant, Omeros Corporation, resubmitted a 351(a) application for Yartemlea (narsoplimab), a fully human immunoglobulin gamma 4 (IgG4) monoclonal antibody directed against mannan-binding lectin-associated serine protease-2 (MASP-2), for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). The Division of Nonmalignant Hematology (DNH) consulted the Division of Pediatrics and Maternal Health (DPMH) on August 20, 2025, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- In 2018, the Agency granted narsoplimab Breakthrough Therapy Designation and Orphan Drug Designation for the treatment of HSCT-TMA.
- The Agency granted narsoplimab a rolling review on September 4, 2019. The first portion of the original BLA application was submitted on October 24, 2019, and the final portion (part 5 of 5) was submitted on November 17, 2020.
- The Agency issued a Complete Response Letter (CRL) on October 15, 2021, then denied Omeros’ formal dispute resolution request on November 3, 2022.
- Following the Agency’s issuance of the CRL, Omeros and FDA had multiple interactions aimed at reaching alignment on the plan to address the concerns raised in the CRL

Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy^{1,2,3,4,5}

Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy (HSCT-TMA or TA-TMA) is a rare, potentially life-threatening complication of transplantation which is caused by transplant-related factors that prompt endothelial injury. The reported incidence of HSCT-TMA varies widely, with an incidence ranging from 0.8 to 39 percent reported in contemporary studies. The wide variation may be explained by the use of different definitions of HSCT-TMA

¹ Young JA, et al. Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis. *Bone Marrow Transplant*. 2021 Aug;56(8):1805-1817. doi: 10.1038/s41409-021-01283-0. Epub 2021 Apr 19. PMID: 33875812; PMCID: PMC8338557.

² Lazana I. Transplant-Associated Thrombotic Microangiopathy in the Context of Allogeneic Hematopoietic Stem Cell Transplantation: Where We Stand. *Int J Mol Sci*. 2023 Jan 6;24(2):1159. doi: 10.3390/ijms24021159.

³ Schoettler ML, et al. 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*. 2023 Mar;29(3):151-163. doi: 10.1016/j.jtct.2022.11.015.

⁴ Negrin, RS. Early complications of hematopoietic cell transplantation. In: *UpToDate*, Connor RF (Ed), Wolters Kluwer. (Accessed 9/15/2025)

⁵ Hingorani, SR, Abudayyeh, AA, Jhaveri, KD. Kidney disease following hematopoietic cell transplantation. In: *UpToDate*, Connor RF (Ed), Wolters Kluwer. (Accessed 9/15/2025)

and the inclusion of both pediatric and adult populations. HSCT-TMA is characterized by microangiopathic hemolytic anemia and thrombocytopenia, as a result of generalized endothelial dysfunction and complement activation, leading to microthrombi formation and usually develops in the first 100 days after transplantation. The clinical presentation ranges from self-limited disease to multi-organ dysfunction and death. Renal insufficiency and/or failure is the most common organ manifestation; however, it can also impact the gastrointestinal tract, central nervous system, heart, lungs and serosal surfaces. Although different diagnostic criteria have been proposed, there are no uniformly accepted definitions, and the diagnosis is usually established based upon the presence of characteristic clinical and laboratory findings. A high index of clinical suspicion is needed as presentation is similar to that of other HSCT complications. Currently, there are no FDA-approved products indicated for the treatment of HSCT-TMA. The optimal approach to treatment is unknown and management is largely supportive, including minimizing transfusions, aggressive management of hypertension, and prompt and aggressive treatment of co-existing infections. Additionally, immunosuppressive anti-GVHD therapies may be reduced or discontinued and/or off-label therapies may be administered. HSCT-TMA is associated with significant morbidity and mortality. Nonrelapse mortality is significantly higher in patients with HSCT-TMA compared to those without HSCT-TMA. Although some patients will have a self-remitting course, more than one-half of patients will progress to multiorgan dysfunction, with mortality rates typically exceeding 50% at 1-year post-transplant. No information specifically related to HSCT-TMA and pregnancy was identified during this review.

II. REVIEW

Nonclinical Experience

The nonclinical team reviewed the Applicant's submission and provided the following information:

Adverse effects on embryofetal development were observed in the Embryo-fetal Development (EFD) studies conducted in mice and rabbits. In mice, embryofetal loss (postimplantation loss, litter of dead fetuses in early decedent female), reduced fetal body weights, and cleft palate malformation occurred with intravenous administration at 22-times the maximum recommended human dose (MRHD). There were no malformations observed in rabbits, however, increased postimplantation loss and reduced fetal body weights were observed with intravenous administration at 91-times the exposure at the MRHD. No adverse effects were observed with narsoplimab when administered subcutaneously up to 3-times and 8-times the exposure at the MRHD in mice and rabbits, respectively. In an enhanced pre-and postnatal development (PPND) study conducted in pregnant mice, no adverse effects were observed in the dams or F1 offspring with either subcutaneous (SC) or intravenous (IV) administration of narsoplimab, resulting in a safety margin of 22-times the MRHD. Additionally, in the PPND study, narsoplimab was present in the serum of F₁ offspring during the lactation period on LD4 and LD21, however, levels of narsoplimab in maternal milk were not measured. In a Fertility and Early Embryonic Development (FEED) study, narsoplimab did not impact fertility in female or male mice.

The reader is referred to the full nonclinical review by Pedro DelValle, Ph.D.

Reviewer comment:

No adverse effects were observed with narsoplimab when administered subcutaneously up to 3-times and 8-times the exposure at the MRHD in mice and rabbits, respectively. Therefore, there were no specific safety signals identified at clinical exposures in the EFD studies. According to the nonclinical team⁶, the presence of narsoplimab in the pups' sera during the lactation period is evidence of transfer through milk despite the lack of maternal milk level measurements.

