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APPLICATION NUMBER:

761152Orig1s000

INTEGRATED REVIEW

CLINICAL, STATISTICAL, AND CLINICAL PHARMACOLOGY JOINT REVIEW

Application Type	BLA
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Review Completion Date	Electronic Stamp
Established/Proper Name	Narsoplimab-wuug
(Proposed) Trade Name	Yartemlea
Applicant	Omeros Corporation
Dosage Form(s)	Injection
Applicant Proposed Dosing Regimen(s)	<u>Starting Dose</u> ≥50 kg body weight: 370 mg intravenously over 30 minutes once weekly. <50 kg body weight: 4 mg/kg intravenously over 30 minutes once weekly (up to a maximum of 370 mg per infusion).
Applicant Proposed Indication(s)/Population(s)	For the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA)
Recommendation on Regulatory Action	Approval (Traditional/Regular)
Recommended Indication(s)/Population(s)	For the treatment of adult and pediatric patients 2 years of age and older with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA)

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Glossary

AE	adverse event
AR	adverse reaction
BLA	biologics license application
BRF	Benefit Risk Framework
CCIT	Container closure integrity test
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNIs	calcineurin inhibitors
CrI	credible intervals
CRL	complete response letter
CRO	contract research organization
CRT	clinical review template
DEPI-1	Division of Epidemiology I
EAP	expanded access program
FDA	Food and Drug Administration
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSCT-TMA	hematopoietic stem cell transplant-associated thrombotic microangiopathy
ICH	International Council for Harmonization
IND	Investigational New Drug Application
KSCTG	Kyoto Stem Cell Transplantation Group
LDH	lactate dehydrogenase
mAb	monoclonal antibody
NPTP	non-pharmacologically treated patients
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PE	plasma exchange
PES	polyethersulfone
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome

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REMS risk evaluation and mitigation strategy

rUPCR urine protein creatinine ratio

SAE serious adverse event

SEE substantial evidence of effectiveness

TA-TMA transplant associated thrombotic microangiopathy

ULN upper limit of normal

1. Executive Summary

1.1. Application Introduction

On October 15, 2021, Omeros Corporation (the Applicant) submitted a Biologics License Application (BLA) 761152 for Yartemlea (narsoplimab-wuug), a monoclonal antibody (mAb) that inhibits mannan-binding lectin-associated serine protease 2 (MASP-2), the effector enzyme of the lectin pathway of complement for the proposed indication of the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA). The proposed dosage of narsoplimab is 4 mg/kg administered as an intravenous infusion once a week (b) (4). On October 15, 2021, the Agency issued a Complete Response Letter (CRL). On March 26, 2025, the Applicant submitted a complete response to the CRL, seeking approval for narsoplimab for the treatment of patients with hematopoietic stem cell transplantation thrombotic microangiopathy (TA-TMA). For the purposes of this review, narsoplimab-wuug will be referred to as narsoplimab.

The basis of the CR was that the data submitted as part of the original BLA failed to demonstrate substantial evidence of effectiveness for narsoplimab for the proposed indication. For details regarding the specific review issues identified during initial review and contributing to the decision to issue a CRL see Section 0. For complete details of the original review see summary review uploaded to DARRTS on October 15, 2021. For a brief summary of the regulatory history see Section 2 of this review.

New information submitted with this resubmission include:

- Response to Deficiencies Cited in the Complete Response Letter, External Control Data, and Summary
- Compassionate Use Expanded Access Data which included pediatric patients

On May 20, 2025, and May 27, 2025, the Applicant submitted new data from the external control, which included individual patient data registered on the Kyoto Stem Cell Transplantation Group (KSCTG) registry. This data had not been previously submitted to or reviewed by the Agency, on July 10, 2025; therefore, the Agency notified the Applicant that these submissions constituted a major amendment to the application and that the goal date would be extended by three months to the current PDUFA date, in order to provide time for a full review of the new data.

Based on the data included with this resubmission, the entire multidisciplinary review team recommends approval of narsoplimab for the treatment of adult and pediatric patients two years of age and older with hematopoietic stem cell transplant-associated thrombotic

microangiopathy (TA-TMA). The proposed dosing regimen is:

- Greater than or equal to 50kg: 370mg by intravenous infusion over 30 minutes once weekly. Increase frequency to twice weekly if there is inadequate improvement in TA-TMA signs and symptoms.
- Less than 50kg: 4mg/kg by intravenous infusion over 30 minutes once weekly. Increase frequency to twice weekly if there is inadequate improvement in TA-TMA signs and symptoms.

1.2. Conclusions on the Substantial Evidence of Effectiveness (SEE)

Substantial evidence of effectiveness (SEE) of narsoplimab in adults with TA-TMA was established based on one adequate and well controlled clinical investigation with confirmatory evidence. The adequate and well-controlled investigation is Study OMS-721-TMA-001 (Study TMA-001). Confirmatory evidence was provided by efficacy data from patients treated under an expanded access program for whom patient level data was available (EAP Subgroup 1).

Study TMA-001 is a single-arm, multicenter trial of narsoplimab in adult patients with TA-TMA, with a control provided by a historical comparator rate in untreated patients based on the literature.

Study TMA-001 enrolled 28 patients with TA-TMA if they had diagnosis of TA-TMA that persisted at least 2 weeks following modification or discontinuation of treatment with calcineurin inhibitors (CNI) or at least 30 days after transplantation, with platelet count $<150,000/\mu\text{L}$, evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH $>$ upper limit of normal (ULN), or haptoglobin $<$ lower limit of normal), and renal dysfunction. All patients also met criteria for high-risk TMA, based on the high-risk criteria as defined by recent proposed consensus guidelines (Schoettler et al., 2023). The primary efficacy endpoint was the proportion of TA-TMA patients who responded to narsoplimab treatment. Treatment response was defined as an improvement in TMA- associated laboratory markers (platelet count and LDH) as well as improvement in clinical status (improvement in organ function at any time point post-baseline during the study or freedom of transfusion).

In Study TMA-001, 17 of 28 patients (61%; 95% CI: 40.6, 78.5) achieved a TMA response. This was compared to a historic response rate of 23.3% (95% CI: 15.1, 34.2), which was based on analysis of 149 patients with TA-TMA identified in the literature who had not received narsoplimab or other pharmacologic treatment for TA-TMA and who had a response in one of the laboratory assessments or a clinical response. The review team concluded that calculating a response rate based on all patients from the selected literature who had not received prior pharmacologic treatment, including those from studies with less stringent response criteria than used in Study TMA-001, would likely overestimate an historic response rate, and therefore could be considered as an acceptable benchmark for study TMA-001 response rate to be

measured against. The TMA-001 response rate of 61% is higher than the selected literature based historic control response rate 23.3% (95% CI: 15.1, 34.2) with non-overlapping confidence intervals.

Confirmatory evidence of effectiveness was demonstrated in 19 patients (13 adult, 6 pediatric) who were treated under the EAP program and for whom patient level data was available (EAP Subgroup 1). The TA-TMA response rate for EAP Subgroup 1 overall was 13/19 (68%), consistent with the findings for the primary endpoint of Study TMA-001.

Substantial evidence of effectiveness for narsoplimab in pediatric patients aged 2 years and older with TA-TMA was based on partial extrapolation of clinical benefit demonstrated in adults. This extrapolation is reasonable given the similarity in the pathophysiology, clinical signs and symptoms, and course of TA-TMA in adults and pediatric patients. Partial extrapolation is supported by response to treatment data from 6 patients in the EAP Subgroup 1 who had baseline disease characteristics and TA-TMA response rates consistent with the adult patients.

Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- TA-TMA is a challenging complication of HSCT associated with significant morbidity and mortality. The complex pathophysiology and multiple contributing factors converge on a final pathway involving endothelial cell injury and complement activation. TA-TMA is characterized by microangiopathic hemolytic anemia, thrombocytopenia, elevated serum lactate dehydrogenase (LDH) and presence of schistocytes on peripheral blood smear. The gold standard for diagnosis is based on characteristic histological tissue findings; however, the high risk for procedural complications and bleeding limits the ability to obtain a tissue diagnosis. - The incidence of TA-TMA varies among studies due to different criteria used for diagnosis. There are several risk factors described in the literature for the development of TA-TMA include older age, female sex, advanced primary cancer disease, unrelated donor transplants, high-dose conditioning regimen, human leukocyte antigen (HLA) mismatch, nonmyeloablative transplants, total body irradiation, calcineurin use, acute graft-versus host disease and infection. - The clinical presentation ranges from mild, self-limited disease to more serious disease involving multi-organ involvement (kidneys, gastrointestinal tract, central nervous system, heart, lung, and serosal surfaces), with severe disease leading to multi-organ failure and death.	TA-TMA is a rare, serious and life-threatening condition. It is a major cause of morbidity and mortality post allogeneic HSCT in both adult and pediatric populations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	TA-TMA has a poor prognosis with mortality rates described in literature in excess of 50% (Schoettler et al., 2023).	
Current Treatment Options	There are no FDA approved therapies for the treatment of TA-TMA. A range of treatments have been used in this condition but none with established efficacy. Therapeutic interventions include removal of the insulting agent, transfusion support, and treating concurrent conditions such as GVHD and infections. While often considered as an initial step in management, modification and/or discontinuation of calcineurin inhibitors and/or sirolimus may not be effective as there is no clear evidence that discontinuation of these agents provides a benefit to patients with TA-TMA. The role of total plasma exchange in TA-TMA remains unclear and is often not beneficial. Off-label therapies such as defibrotide and rituximab have demonstrated variable response rates and have an unclear impact on mortality. Other complement inhibitors such as C5 inhibitors are currently being investigated and frequently used off-label in treatment of TA-TMA.	There are no approved therapies for pediatric or adult patients with TA-TMA. There is an unmet clinical need for an effective approved therapy for patients with TA-TMA.
Benefit	- The benefit of narsoplimab was assessed in a single-arm, externally controlled, open-label study (Study TMA-001), which enrolled 28 patients with TA-TMA who received narsoplimab every week for 4 to 8 weeks. The primary endpoint was response rate, which was defined as improvement in two laboratory TMA markers (LDH and platelet counts) and either improvement in organ function or independence from transfusions. - In Study TMA-001, 17 of 28 patients (61%; 95% CI: 40.6, 78.5) achieved a TMA response. This was compared to an historic	The submitted data demonstrate substantial evidence of effectiveness on TA-TMA response. The magnitude of response rate to treatment, compared to literature based historic control, demonstrates that narsoplimab is active in this disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	response rate of 23.3% (95% CI: 15.1, 34.2), which was based on analysis of 149 patients with TA-TMA identified in the literature who had not received narsoplimab or other pharmacologic treatment for TA-TMA and who had a response in one of the laboratory assessments or a clinical response. - Confirmatory evidence came from a group of patients treated under an expanded access (EAP). EAP Subgroup 1 comprised 19 patients (13 adults and 6 pediatric) for which there is patient level information, provided. The response definition was consistent with that in Study TMA-001. In total, 13 of 19 patients with TA-TMA (68.4%, 95% CI: 43.4, 87.4) in EAP Subgroup 1 responded to narsoplimab treatment, including 9 of 13 adult patients (69.2%, 95% CI: 38.6, 90.9) and 4 of 6 pediatric patients (66.7%, 95% CI: 22.3, 95.7). - In the 6 pediatric patients with subject level data available, the baseline disease characteristics and TMA response rates were consistent with what was observed in the adult population.	Partial extrapolation of efficacy data from the adult population is adequate to support the pediatric indication in pediatric patients 2 years of age and older with TA-TMA because of similar disease pathophysiology.
Risk and Risk Management	- Primary safety profile is based on data from the 28 patients treated with narsoplimab on 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 who received narsoplimab included, acute kidney injury, confusional state, acute respiratory failure,	The safety database is limited, as would be expected given the size of the affected population, and the lack of concurrent control. All important or frequent adverse events were presumed to be potentially drug-related for the purposes of labeling and risk mitigation, although it is likely that many of the events were caused by the underlying malignancy or chemotherapy. The identified risks can be adequately addressed in labeling. To minimize risk, labeling should

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	neutropenic sepsis, septic shock, pulmonary edema and vomiting. - o Fatal adverse reactions occurred in 7% of patients, including neutropenic sepsis, and septic shock. - o Dosage interruptions due to an adverse reaction occurred in 7% of patients who received narsoplimab include, Escherichia sepsis, pyrexia, pulmonary alveolar hemorrhage, and acute myocardial infarction. - o Serious infections occurred in 10/28 (36%) of patients. Neutropenic sepsis and septic shock occurred in two patients with TA-TMA. - o One patient with aHUS in clinical trials had an adverse reaction of granulomatous orchitis. • Safety data for an additional 221 adult and pediatric patients with TA-TMA who received narsoplimab under a global expanded EAP was reviewed. The safety profile for these patients did not differ from that seen in the overall clinical development program for narsoplimab.	include Warnings and Precautions for serious infections. The risk of serious infections will be further assessed in a registry postmarketing requirement (PMR).