Review of Applicant's Pharmacovigilance Database^{7,8}

Narsoplimab has not been approved in any region. The Applicant conducted a cumulative review of the narsoplimab safety database and identified four pregnancy cases during the clinical development program, all of which occurred in the context of IgA nephropathy clinical trials. No pregnancies were reported in the narsoplimab clinical development program for hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). Two of the four pregnancy cases involved participants receiving narsoplimab. The other two cases involved one pregnancy reported in the female partner of a male participant with the pregnancy occurring approximately 7 months following the participant's last exposure to narsoplimab, and one pregnancy in a participant receiving placebo. The summary of the two pregnancy cases in narsoplimab-treated participants are as follows:

- Participant (b) (6) in Study OMS721-GNP-001: A 36-year-old female with a medical history significant for chronic kidney disease secondary to IgA nephropathy, hypertension, hyperlipidemia, chronic pain syndrome and a past obstetrical history significant for one previous spontaneous abortion in 2016 received narsoplimab 370 mg IV once weekly for 24 weeks. The last dose of narsoplimab was on (b) (6), and she had a positive serum pregnancy test on (b) (6). Her last menstrual period (LMP) was (b) (6). At the time of the positive pregnancy test, the estimated gestational age was 3 weeks. Concomitant medications, at least once, from 30 days prior to date of LMP, included Valsartan, Carvedilol, Tramadol, Norethindrone, Atorvastatin, Ergocalciferol, Sertraline, Furosemide, Hydrocodone, Acetaminophen, Carisprodol, Melatonin, Heparin Sodium, Sodium Bicarbonate, Sodium Chloride 0.9%, and Ciprofloxacin. The pregnancy ended in a spontaneous abortion at 14 weeks gestation. No pathologic or diagnostic tests were performed on the fetus. The placenta was noted to have "abnormal villus morphology suggestive of chromosomal anomaly." No further details were reported.
- Participant (b) (6) in Study OMS721-IGA-001: A 29-year-old female, with a medical history significant for IgA nephropathy, hypertension, and obstetrical history significant for a full-term birth via cesarean section, received narsoplimab 370 mg IV once weekly for approximately 18 weeks (from (b) (6)). On (b) (6), approximately 2 months after the last dose of narsoplimab, the participant's pregnancy was diagnosed with an estimated gestational age of 6 weeks. Concomitant medications at the time of pregnancy diagnosis included lisinopril which was discontinued due to pregnancy. The participant delivered a full-term, healthy, male

⁶ Personal communication with Bo Lee, Ph.D., Pharmacology/Toxicology Review Team, dated 9/12/2025.

⁷ BLA 761152 SN 0007, Module 2.7.4, Summary of Clinical Safety and 5.3.5.4 Safety Narratives.

⁸ BLA 761152, SN 0099, Applicant's response to DPMH IR, dated 8/28/2025.

infant via cesarean section at 39 weeks, 1 day gestation. The infant's birth weight was 3380 grams, and the Apgar scores were 9 and 10 at 1 minute and 5 minutes, respectively. No perinatal complications were reported. No further details were reported.

The Applicant did not report any cases of narsoplimab exposure during lactation or cases reporting effects of narsoplimab on female or male fertility.

Reviewer comment:

Both pregnancy cases occurred in females with IgA nephropathy and the half-life of narsoplimab in the IgA nephropathy population is unknown. Narsoplimab has an estimated mean terminal half-life ($t_{1/2}$) of 198 hours in healthy subjects and an estimated mean terminal $t_{1/2}$ of 209 hours in patients with HSCT-TMA. According to the Clinical Pharmacology team, given the terminal half-life is so long, there is not a clinically meaningful or significant difference between these two values⁹. Using the mean terminal half-life of 209 hours, narsoplimab is mostly cleared from systemic circulation in approximately 6 weeks. Based on the estimated gestational age at the time of pregnancy diagnosis, it is possible that early pregnancy narsoplimab-exposure occurred in both pregnancy cases.

With respect to the spontaneous abortion experienced by study participant (b) (6), the maternal chronic kidney disease, history of previous spontaneous abortion, and the concomitant medication exposures confound the relationship between narsoplimab-exposure and this adverse pregnancy outcome. The second pregnancy case resulted in a full-term, liveborn infant with no reported congenital anomalies or perinatal complications. There are insufficient pregnancy data from the clinical development program to inform the safety of narsoplimab use in pregnancy.

Review of Literature

The Applicant did not perform a literature search. DPMH conducted a search of published human studies in PubMed and Embase, using the search terms “narsoplimab” and “pregnancy”, “pregnancy outcomes”, “pregnant”, “major birth defects”, “birth defects”, “congenital malformations”, “congenital anomalies”, “teratogenicity”, “miscarriage”, “spontaneous abortion”, “elective abortion”, “pregnancy loss”, “stillbirth”, “fetal loss”, “fetal demise”, “fetotoxicity”, “adverse pregnancy outcomes”, “prematurity”, “low birth weight”, “lactating”, “lactation”, “human milk”, “breastfeeding”, “breastfed”, “neonates”, “infants”, “fertility”, “infertility”, “decreased sperm count”, “contraception”, “oral contraceptives”, “effects on fertility”, and “reproduction”. In addition, DPMH conducted a search for narsoplimab in Micromedex¹⁰, Reprotox¹¹, TERIS¹², Shepard's¹³, *Briggs Drugs in Pregnancy and Lactation: A*

⁹ Personal communication with Sudharshan Hariharan, Ph.D., Clinical Pharmacology Review Team, dated 9/24/2025.

¹⁰ Truven Health Analytics information, <http://www.micromedexsolutions.com> Accessed 8/18/2025.

¹¹ Reprotox Website: www.Reprotox.org. Accessed 8/18/2025.

¹² TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/18/2025.

¹³ Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 8/18/2025.

*Reference Guide to Fetal and Neonatal Risk*¹⁴, *Hale's Medications and Mothers' Milk*¹⁵, and the Drugs and Lactation Database (LactMed)¹⁶. No relevant publications on the use of narsoplimab during pregnancy or lactation, or the effects of narsoplimab on female and male reproductive potential were found.