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; TA-TMA, transplant associated thrombotic microangiopathy; CNIs, calcineurin inhibitors; GVHD, graft-versus-host disease; FDA, Food and Drug Administration; EAP, expanded access program; HLA, human leukocyte antigen; ULN, upper limit of normal; rUPCR, urine protein creatine ratio; PMR, postmarketing requirement

1.4. Conclusions and Recommendations

TA-TMA is a rare, serious and life-threatening disease associated with a high mortality rate. There are no approved treatments for this condition in adults or pediatric patients. Thus, TA-TMA represents an unmet medical need.

The benefit of narsoplimab was evaluated in a single-arm, externally controlled, open-label trial (Study TMA-001) of 28 patients with high-risk TA-TMA who received narsoplimab for 4 to 8 weeks, supported by detailed patient-level data for 19 high-risk patients treated under the narsoplimab EAP (EAP Subgroup 1). TMA response, defined as improvement in (i) both of two laboratory TMA markers (LDH levels and platelet counts) and (ii) at least one of two clinical findings, specifically improvement in organ function and freedom from transfusion, was achieved in 17/28 (61%) patients in Study TMA-001 and 13/19 (68.4%) of the EAP Subgroup 1 patients. These results were compared to a threshold based on historical literature review.

The study protocol for Study TMA-001 specified study objectives, enrollment criteria, outcome measures and an analysis plan to evaluate outcomes, which helped inform FDA's determination that the characteristics of an adequate and well-controlled study are present in Study TMA-001.

The primary evidence supporting the safety and efficacy assessment in this resubmission derives from Study TMA-001 submitted with the original BLA along with the new information provided by the Applicant with this submission. Study TMA-001 is a single-arm, multicenter trial of narsoplimab in adult patients with TA-TMA. Study TMA-001 enrolled 28 patients with TA-TMA if they had diagnosis of TA-TMA that persisted at least 2 weeks following modification or discontinuation of CNI treatment or at least 30 days after transplantation with platelet count < 150,000/ μ L, evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > upper limit of normal (ULN), or haptoglobin < lower limit of normal) and renal dysfunction.

During this review, after consideration of the additional submitted data for the 5 patients for which the review team disagreed with the Applicant's assessment as responders during the review of the initial cycle, the Agency verified the Applicant's primary outcome measure assessed as the proportion of patients with TA-TMA who responded to narsoplimab treatment with a response rate of 61% (17/28) with a 95% CI of (40.6 to 78.5).

Although the Applicant did not identify any new literature sources in this resubmission, after additional consideration, the review team concluded that calculating a response rate based on all patients in the non-pharmacologically NPTP group, including those from studies with less stringent response criteria than Study TMA-001, would likely overestimate an historic response rate and therefore, could be considered as a benchmark for Study TMA-001 to be measured against. The TMA-001 response rate of 61% is higher than the selected literature based historic control response rate 23.3% (95% CI: 15.1, 34.2), with non-overlapping confidence intervals.

The Division concludes that there is a treatment effect of narsoplimab in patients with high-risk TA-TMA based on response rate.

Confirmatory evidence is derived from data for 19 patients from the EAP for which there was patient level data and was discussed in Castelli et al (Castelli et al., 2024). (EAP Subgroup 1). Patients in EAP Subgroup 1 were thrombocytopenic, had evidence of microangiopathic hemolytic anemia, and had at least one feature of high-risk TMA. The overall response rate in EAP Subgroup 1 was 68% (13/19) with a 95% CI of (43.4, 87.4). When examined by age, 9 of 13 adult patients (69%; 95% CI: 38.6, 90.9) and 4 of 6 pediatric patients (67%; 95% CI: 22.3, 95.7) were responders. Thus, the overall response rate and for adults and for the pediatric subsets of EAP Subgroup 1 were consistent with the response rate seen in Study TMA-001.

The Sponsor also submitted analysis and data from a subset of patients enrolled on the Kyoto Stem Cell Transplantation Group registry to serve as an external control for survival endpoints. Due to significant limitations with comparability of the KSTG registry, results cannot be used as comparator for survival data to provide primary evidence or confirmatory evidence for regulatory decision making. See Section 5.3.6.2 for details.

The safety of narsoplimab was primarily assessed in the 28 patients from Study TMA-001. The 221 patients enrolled in the EAP provided supportive safety data. As expected, based on the mechanism of action (MOA) of the drug, narsoplimab has risk of serious infections. In addition, based on the MOA and literature review, there may be a risk of increased susceptibility to tuberculosis. While no patient in clinical trials with narsoplimab were reported to have a positive mycobacterium culture, one patient developed granulomatous orchitis. No information regarding tuberculosis nor granulomatous orchitis will be included in the label because the patient was found to be culture negative (including for mycobacteria) and the infection resolved without treatment. The long-term risk of serious infections will be further assessed in a PMR.

Pediatric and adult TA-TMA share similar underlying pathophysiology with similar characteristics such as endothelial damage and complement activation after HSCT with similar pattern of organ involvement, microangiopathic anemia. In the 6 pediatric patients with subject level data available, the baseline disease characteristics and TMA response rates were consistent with what was observed in the adult population. Safety data is derived from a total of 97 pediatric patients age less than 17 from the EAP. No new safety signals were observed. Given the similar pathophysiology between adults and pediatric patients reasonable to consider partial extrapolation of efficacy from the adult population to support the pediatric indication in pediatric patients age > 2 with TA-TMA.

The proposed dosing regimen allows for an escalation of dosing frequency. Study TMA-001 studied a once weekly regimen, and the EAP employed a twice weekly regimen of narsoplimab. During the review, the Applicant clarified that once weekly administration is appropriate as the starting regimen, however, given inter-patient variability in disease severity and level of lectin

pathway hyperactivation, increasing the frequency to twice weekly administration may be clinically justified in patients who do not respond adequately to narsoplimab treatment. Although direct evidence showing improvement in patient response escalating from once weekly to twice weekly regimen is not available, from a pharmacodynamic (PD) perspective, a more frequent (e.g., twice weekly) dosing regimen is expected to maintain higher lectin pathway inhibition throughout the inter-dosing interval compared to once weekly regimen. It is also reassuring that the safety profile of a twice weekly regimen employed in the EAP is acceptable ensuring no additional safety risk to patients escalating to a more frequent regimen. Although the typical duration of treatment for TA-TMA is relatively shorter (<10 weeks), as patients are frequently monitored, it is still practically feasible to escalate the dosing frequency based on inadequate treatment response.

Narsoplimab addresses an unmet medical need, as this will be the first FDA-approved drug to treat patients with TA-TMA. The benefit-risk profile is favorable for narsoplimab for the treatment of adult and pediatric (age 2 and greater) patients for the treatment of high-risk TMA.

This application resubmission was reviewed by a multidisciplinary review team. The Applicant has adequately addressed all deficiencies in the CRL. Safety review issues were resolved in the original review of the application, see finalized review in DARRTS on October 15, 2021. Each discipline recommends approval, and the signatory authority concurs that the application should be approved. The overall benefit-risk profile is favorable as described in the Benefit-Risk Framework above.

2. Therapeutic Context

2.1. Analysis of Condition

TA-TMA occurs when endothelial injury and a complex underlying pathophysiology (Meri S et al., 2022), in the context of an allogeneic hematopoietic cell transplantation, causes microangiopathic anemia and platelet consumption leading to microvascular thrombosis and fibrin deposition. TA-TMA may present with new onset of increasing proteinuria, hypertension, elevated serum creatinine and an increase in transfusion requirements with evidence of intravascular hemolysis. TA-TMA survival rates vary in the reported literature due to different diagnostic criteria, heterogeneous populations in terms of severity, index dates (e.g. date of HSCT, date of diagnosis of TMA) and other factors. Some patients will have a self-remitting course but more than one-half of patients will progress to multi-organ failure with mortality rates of greater than 50% at 1 year post-HSCT (Schoettler, 2022) with some literature citing mortality rates for severe TA-TMA exceeding 80% (Jodele et al., 2024, Acosta-Medina et al., 2025, Cho et al., 2008) and reported non-relapse mortality at 42% for patients identified with severe TA-TMA (Vasu et al., 2025).

2.2. Available Therapy

There are no FDA approved products for the treatment of TA-TMA. The first line of treatment is generally limited to supportive therapy. Initial first line therapy has included withdrawal or minimization of CNIs (i.e. sirolimus, tacrolimus, or both) as these agents have been implicated as risk factors although there is ongoing debate as to whether withdrawal is beneficial. Additional measures include treatment of infections, GVHD and aggressive hypertension management. Off-label medications such as rituximab¹, defibrotide² and complement inhibitors such as C5 inhibitors (ravulizumab³, eculizumab⁴) have emerged as potential therapeutic agents in TA-TMA.

¹Rituximab is CD20 directed cytolytic antibody indicated for the treatment of adult patients with Non-Hodgkins Lymphoma, adult patients with chronic lymphocytic leukemia, rheumatoid arthritis in combination with methotrexate in adult patients, granulomatosis with polyangiitis and microscopic polyangiitis in adult and pediatric patients 2 years of age and older, moderate to severe pemphigus vulgaris in adult patients.

² Defibrotide is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD).

³ Ravulizumab is a complement inhibitor indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome.

⁴ Eculizumab is a complement inhibitor indicated for the treatment of patients with PNH, treatment of patients with aHUS, treatment of generalized myasthenia gravis in adult patients, treatment of neuromyelitis optica spectrum disorder in adult patients.

3. Regulatory Background

On November 17, 2020, Omeros Corporation submitted an original BLA for narsoplimab for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). The Applicant received a Complete Response Letter (CRL) on October 15, 2021.

Key regulatory issues discussed with the Applicant in meetings prior to the October 15, 2021, CRL are described in the BLA 761152 clinical review dated October 15, 2021.

Table 1 describes the regulatory meetings with the Sponsor from October 15, 2021, until the submission of the response to the CRL with more detailed summaries in the Appendix (Section 14.5).

Table 1. Summary of Regulatory Meetings from October 15, 2021, to date of current submission

Date	Meeting Type	High Level Summary
April 30, 2025	Applicant-requested	Discuss Incomplete Response letter issued April 28, 2025
September 5, 2024	Type B Post-action	Review planned content for the resubmission
May 11, 2023	Type B Post-action	Resubmission plans and clinical contents
July 15, 2022	Type A Formal Dispute Resolution	Formal dispute resolution concerning the October 15, 2021, Complete Response letter
February 9, 2022	Type A Guidance	Discuss the Complete Response Letter (CRL)

Source: FDA Reviewer

4. Approach to Review of the Resubmission for Efficacy

In this resubmission, the Applicant included the original efficacy data from Study TMA-001 along with efficacy data (response and survival) for 19 patients treated on the EAP for whom there were patient-level data (EAP Subgroup 1), efficacy data (survival) for 221 patients treated on the EAP (EAP Subgroup 2), and data from 121 patients with TA-TMA who did not receive narsoplimab from the Kyoto Stem Cell Transplantation Group (KSCTG) registry intended to provide a comparator group for the survival endpoints. In addition, the Applicant provided additional data for the 5 responders from the original submission who were assessed by the Agency as non-responders in the original review.

The approach to the review consisted of the following:

1. Evaluate evidence of benefit based on primary endpoint of response rate:
 - a. Reviewed and assess Sponsor's rationale for the 5 disputed responders in Study TMA-001 and re-adjudicate the Divisions assessment.
 - b. Reviewed the literature based historic response rate.
 - c. Analyzed data for EAP Subgroup 1 for response rate.
 - d. Integrated efficacy analysis data from TMA-001 and EAP Subgroup1 for the primary response endpoint.
 - e. Provided overall summary and conclusions for the primary endpoint.
2. Evaluate evidence of benefit based on survival data:
 - a. Analyzed survival data for TMA-001, EAP Subgroup 1, and Pooled (TMA-001 + EAP Subgroup 1), and EAP Subgroup 2.