III. DISCUSSION AND CONCLUSIONS

The animal reproduction studies did not identify a specific safety signal indicating an increased risk for embryo-fetal toxicity at clinical exposures. Animal reproduction data do not suggest a serious risk of developmental toxicity during pregnancy. Human data on narsoplimab exposure during pregnancy are insufficient to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Narsoplimab is a fully human immunoglobulin gamma 4 (IgG4) monoclonal antibody directed against mannan-binding lectin-associated serine protease-2 (MASP-2), inhibiting the lectin pathway of the complement system. Although the classical and alternative pathways of the complement system would remain intact, as a complement inhibitor, there is a theoretical increased risk of infection in the treated population. Additionally, as a monoclonal antibody, narsoplimab is expected to cross the placenta like endogenous IgG, with its transport increasing as pregnancy progresses and peaking in the third trimester. As such, narsoplimab is expected to be present in infants exposed *in utero* during the third trimester; however, the potential clinical impact of *in utero* narsoplimab-exposure is unknown. Therefore, DPMH recommends including a Clinical Considerations, *Fetal/Neonatal Adverse Reactions* subheading in subsection 8.1 Pregnancy to convey that the potential clinical impact of *in utero* narsoplimab-exposure warrants deliberation.

There are no available data on the presence of narsoplimab in human breast milk, the effects of narsoplimab on the breastfed infant, or the effects on milk production. In the PPND study, narsoplimab was detected in the plasma of the newborn pups during the lactation period, indicating transfer into animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. In addition, narsoplimab is a monoclonal antibody, and monoclonal antibodies, like endogenous IgG, are transferred into human milk; however, the effects of local gastrointestinal exposure and the extent of systemic exposure in the breastfed infant to narsoplimab are unknown.

Although females of reproductive potential undergo HSCT in general, and may develop HSCT-TMA as a complication, HSCT-TMA is a rare condition that has a high mortality rate. Therefore, DPMH does not recommend postmarketing pregnancy safety or clinical lactation studies at this time. Routine drug pharmacovigilance and literature reviews would be reasonable.

There are no available human data to inform labeling related to the effects of narsoplimab on human fertility. Animal fertility studies do not indicate any adverse effects at clinical exposures.

¹⁴ Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. *Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk*. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021.

¹⁵ Hale, Thomas W. *Hale's Medications and Mother's Milk 2021: A Manual of Lactational Pharmacology*. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com. Accessed 8/18/2025.

¹⁶ Drugs and Lactation Database (LactMed). Accessed 8/18/2025.

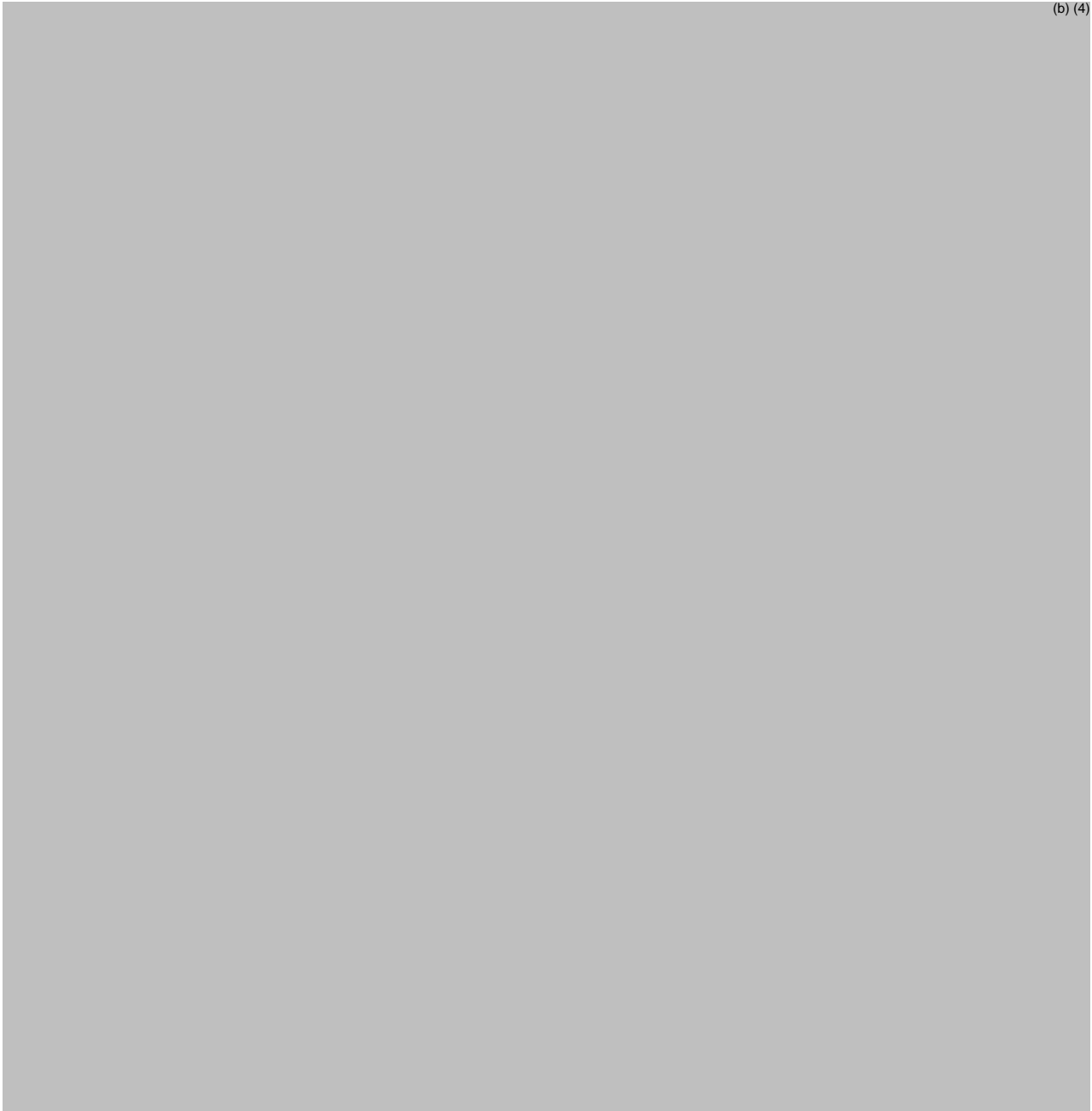
In addition, there is no evidence of fetal harm that would require pregnancy testing or contraceptive use during treatment with narsoplimab. Therefore, DPMH recommends omitting labeling subsection 8.3 Females and Males of Reproductive Potential.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. DPMH recommendations are below. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION



(b) (4)

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APPENDIX A –

Drug Characteristics¹⁷

Drug Class	A mannose binding protein-associated serine protease 2 (MASP-2) inhibitor
Proposed Mechanism of Action	(b) (4)
Proposed dosage form and administration	Injection: 370 mg/2 mL in a single-dose vial (b) (4) 4 mg/kg (b) (4) given as an intravenous infusion over 30 minutes once (b) (4) weekly.
Molecular weight	143 kDa
Mean terminal Half-life	Estimated to be 209 hours in patients with HSCT-TMA

¹⁷ BLA 761152, draft Annotated Labeling with DNH review team edits, review ongoing.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 16, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761152
Product Name, Dosage Form, and Strength:	Yartemlea (narsoplimab-wuug) ^a injection, 370 mg/2 mL (185 mg/mL)
Applicant Name:	Omeros Corporation (Omeros)
FDA Received Date:	September 2, 2025
TTT ID #:	2025-13872-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

^a The non-proprietary name "narsoplimab-wuug" was found conditionally acceptable for this BLA 761152 on June 9, 2025.

1 PURPOSE OF MEMORANDUM

Omeros Corporation submitted revised container label and carton labeling received on September 2, 2025 for Yartemlea. We reviewed the revised container label and carton labeling for Yartemlea (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

Omeros Corporation implemented most of our recommendations. Omeros confirmed the expiration date format (i.e., MM/YYYY) will be presented in numerical characters for both month and year. In addition, Omeros confirmed the white box on the carton labeling is the placeholder for the 2D data matrix barcode.

The container label and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Omeros Corporation in Section 3.

3 RECOMMENDATIONS FOR OMEROS CORPORATION

A. General Comments (Container Label and Carton Labeling)

1. As currently presented, we are unable to assess if the established name is at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Please confirm that the established name is at least half the size of the established name in accordance with 21 CFR 201.10(g)(2).

B. Carton Labeling

1. The placement of the wave graphic directly above the proprietary name (i.e., above the letter string "LEA") continues to compete with critical information on the principal display panel (PDP). The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. Decrease the prominence of your graphic relative to the prominence of the proprietary name, established name, and strength on the PDP needed for proper

^b Black, S. Label and Labeling Review for Yartemlea (BLA 761152). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 AUG 22. TTT ID: 2025-13872.

identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6).

2. The “Rx only” statement appears more prominent than other critical information (e.g., dosage form, route of administration) on the principal display panel. The “Rx only” statement should not compete in size and prominence with critical information on the principal display panel. We continue to recommend debolding the “Rx only” statement so that it does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. As currently presented, the manufacturer information (e.g., Omeros and logo) competes in prominence with product important information (e.g., storage, vial content information) on the side panels. Manufacturer information should not be the most prominent information on the side panel and as currently presented it distracts the reader from other important information. We recommend decreasing the size of the manufacturer information on the side panels, so it does not compete with the prominence of other important product information.
4. As currently presented, the temperature range of the storage statement is bolded. Bolding only the temperature range distracts the user from the rest of the important storage information. We recommend revising to bold “Store refrigerated” only: “Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. Do not shake.” to minimize the risk of important storage information being overlooked.
5. As currently presented, the dosage form lacks prominence. The proprietary name and established name along with the product strength, route of administration, dosage form, and warnings or cautionary statements (if any) should be the most prominent information on the labeling. For increased prominence, we recommend increasing the font size of the dosage form “Injection” on the carton labeling.
6. As currently presented, the back panel of the carton labeling contains a green box. Please clarify the purpose of the green box.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 22, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761152
Product Name, Dosage Form, and Strength:	Yartemlea (narsoplimab-wuug) ^a injection, 370 mg/2 mL (185 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Omeros Corporation (Omeros)
FDA Received Date:	August 16, 2021 and March 26, 2025
TTT ID #:	2025-13872
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

^a The non-proprietary name "narsoplimab-wuug" was found conditionally acceptable for this BLA 761152 on June 9, 2025.

1 INTRODUCTION

As part of the approval process for Yartemlea (narsoplimab-wuug) injection, we reviewed the proposed Yartemlea Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Omeros Corporation previously submitted BLA 761152 on October 24, 2019. We previously completed a label and labeling review and provided recommendations for the PI, container label and carton labeling^b. Our recommendations were provided to the Applicant and revised labels and labeling were submitted^c. However, the application received a Complete Response (CR) letter on October 15, 2021 due to clinical and statistical issues. The CR letter stated that FDA reserved comments on the proposed labels and labeling until the application is otherwise adequate^d.

Thus, Omeros Corporation submitted a Class 2 Resubmission on March 26, 2025.^e

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), container label and carton labeling for Yartemlea to identify deficiencies that may lead to medication errors and other areas of improvement.

We note the carton labeling contains the statement “Do not shake.” However, this information is missing in Section 16 *How Supplied/Storage and Handling*. We reached out to OPQ (Office of

^b DeGraw, S. Label and Labeling Review for Yartemlea (BLA 761152). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 05. OSE RCM No.: 2020-2403.

^c Response to Labeling Recommendations (BLA 761152 and Yartemlea). Seattle (WA): Omeros Corporation; 2021 APR 19. Available from: <\\CDSESUB1\EVSPROD\bla761152\0025\m1\us\12-cover-letters\0025-cover-letter-draft-labeling-response-19-apr-2021.pdf>.

^d Hamilton, Courtney on behalf of Lisa Yanoff. Complete Response for BLA 761152. Silver Spring (MD): FDA, CDER, OND, Division of Non-Malignant Hematology (DNH) (US); 2021 OCT 15. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061e685>.

^e Resubmission Cover Letter (BLA 761152 and Yartemlea). Seattle (WA): Omeros Corporation; 2025 MAR 26. Available from: <\\CDSESUB1\EVSPROD\bla761152\0079\m1\us\12-cover-letters\0079-resubmission-cover-letter-26mar2025.pdf>.