- b. Assessed KSCTG registry and analysis of 1 year survival and Day 100 survival for adequacy as external control for survival endpoints for the TMA-001 and EAP Subgroup 1 populations.
- c. Provided overall summary and conclusions for the overall survival endpoints.

5. Evidence of Benefit

5.1.Sources of Data

5.1.1. Study TMA-001

Study TMA-001 is a single-arm, open-label study in which 28 patients with TA-TMA received narsoplimab once weekly for a median of 8 weeks (range: 2-16). In total, 24 patients received narsoplimab 4 mg/kg intravenously once weekly and 4 patients received narsoplimab 370 mg intravenously once weekly. Key inclusion criteria were a diagnosis of TA-TMA that persisted at least 2 weeks following modification or discontinuation of treatment with calcineurin inhibitor (CNI) or at least 30 days after transplant with platelet count $<150,000/\mu\text{L}$, evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH $>$ upper limit of normal (ULN), or haptoglobin $<$ lower limit of normal), and renal dysfunction.

The primary efficacy endpoint was the proportion of TA-TMA patients who responded to narsoplimab treatment. There were several secondary endpoints to include 100day survival from date of TMA diagnosis and overall survival from the date of TMA diagnosis. For a full list of all the secondary endpoints, refer to the initial review date October 15, 2021 in DARRTS.

Efficacy data from TMA-001 was analyzed for the response (primary) and survival endpoints.

5.1.2. Compassionate Use Expanded Access Program (EAP)

The single patient expanded access treatment plan (EAP; also known as a compassionate use plan) provides patients access to the investigational product narsoplimab. The purpose of the EAP is to provide access to patients with TA-TMA who are not able to participate in a study and who may benefit from treatment based on the medical judgment of their respective physicians. This is an uncontrolled, case-by-case patient EAP. Dosing for patients ≥ 50 kg is narsoplimab 370 mg initially twice weekly and for at least 8 weeks. Dosing for patients ≤ 50 kg is 4 mg/kg initially twice weekly and for at least 8 weeks. Change in dose frequency is determined by treatment response.

The treatment course included the following parameters and measurements:

- Terminate treatment after 8 weeks if the patient has not demonstrated improvement in at least platelet count or LDH defined for each as return to pre-TMA baseline level.

- Reduce treatment frequency to once weekly when the patient achieves all of following:
 - o Platelet count return to pre-TMA level
 - o LDH return to pre-TMA level
 - o Reduction of platelet and red blood cell transfusions to their respective pre-TMA frequencies
 - o Urine protein/creatinine ratio (uPCR) < 2.0
 - o Resolution of reversible TMA-related neurological abnormalities (e.g., headache, seizure, hallucination, or confusion) or stabilization of irreversible neurological abnormalities (e.g., stroke deficits)
 - o Resolution of TMA-related gastrointestinal signs and symptoms
 - o Age-appropriate control of blood pressure on ≤ 2 anti-hypertensive medications.
- Discontinue treatment when the patient maintains all of the above criteria for 2 weeks while receiving narsoplimab once weekly.
- The patient will be retreated according to the original treatment regimen if they experience a relapse of TMA that includes organ dysfunction.

Patient Eligibility

Main Inclusion Criteria

1. Patient (adult or pediatric) must have undergone allogeneic or autologous hematopoietic stem cell transplant (HSCT).
2. Patient, parent or legal guardian must be capable of understanding and complying with the treatment protocol.
3. Patient must be capable of understanding an informed consent form (ICF) or the parent or legal guardian of the patient is able to understand and sign a written ICF prior to the initiation of any treatment procedures.
4. Patient, parent or legal guardian must voluntarily provide informed consent in accordance with local regulations and governing ethics committee requirements prior to any procedures or evaluations performed specifically for the sole purpose of the program
5. If sexually active and of childbearing potential, the patient must agree to practice a highly effective method of birth control throughout treatment with narsoplimab and for at least 12 weeks after the last dose of the drug, such birth-control method defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence (abstinence is acceptable when it is in line with the patient's medical condition or preferred and usual lifestyle and is defined as complete abstinence of sexual intercourse, not periodic abstinence or withdrawal), or vasectomized partner.
6. Patient must have TA-TMA defined as having thrombocytopenia and evidence of microangiopathic hemolytic anemia.

7. Based on the physician's judgement, other treatment options or clinical trials in TA-TMA are deemed unsuitable.

Main Exclusion Criteria

1. Patient has a clinically significant viral, bacterial, or fungal infection not controlled with antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care is allowed).
2. Patient has malignant hypertension (diastolic blood pressure [BP] > 120 mm Hg [for pediatric patients BP > 99th percentile + 5 mm Hg] with bilateral hemorrhages or "cottonwool" exudates on funduscopic examination).
3. Patient is pregnant or lactating.
4. Patient has a known hypersensitivity to any constituent of the product.
5. Presence of any condition that the physician believes would put the patient at risk when receiving narsoplimab.

5.1.2.1. EAP Subgroup 1 (Castelli et. al.)

The review team identified an article by the Castelli group (Castelli et al., 2024), which describes a retrospective study that took place between January 2018 and August 2023 in Italy. This retrospective study included 20 patients diagnosed with high-risk TA-TMA who received narsoplimab under the EAP compassionate use program and for whom patient level data was available. One patient was included in both Study TMA-001 and this retrospective study. For analysis of the BLA, this patient was analyzed with Study TMA-001 only. This group of patients, referred to as EAP Subgroup 1, comprises 19 patients (13 adult and 6 were pediatric).