Pharmaceutical Quality) to confirm if the product should not be shaken. OPQ agreed that “Do not Shake” is appropriate and should be added to section 16 for consistency with the carton labeling.

During an internal team meeting, OPQ informed they plan to add details to the preparation and administration instructions (b) (4) in order to minimize the risk of visible particles (i.e., inverting the diluted solution a specific number of times, etc.). However, at this time, the details to the preparation and administration instructions from OPQ are still pending.

4 CONCLUSION

The proposed Yartemlea Prescribing Information (PI), container label, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Non-Malignant Hematology (DNH) in Section 5 and for Omeros Corporation in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. General Issues

- a. As currently presented, the dosing frequency is “ (b) (4) ”. However, it is not clear when to prescribe the product “ (b) (4) ”. We recommend including information to guide healthcare providers on selection of the appropriate dosing frequency.

2. Highlights of Prescribing Information

a. Dosage and Administration

- i. As currently presented, the recommended dosage statement may be improved for clarity. In addition, (b) (4). For clarity, we recommend revising the recommended dosage statement as follows:

(b) (4)

b. Dosage Forms and Strengths

- i. As currently presented, the dosage form (b) (4) “ (b) (4) ” is inconsistent with the dosage form “injection” on the container label and carton labeling. For consistency, we recommend revising the dosage form to “Injection: 370 mg/2 mL (185 mg/mL) in a single-dose vial.”

3. Section 2 Dosage and Administration

a. As currently presented in Section 2.1 *Recommended Dosage*, the [REDACTED] (b) (4). We recommend revising the first statement [REDACTED] (b) (4)

as follows:

[REDACTED] (b) (4)

b. As currently presented, Section 2.2 [REDACTED] (b) (4) describes both preparation (dilution) and administration instructions. As such, we recommend revising this section title to read "Section 2.2 *Preparation and Administration*".

c. As currently presented, the preparation and administration instructions [REDACTED] (b) (4) may be improved for clarity and to use active voice. We recommend revising as follows:

[REDACTED] (b) (4)

d. As currently presented, the missed dose information “If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.” (b) (4)

(b) (4). We recommend relocating missed dose information to 2.1 *Recommended Dosage* after the recommended dosage statements.

4. Section 3 Dosage Forms and Strengths

i. As currently presented, the dosage form “ (b) (4) ” (b) (4) is inconsistent with the dosage form “injection” on the container label and carton labeling. For consistency, we recommend revising the dosage form to “injection” as follows:

(b) (4)

5. Section 16 How Supplied/Storage and Handling

a. The dosage form (i.e., injection) is not provided in Section 16. The dosage form is required per 21 CFR 201.57(c)(17). Add the dosage form in Section 16 in accordance with 21 CFR 201.57(c)(17) as follows:

(b) (4)

b. The product strength is not expressed as a total quantity per total volume followed by the concentration per mL. The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. Express the product strength as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7>. See example of revision in 5a.

c. A description of the dosage form is not provided (e.g., color). A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(17)(iii). Provide a description of identifying characteristics of the [dosage form] in accordance with 21 CFR 201.57(c)(17)(iii). See example of revision in 5a.

d. The description of the packaging configuration [i.e. one 370 mg/2 mL (185 mg/mL) single-dose vial in a carton] is missing. The packaging configuration is required to appear in Section 16 in accordance with 21 CFR 201.57(c)(17)(iii). Revise Section 16 of the Prescribing Information to comply with the content requirements in accordance with 21 CFR 201.57(c)(17)(iii). In addition, we recommend including the NDC number associated with the package. See example of revision in 5a.

- e. The package type term, single-dose vial, is not provided. Consistent use of the correct package type term will promote proper use of the drug product. The lack of this information may lead to wrong technique medication errors during preparation or administration of the product. We recommend adding the appropriate package type term (i.e., Single-dose vial). See Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018). See example of revision in 5a.
- f. As currently presented, the carton labeling contains the storage statements "Do not shake.". However, this information is missing in Section 16. We recommend incorporating this into the storage and revising as follows:

(b) (4)

6 RECOMMENDATIONS FOR OMEROS CORPORATION

A. General Comments (Container Label and Carton Labeling)

1. As currently presented, the net quantity statement contains a "dash" symbol (2-mL). Error prone symbols may lead to misinterpretation and medication error. We recommend revising the net quantity statement to "2 mL Single-Dose Vial. Discard Unused Portion."
2. The format for the month portion of the expiration date is unclear on the carton labeling. We are unable to assess the month portion of the expiration date from a safety perspective. Confusion regarding the expiration date may lead to use of expired drug product. Please clarify the format for the expiration date and whether alphabetical or numerical characters will be used to represent the month. If using alphabetical characters, then we recommend you revise the format for the month portion to three characters (for example, "JUL" versus "JU" to represent July) to prevent confusion. In addition, please clarify the format of the expiration date on the container label.

B. Container Label

1. As currently presented, the route of administration statement on the carton labeling ("For Intravenous Infusion After Dilution") is inconsistent with the route of administration statement on the container label (b) (4). For consistency, we recommend revising the route of administration on the container label to "For Intravenous Infusion After Dilution". In addition, we recommend removing the separate statement "(b) (4)" on the side panel of the container label as it has been incorporated into the route of administration statement.

2. As currently presented, the container label does not include the assigned NDC number on the principal display panel, but on the side panel. The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. It is an important safety feature that is recommended to be prominently displayed on the principal display panel of the container label. We request that you relocate the NDC number to the principal display panel of the container label per 21 CFR 201.2.
3. As currently presented, it is unclear if the "LOT EXP" statements will be expressed as "LOT XX EXP YY" or "LOT EXP XX/YY". To minimize misinterpretation, ensure the lot number and expiration date align with the lot number and expiration date abbreviations (i.e., LOT and EXP). In addition, ensure sufficient spacing between the lot number and expiration date for increased readability.
4. The "Rx only" statement appears more prominent than other critical information (e.g., established name, route of administration) on the principal display panel. The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel. We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

C. Carton Labeling

1. The placement of the graphic at the directly above the proprietary name competes with critical information on the principal display panel (PDP). The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. Decrease the prominence of your graphic relative to the prominence of the proprietary name, established name, and strength on the PDP needed for proper identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6).
2. The established name is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
3. As currently presented, the back panel appears nearly identical to the principal display panel (PDP) apart from the green box at the bottom of the back panel, which may lead to confusion on which panel is the PDP. We recommend

removing [REDACTED] (b) (4) from the back panel to distinguish it from the PDP.