The retrospective Castelli study (EAP Subgroup 1) defined high-risk as "the presence of at least one of the following poor prognostic features: (1) rUPCR (urine protein creatinine ratio) ≥ 1 mg/mg; (2) the presence of organ dysfunction; (3) LDH levels exceeding two times the ULN; (4) concurrent grade II–IV acute graft-versus-host disease (GvHD); (5) concurrent infections (bacterial or viral)". This is slightly different than the definition in study TMA-001, in which high-risk was defined as having at least one of the following (1) LDH $\geq 2\times$ upper limit of normal (ULN), (2) presence of infection, (3) acute GvHD Grade II-IV, and (4) evidence of organ dysfunction. However, a patient with the presence of any one of these features can be considered as having high-risk TA-TMA per Schoettler et al.

For the EAP Subgroup 1, the Applicant provided TMA response results based on two criteria: 1) TMA response using the TMA-001 study response criteria and 2) TMA response as determined by Castelli investigators' opinion regarding whether the patient's TMA signs/symptoms improved/resolved following narsoplimab treatment. The response assessments were identical for the two criteria. For this review, we report the results from analysis based on the criteria used in TMA-001.

The EAP Subgroup 1 was also analyzed for the survival endpoints (overall survival and Day 100 survival) and results described in Section 5.3.3.

5.1.2.2. EAP Subgroup 2

The Applicant also submitted high level data for all 221 patients treated in the EAP as of March 31, 2025, referred to as EAP Subgroup 2, which included with 124 adults and 97 pediatric (defined as < 17 years of age) patients. This group includes the patients in EAP Subgroup 1. Refer to Section 5.1.2 for overall description of the EAP. The EAP subgroup was analyzed for survival data. Refer to Section 4.3 for discussion on survival.

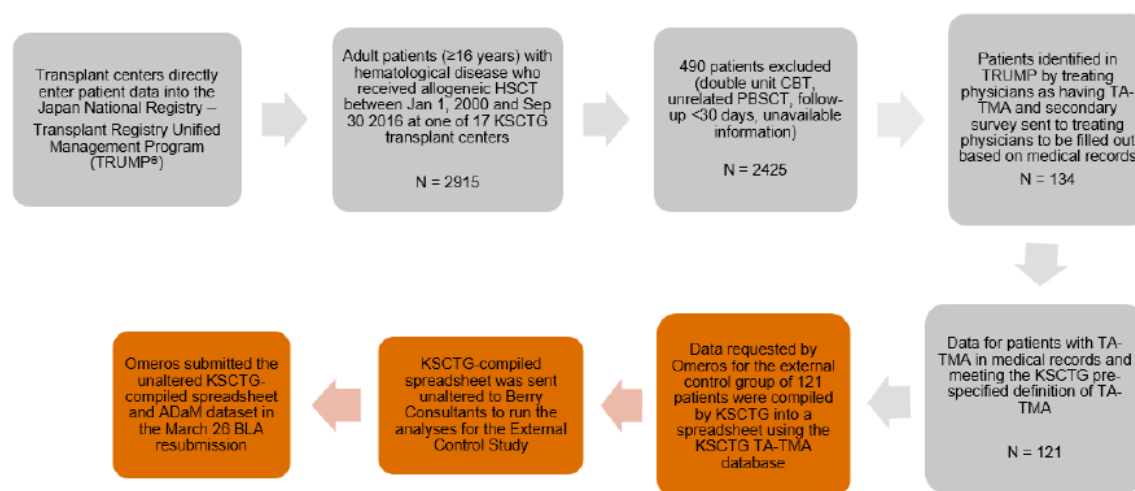
5.1.3. Kyoto Stem Cell Transplantation Group (KSCTG) registry

With the resubmission, the Sponsor submitted new clinical information which included data from the Kyoto Stem Cell Transplantation Group (KSCTG) registry intended to serve as an external control dataset for Study TMA-001 for survival endpoints. The KSCTG is a multicenter collaboration of transplantation centers across Japan which collects detailed clinical information on patients undergoing allogeneic and autologous hematopoietic stem cell transplantation (HSCT). The registry includes patient demographics, disease characteristics, treatment details, and key outcomes such as graft-versus-host disease, relapse, and survival. The KSCTG registry draws its foundational data from Japan's national Transplant Registry Unified Management Program (TRUMP), which systematically collects standardized HSCT data across Japan and captures over 1,000 discrete data elements related to clinical outcomes.

The external control dataset of patients with transplantation-associated thrombotic microangiopathy (TA-TMA) was derived through the following systematic process. KSCTG investigators accessed TRUMP data for 2,915 adult patients who received allogeneic HSCT between January 2000 and September 2016 at 17 KSCTG-affiliated institutions. After applying predefined exclusion criteria, the cohort was refined to 2,425 patients, of whom 134 were flagged by treating physicians as having TA-TMA. Through a secondary survey process involving standardized questionnaires sent to treating physicians and subsequent medical record verification, 121 patients were confirmed to have documented evidence of TA-TMA diagnosis in their medical records and met the predefined diagnostic criteria established by KSCTG investigators, forming the final external control cohort for the comparative analysis. The data flow for the efficacy dataset is shown in

Figure 1

Figure 1. Data Flow for the Efficacy Dataset



Source: Applicant's response dated May 20, 2025, to FDA information request

The Applicant submitted the KSCTG registry dataset comprising 2,425 HSCT patients, among whom 134 were flagged with “Possible TMA Diagnosis”, and 121 were labeled as “Confirmed TMA Diagnosis”. The Applicant stated that all patients included in the KSCTG TA-TMA database had been confirmed and documented to have TA-TMA by KSCTG investigators before the Applicant became involved with the KSCTG. The Applicant also stated that that they had no role in either the identification of the 134 “possible TMA” patients within the TRUMP registry or in the confirmation process that resulted in the final 121 patients included in the KSCTG TA-TMA database. The external control population comprised the 121 patients with confirmed TA-TMA.

The KSCTG registry data was evaluated for adequacy as an external control for the TMA-001 and the EAP Subgroup 1 survival endpoints. This analysis and interpretation of data is presented in Section 4.3.6.

5.1.4. Applicant's Summary Report of Literature to Provide External Control for Response for Study TMA-001

In the initial BLA submission, the Applicant proposed a benchmark response rate of 15% in patients with TA-TMA who did not receive narsoplimab to be used as an external control for the primary endpoint. This was based on the Applicant's discussions with clinical experts on TA-TMA. The Applicant's rationale was not acceptable, and FDA requested additional data to justify this 15% response rate to serve as a reference rate for Study TMA-001.

The Applicant submitted their response, which included a summary report¹ based on a literature search. The retrospective study population included on HSCT-TMA patients age ≥ 18 who had identifiable patient-level data and had data including (i) a response in at least one of the primary response variables used in the TMA-001 study (platelet count, lactate dehydrogenase [LDH], organ function or transfusions) or (ii) report of response AND at least 1 risk factor present in the narsoplimab pivotal trial patients (i.e., GVHD, neurological dysfunction, infection, pulmonary dysfunction, renal dysfunction, gastrointestinal dysfunction, relapse or persistence of underlying malignancy). Excluded from the study were patients who had received eculizumab and/or defibrotide therapy. The report included a description of the demographic and baseline reported risk factors e.g., GVHD, renal dysfunction, neurological dysfunction, along with analysis of the literature-reported frequency of TA-TMA improvement/resolution. This was provided for all patients who met the eligibility criteria ((AP group) and for a subset of patients who had not received any pharmacological treatment (non-pharmacologically treated patients or NPTP group). The report included 35 studies, 25 of which included patients (N=149) in the NPTP group.

Because the literature reports a variety of response criteria, which are not as rigorous as the response endpoint used in Study TMA-001, the Applicant analyzed the criteria according to a definition of stringency i.e., less stringent or equally stringent compared to the TMA-001 criteria, or incomplete. A meta-analysis was performed using a random-effect logistic regression model with the selected studies as the random effect to estimate the overall response rate and the corresponding 95% CI.

The review team identified several significant limitations to the Applicant's literature-based review, including unknown validity and accuracy of data, potential measurement errors associated with endpoints (response rates), propensity score analysis performed on limited confounding variables, timing of treatment visits not standardized across different publications, study conducted using convenience samples and likely selection bias affecting generalizability of the results. Therefore, during the first submission, the review team determined the literature-based review could not be considered sufficient to estimate response rate in an untreated group.

¹ Report on Hematopoietic Stem Cell Transplant-associated Thrombotic Microangiopathy Literature review: Data Extraction, Analysis, and Interpretation; Omeros Corporation, BLA 761152, April 23, 2021.

For the resubmission, the Applicant conducted a new literature review covering publications from 2000-2020 to identify patients with TA-TMA with individual patient-level data and response outcomes, along with an updated search extending from January 2021 to August 2025. However, this new search did not identify any additional studies with necessary patient-level data on TMA response.

For review of this resubmission, the Division re-evaluated the data from the literature and a reasonable historic external control was identified for use as a comparator for response endpoint for Study TMA-001 and EAP Subgroup 1. This is discussed in Section 4.2.1.

5.2. Analysis of Primary Efficacy Endpoint: TMA Response

The primary efficacy endpoint was the proportion of TA-TMA patients who responded to narsoplimab treatment. Treatment response was defined as both an improvement in TMA-associated laboratory markers (Requirement 1): platelet count and LDH, as well as improvement in clinical status (Requirement 2): either improvement in organ function (renal, pulmonary, GI or neurological) at any time point post-baseline during the study or freedom of transfusion defined as no transfusions (RBC, platelet) for at least 4 weeks from the last transfusion except for patients who died within 4 weeks of the last transfusion. Improvement in organ function was determined by a clinical review of the data by the local site investigators. See the original clinical review in DARRTS dated October 15, 2021, for a detailed description of the study design and statistical analysis plan.

5.2.1. Literature Review for External Control for Response Rate

To provide an external historic control, the Applicant performed a literature-based study, is described in Section 5.1.4. As previously noted, the Applicant performed analysis on all patients (AP) group and for a subgroup of non-pharmacologically treated patients (NPTP), and within each of these groups an analysis based on comparability to the TMA-001 response criteria (i.e., all criteria, less stringent, equally stringent). These results are provided in Table 19 of the original integrated review for BLA 761152. To remove potential effect of other pharmacological treatments, the Division considered the NPTP group to most closely match the enrolled population in TMA-001.

Using a liberal response definition that identified patients as responders if they met any of the TMA-001 response criteria (rather than requiring improvement in both laboratory markers plus clinical benefit), the response rate in the non-pharmacologically treated patient (NPTP) group was 23.3% (95% CI: 15.1, 34.2). Although an analysis was performed for the subgroup of studies that used a response criterion that was equally stringent as that used in the TMA-001 study, the calculated response rate was higher than in the less stringent group, which would

not be expected. This is most likely due to chance as this subgroup (NPTP-equally stringent) included only 6 studies with a total of 56 patients. The review team chose to use the response rate calculated for the NPTP-all studies, which includes 25 studies and 149 patients, for the comparison historic external control response rate, noting this definition likely overestimates the response rate compared to what would be obtained using the rigorous study criteria.

5.2.2. Study TMA-001

During the initial review of the application, there were 5 patients whom the Applicant considered responders but whom the review team adjudicated as non-responders. The review team re-analyzed the data for these 5 patients, incorporating additional information for each patient provided by the Applicant in the resubmission. Our original assessment and re-assessment for each of these patients is detailed in Appendix 16.6. The re-assessment incorporated key concepts from a proposed consensus diagnostic criteria and prognostic criteria for TA-TMA published since the initial review (Schoettler et al., 2023). The article defines a group of high-risk TA-TMA patients based on the presence of several poor prognostic factors. All patients (N=28) in Study TMA-001 met at least one of the high-risk criteria for TA-TMA per the proposed consensus diagnostic criteria. See Appendix 14.6 for summary of proposed definition for high-risk TA-TMA.

After careful review, the review team amended its original assessment of response for each of these patients to “responder”. Reasons include:

- Response criteria 1 requirement of demonstration of improvement for both platelets and LDH excluded patients who had not had platelet engraftment as potential responders. For patients who did not have patient engraftment, only LDH response was required to satisfy response criteria 1.
- The medical complexity of these patients, including use of agents that potentially confounded evidence of response, necessitates closer review of exposure timelines for narsoplimab and concurrent agents. In the re-assessment, the review team considered for each case, the likelihood of the concurrent drug contributing to the observed response rather than applying an assumption of contribution.

The Division therefore concludes that response was achieved in 17/28 in Study TMA-001 yielding a response rate of 61% with a 95% CI of (40.6, 78.5), the same results the Applicant reported.