4. As currently presented, the storage statement is inconsistent with the Prescribing Information. For consistency, we recommend revising to “Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. Do not shake.”
5. As currently presented, it is unclear if the white box is the placeholder for the 2D data matrix barcode. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product’s labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). Confirm if the white box will be a 2D data matrix barcode.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Yartemlea received on March 26, 2025 from Omeros Corporation.

Table 2. Relevant Product Information for Yartemlea	
Initial Approval Date	N/A
Nonproprietary Name	narsoplimab-wuug
Indication	Treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA)
Dosage Form	injection
Strength	370 mg/2 mL (185 mg/mL)
Route of Administration	Intravenous infusion
Dose and Frequency	(b) (4)
How Supplied	YARTEMLEA is supplied as 370-mg (b) (4) vials (b) (4) 2 mL (b) (4) 185 mg/mL sterile solution (b) (4)
Storage	Store YARTEMLEA vials refrigerated at 2 °C to 8 °C (36 °F to 46 °F) in the original carton to protect from light until time of use. Do not freeze. Do not use beyond the expiration date stamped on the carton.
Container Closure	Not provided

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Yartemlea labels and labeling submitted by Omeros Corporation.

- Prescribing Information received on March 26, 2025, available from <\\CDSESUB1\EVSPROD\bla761152\0079\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf>
- Container label received on August 16, 2021
- Carton labeling received on August 16, 2021

B.2 Container Label and Carton Labeling Images

Container Label:



Carton Labeling:

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^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On June 6, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, 761152. Our search identified 2 previous review(s)^{g,h}, and we considered our previous recommendations to see if they are applicable for this current review.

^g DeGraw, S. Label and Labeling Review for Yartemlea (BLA 761152). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 05. OSE RCM No.: 2020-2403.

^h DeGraw, S. Review of Revised Label and Labeling for Yartemlea (BLA 761152). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 09. OSE RCM No.: 2020-2403-1.

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: October 20, 2021

To: Courtney Hamilton, PharmD, BCPS, Regulatory Project Manager,
Division of Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DNH

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for YARTEMLEA (narsoplimab-wuug)
injection, for intravenous use

BLA: 761152

This memo is in response to DNH's labeling consult request dated November 17, 2020. Reference is made to a Complete Response letter that was issued on October 15, 2021. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DNH submit a new consult request during the subsequent review cycle. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
10/20/2021 11:23:58 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 9, 2021
Requesting Office or Division: Division of Non-Malignant Hematology (DNH)
Application Type and Number: BLA 761152
Product Name and Strength: Yartemlea (narsoplimab-wuug) injection, 370 mg/2 mL (185 mg/mL)
Applicant/Sponsor Name: Omeros Corporation
OSE RCM #: 2020-2403-1
DMEPA 2 Safety Evaluator: Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Omeros Corporation submitted revised container label and carton labeling received on August 16, 2021 for Yartemlea. The revisions are in response to recommendations that we made during a previous label and labeling review.^a We reviewed the revised label and labeling to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

^a DeGraw, S. Label and Labeling Review for Yartemlea (BLA 761152). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 05. RCM No.: 2020-2403.

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/s/

CELESTE A KARPOW
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HINA S MEHTA
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 5, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761152
Product Name, Dosage Form, and Strength:	Yartemlea (narsoplimab-xxxx) ^a injection 370 mg/2 mL (185 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Omeros
FDA Received Date:	November 17, 2020 and February 10, 2021
OSE RCM #:	2020-2403
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

^a The nonproprietary name suffix for this BLA has not yet been determined; therefore, the placeholder, narsoplimab-xxxx, is used throughout this review to refer to the nonproprietary name and suffix for this product.

1. REASON FOR REVIEW

Omeros submitted BLA 761152 for Yartemlea (narsoplimab-xxxx) injection on November 17, 2020. Yartemlea is a complement inhibitor proposed for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). We evaluated the proposed container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for Yartemlea to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed PI, container label, and carton labeling identified areas that can be modified to improve the clarity of the information presented. For the Division, we note the PI lacks clarity in the preparation instructions, storage instructions, lack of information on total strength per total quantity, and clarity on storage information. For the Applicant, we note the color font of the proprietary name is not consistent, the finished dosage form is missing, clarity on language for route of administration is needed, the total contents of the vial is missing on the container label, lack of linear barcode on the container label, and the format of expiration date is not defined on the container label.

We provide recommendations for the Division in Section 4.1 and recommendations for Omeros in Section 4.2 below.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Omeros in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. Highlights of Prescribing Information

1. Dosage and Administration

- a. We recommend revising the first statement to improve clarity of the information presented. For example, “ (b) (4)

“ (b) (4) ”

2. Dosage Forms and Strengths

- a. We recommend revising this statement to state the correct dosage form and total concentration of the vial, as well as remove the (b) (4) (b) (4) which is not appropriate in the Highlights section. For example, “Injection: 370 mg/2 mL (185 mg/mL) in a single-dose vial”.

B. Dosage and Administration [2]

1. Recommended Dosage [2.1]

- a. We recommend revising the first statement (b) (4) (b) (4) . For example, “ (b) (4) (b) (4) ”

2. Administration Instructions [2.2]

- a. This section describes both preparation (dilution) and administration instructions. As such, we recommend revising this section title to read “Preparation and Administration”.
- b. We recommend revising this section (b) (4) , to use active voice, and to improve the clarity of information presented. For example:

(b) (4)

C. Dosage Forms and Strengths [3]

1. We recommend revising this statement to state the correct dosage form and total concentration of the vial. For example, "Injection: 370 mg/2 mL (185 mg/mL) as a clear to slightly opalescent, slightly yellow to yellow/brown solution in a single-dose vial".

D. How Supplied / Storage and Handling [16]

1. We recommend revising the How Supplied statement to improve clarity and to include the identifying product characteristics, total vial concentration, the correct package type term, and NDC. For example:

YARTEMLEA (narsoplimab-xxxx) is a clear to slightly opalescent, slightly yellow to yellow/brown sterile solution supplied as:

Carton containing one 370 mg/2 mL (185 mg/mL) single-dose vial (NDC 62225-300-00).

2. We recommend revising the storage statement to include a degree symbol after each number and the temperature in Fahrenheit in addition to Celsius and to include the "Do not freeze" and "Do not shake" warning statements that are included on the carton labeling. For example:

Store refrigerated at 2° to 8°C (36° to 46°F) in the original carton to protect from light until time of use. Do not freeze. Do not shake

4.2 RECOMMENDATIONS FOR OMEROS

A. General Comments for All Labels and Labeling

1. We note the proposed proprietary name, YARTEMLEA, is prominently displayed on the container label and carton labeling with the (b) (4) letters of the proposed proprietary name displayed in purple font. Presenting the proprietary name in different font colors may cause confusion (b) (4). Thus, we recommend revising the font color of the proposed proprietary name (b) (4) in order to avoid confusion and misinterpretation.”
2. Consider including the finished dosage formulation, “Injection”, directly beneath the proper name on the principal display panel.

B. Container Label

1. As currently presented, the product strength is not expressed as a total quantity per total volume followed by the concentration per mL in parentheses. A number of overdoses have occurred with small-volume parenteral products due to healthcare practitioner confusion when determining the quantity of drug in the container. Express the product strength as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7>. We recommend expressing the total quantity per volume in larger font than the concentration per mL. For example:

370 mg/2 mL (185 mg/mL)

2. As currently presented, the label does not contain a linear barcode. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label. Add the product’s linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.^b
3. As currently presented, the route of administration on the principal display panel (PDP) is “For IV infusion”. Presenting the route of administration as an abbreviation (i.e., IV) may lead to misinterpretation. We recommend revising this statement to read “For Intravenous Infusion”.

^b Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

4. Replace the (b) (4) statement on the side panel with the appropriate package-type term "Single-dose vial". This will also maintain consistency with the language in the prescribing information.
5. We recommend moving "Discard unused portion" on the side panel so that it appears immediately after "Single-dose vial".
6. As the route of administration is conveyed on the PDP, we recommend (b) (4) on the side panel (b) (4) (b) (4) to ensure the dilution information is not overlooked.
7. As currently presented, the format for the expiration date is not indicated. Please confirm the format for the expiration date is the same as the format on the carton labeling (i.e. MM/YYYY).

C. Carton Labeling

1. We recommend revising the strength statement so that the total quantity per total volume is larger than concentration per mL to prevent healthcare practitioner confusion when determining the quantity of drug in the container. For example:

370 mg/2 mL (185 mg/mL)

2. We recommend revising the administration statement " (b) (4) " to read "For Intravenous Infusion After Dilution" to ensure this important information is not overlooked. In addition, the " (b) (4) " statement on the bottom left corner of the PDP may be deleted.
3. Revise (b) (4) " to include the carton contents, to reflect the appropriate package-type term, and to include the discard statement. Revise to read "1 single-dose vial. Discard unused portion." The statements (b) (4) " on the top left of the PDP and " (b) (4) " on the side panel may be deleted.
4. To minimize the risk of storage information being overlooked, we recommend revising the storage information to include bold font for the refrigerated statement, to state that the vial should be store in the carton, and to round to the nearest whole degree. For example, revise to read, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake. Do not freeze."

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Yartemlea received on November 17, 2020 and February 10, 2021 from Omeros

Table 2. Relevant Product Information for trilaciclib	
Initial Approval Date	N/A
Active Ingredient	narsoplimab-xxxx
Indication	Treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA)
Route of Administration	intravenous infusion
Dosage Form	injection (solution)
Strength	370 mg/2 mL (185 mg/mL)
Dose and Frequency	(b) (4)
Preparation and Administration	Dilute YARTEMLEA in 5% Dextrose Injection, (b) (4) to a concentration of 0.8 mg/mL to 8.0 mg/mL.
How Supplied	Clear to slightly opalescent, slightly yellow to yellow/brown solution supplied (b) (4) 370 mg/2 mL (185 mg/mL) single-dose vial
Storage	Store refrigerated at 2° to 8°C in the original carton to protect from light until time of use. (b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,^c along with post-market medication error data, we reviewed the following labels and labeling submitted by Omeros:

- Container Label received on November 17, 2020
- Carton Labeling received on November 17, 2020
- Prescribing Information (no image shown) received on February 10, 2021
<\\CDSESUB1\evsprod\bla761152\0016\m1\us\114-labeling\draft\labeling\draft-labeling-text-word.docx>

G.2 Labels and Labeling

Container Label

(b) (4)



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^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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HINA S MEHTA
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CLINICAL INSPECTION SUMMARY

Date	March 10, 2021
From	Anthony Orenca M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Carrie Diamond, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Division Director Courtney Hamilton, PharmD, Regulatory Health Project Manager Division of Nonmalignant Hematology OCHEN
BLA	BLA 761152
Applicant	Omeros Corporation
Drug	Narsoplimab
NME	Yes
Division Classification	Human IgG4 monoclonal antibody
Proposed Indication	Treatment of adult patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA)
Consultation Request Date	November 30, 2020
Summary Goal Date	March 31, 2021
Action Goal Date	May 1, 2021
PDUFA Date	May 17, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single study, Study OMS721-TMA-001, was submitted to the Agency in support of a Biologics Licensing Application (BLA 761152) for narsoplimab (OMS721), proposed for treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). A single clinical investigator site (Samer Khaled, M.D.) and sponsor (Omeros Corporation) were inspected, in support of BLA 761152.

Based on these inspections, the conduct of the above Study OMS721-TMA-001 appears to be adequate. The study data derived from the clinical investigator's site and the sponsor are considered reliable. The study data submitted to the Agency appear acceptable in support of this NDA and the proposed indication.

II. BACKGROUND

Narsoplimab (OMS721), a human IgG4 monoclonal antibody directed against mannan-binding lectin-associated serine protease 2 (MASP-2), is developed for the treatment of lectin complement pathway-mediated diseases. Narsoplimab blocks the action of MASP-2, thereby inhibiting the lectin pathway of complement activation. The alternative pathway, by contrast, is continuously activated at a low level and is kept in check by a series of regulatory proteins.

The data submitted in this application is to support the proposed indication for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). Narsoplimab received the breakthrough therapy designation for the treatment of patients with HSCT-TMA who have persistent TMA despite modification of immunosuppressive therapy.

A single study, Study OMS721-TMA-001, forms the basis for the regulatory decision-making process for this application.

Study OMS721-TMA-001

Study OMS721-TMA-001 was a phase 2, open-label, uncontrolled, 3-stage ascending-dose-escalation study in patients with TMA. This study was originally designed to provide preliminary information on the safety and efficacy of narsoplimab for the treatment of the included three types of TMA.

The co-primary objectives were (1) to assess the safety and tolerability of multiple-dose administration of narsoplimab in patients with thrombotic microangiopathy (TMA), including patients with hematopoietic stem cell transplant-associated-TMA (HSCT-TMA), atypical hemolytic uremic syndrome (aHUS), and thrombotic thrombocytopenic purpura (TTP), and (2) to evaluate the efficacy of narsoplimab in patients with HSCT-TMA by response. Response was defined as improvement in TMA laboratory markers of platelet count and lactate dehydrogenase (LDH), plus improved clinical status

The primary efficacy endpoint was the proportion of HSCT-TMA patients who responded to narsoplimab treatment. Treatment response was defined as a patient with HSCT-TMA who demonstrated both an improvement in laboratory TMA markers (platelet count and LDH) as well as improvement in clinical status (that is, either improvement in organ function or freedom from transfusion) at any time point post-baseline during the study.

The study was conducted at 27 study centers that enrolled at least 1 patient across 12 countries (Belgium, Bulgaria, Hong Kong, Italy, Lithuania, Malaysia, New Zealand, Poland, Singapore, Taiwan, Thailand, and United States)

The date of first patient enrollment was [REDACTED]^{(b) (6)}. The last study patient completed on [REDACTED]^{(b) (6)} [REDACTED]^{(b) (6)} (last efficacy observation for this report).

The Division of Nonmalignant Hematology (DNH) requested inspection of a single investigator site, among the highest accrual sites within the US. The review division also requested inspection of the sponsor's site, in part, for the Agency to assess clinical trial monitoring and study oversight.

III. RESULTS (by site)

1. Samer K. Khaled, M.D. / Site 302

City of Hope National Medical Center
1500 East Duarte Road
Duarte, CA 91010

Note: Official Correspondence and FMD-145 should be addressed to: 8354 Beverly Dr.
San Gabriel, CA 91775

Inspection dates: December 17 to 23, 2020

A total of four study subjects were screened, enrolled and received study treatment. All the enrolled study patients completed the study. Of the four study subjects who received the investigational drug: (a) one subject completed Stage 1 but did not continue onto Stages 2 or 3 of the study; (b) a single study subject's family withdrew consent for further active treatment and transitioned the subject to comfort care and later died, and (c) two study subjects died while on study, due to complications from transplant-associated thrombotic microangiopathy.

Records reviewed included but were not limited to: investigator agreements, financial disclosure forms, Institutional Review Board approvals and documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, subject source records, test article control records, adverse event documentation, and informed consent documentation.

Source records for all enrolled study patients at the site were reviewed and compared with the Applicant's submitted data listings for the site. The clinical study site retained study records, and submitted required reports, per the study protocol and per applicable FDA regulations. The primary efficacy endpoint data were verifiable against the data line listings.

A FDA Form 483, Inspectional Observations, was issued at the end of the inspections for failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically,

- a) Subject (b) (6) had a serious adverse event (worsening hospitalization for acute Graft versus Host Disease) that was not reported immediately.
- b) Subject (b) (6) had three adverse events that were not recorded to an electronic data capture (EDC) system in a timely manner. The adverse events were coagulase negative staphylococcus bacteremia due to a central line infection, metabolic acidosis secondary to renal dysfunction and elevated alkaline phosphatase levels.

Dr. Khaled's response to the FDA Form 483, dated January 12, 2021, appeared adequate. For contemporaneous notification of adverse events, in December 2017, the clinical study site deployed a new electronic medical record system, Epic, that sent abnormal laboratory results, hospitalizations, and death events to the study team. Further, in January 2019, the clinical study site implemented a clinical trials management system. The clinical study site developed procedures that includes a process to ensure timely event reporting.

Reviewer's comments: Although the above findings are regulatory violations, these adverse events were included in the submission, and these findings do not appear to have a significant impact on the safety assessments of the study.

2. **Omeros Corporation**

The Omeros Building
201 Elliott Avenue W
Seattle, WA 98119

Inspection dates: January 8-14, 2021

An inspection was conducted to assess Omeros Corporation's responsibilities concerning its monitoring and oversight of a Phase 2 clinical trial, Study OMS721-TMA-001.

The sponsor site audit reviewed the organizational charts, financial disclosure forms, FDA Form 1572 Statement of Investigators, standard operating procedures, contract agreements, sponsor oversight, vendor selection process, adverse event reporting system, drug discontinuation due to treatment emergent adverse event, selection and monitoring of sites, investigational drug supply chain, and drug master label.

The subject data line listings were consistent with the data found in the electronic case report forms at the sponsor site. Data included protocol deviations, study eligibility, and efficacy co-endpoint components (such as evaluability criteria of the treatment response criteria for HSCT-TMA, platelet and LDH values, freedom from transfusion, improvement in thrombotic microangiopathy markers over time, improvements in creatinine function overtime, and duration of treatment response for HSCT-TMA study subjects).

In general, no regulatory deficiencies were observed during the inspection. There were no Form FDA-483, Inspectional Observations, issued. No observations or inspectional findings appeared to have an impact on data integrity or reliability.

{See appended electronic signature page}

Anthony Orenca, M.D., Ph.D.

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.

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CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.

Branch Chief

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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