5.2.3. EAP Subgroup 1

TMA Response was assessed in the EAP 1 subset using the same definition as used in Study TMA-001: Improvement in both of two laboratory TMA markers (LDH and platelet counts) and either improvement in organ function or independence from transfusions.

Improvement in platelet count was defined as:

- For baseline platelet count $\leq 20,000/\mu\text{L}$: (i) ≥ 3 -fold increase in platelet count, (ii) post-baseline platelet count $> 30,000/\mu\text{L}$, and (iii) receipt of no platelet transfusions within 2 days prior to the platelet count assessment.
- For baseline platelet count $> 20,000/\mu\text{L}$: (i) $\geq 50\%$ increase in platelet count, (ii) platelet count $> 75,000/\mu\text{L}$, and (iii) receipt of no platelet transfusions within 2 days prior to the platelet count assessment.

Improvement in LDH was defined as $\text{LDH} < 1.5 \times \text{ULN}$.

Results for the primary response endpoint overall and by component for the EAP Subgroup 1 are summarized in Table 2. The overall response rate in the EAP Subgroup 1 was 68% (13/19) with a 95% CI of (43.4, 87.4). The point estimates were similar in adults (N=13) with a 69% response rate (95% CI: 38.6, 90.9) and in pediatric (< 17 years of age) patients (N=6) with a 67% response rate (95% CI: 22.3, 95.7).

Table 2. Primary Response Endpoint overall and by component for the EAP Subgroup 1

	Adult N=13	Pediatric ¹ N=6	Overall N=19
TMA response, n (%) 95% CI (Clopper–Pearson)	9/13 (69) (38.6, 90.9)	4/6 (67) (22.3, 95.7)	13/19 (68) (43.4, 87.4)
Improvement in TMA markers n (%)	9/13 (69)	4/6 (67)	13/19 (68)
Platelet count	9/13 (69)	4/6 (67)	13/19 (68)
LDH	11/13 (85)	5/6 (83)	16/19 (84)
Improvement in organ function n (%)	11/13 (85)	5/6 (83)	16/19 (84)
Freedom from transfusion n (%)	9/13 (69)	3/5 (60)	12/19 (63)

Source: FDA Analysis

¹ Pediatric defined as < 17 years of age

5.2.4. Analysis, TMA-001 and EAP Subgroup 1, Response

Although the baseline characteristics, risk stratification factors and TMA response metrics were similar between the EAP Subgroup 1 and the TMA-001 study, there were differences in dosing and use of CNIs limiting a comprehensive integrated analysis for labeling purposes.

5.2.4.1. Population

As seen in the tables (Table 3 and Table 4), the demographics and baseline disease characteristics are similar between these TMA-001 and the EAP Subgroup 1 patients. In addition, patients in both TA-TMA 001 and the EAP 1 subgroup had at least one feature of high-risk TMA as described by Schoettler et al.

Table 3. Demographics, TMA-001, EAP Subgroup 1

Characteristic ¹	TMA-001 N = 28	EAP subset		Overall Adults N = 41	Overall N = 47
		Adult N = 13	Pediatric ² N = 6		
Age (years)					
n	28	13	6	41	47
Mean (SD)	48 (13.3)	55.5 (15.2)	10.3 (4.5)	50.3 (14.2)	45.2 (19)
Median	48	62	10.5	51	48
Min, max	22, 68	19, 71	5, 15	19, 71	5, 71
Sex					
Female	8 (28.6%)	8 (61.5%)	4 (66.7%)	16 (39%)	20 (42.6%)
Male	20 (71.4%)	5 (38.5%)	2 (33.3%)	25 (61%)	27 (57.4%)
Ethnicity					
Hispanic or Latino	2 (7.1%)	-	-	2 (4.9%)	2 (4.3%)
Not Hispanic or Latino	26 (92.9%)	-	-	26 (63.4%)	26 (55.3%)
Unknown	-	13 (100%)	6 (100%)	13 (31.7%)	19 (40.4%)
Race					
Asian	7 (25%)	-	-	7 (17.1%)	7 (14.9%)
Black Or African American	2 (7.1%)	-	-	2 (4.9%)	2 (4.3%)
Native Hawaiian or Other Pacific Islander	1 (3.6%)	-	-	1 (2.4%)	1 (2.1%)
White	17 (60.7%)	-	-	17 (41.5%)	17 (36.2%)
Other	1 (3.6%)	-	-	1 (2.4%)	1 (2.1%)
Unknown	-	13 (100%)	6 (100%)	13 (31.7%)	19 (40.4%)
Baseline weight (kg)					
n	28	0	0	28	28
Mean (SD)	75 (21.5)	-	-	75 (21.5)	75 (21.5)
Median	69	-	-	69	69
Min, max	51, 134.1	-	-	51, 134.1	51, 134.1
Time from transplant to TMA diagnosis (days)					
n	28	13	6	41	47
Mean (SD)	121 (108.8)	147.6 (134.8)	128.7 (89.2)	129.4 (116.6)	129.3 (112.7)
Median	73.5	81	119.5	76	78
Min, max	21, 436	30, 452	24, 246	21, 452	21, 452
Time from transplant to first treatment (days)					
n	28	13	6	41	47
Mean (SD)	145.4 (108.4)	152.4 (134.4)	148.5 (103.9)	147.6 (115.6)	147.7 (113.1)
Median	119	84	148	92	104
Min, max	33, 444	31, 454	24, 298	31, 454	24, 454

Source: Statistical review team analysis based on submitted data.

¹ Categorical variables presented as n (%)

² Pediatric defined as < 17 years of age

Table 4. Baseline Patient Characteristics, TMA-001, EAP Subgroup 1

Parameter	TA-TMA-001 (N = 28)	EAP Subgroup 1 (N = 19)		Overall (N= 47)
		Pediatric (N = 6)	Adult (N = 13)	
Elevated LDH $\geq$ 2x ULN, n (%)	20 (71%)	6 (100%)	7 (54%)	33 (70%)
Grade II-IV acute GvHD, n (%)	19 (68%)	5 (83%)	11 (85%)	35 (74%)
Organ dysfunction				
Renal dysfunction at baseline, n (%)	21 (75%)	5 (83%)	13 (100%)	39 (83%)
Pulmonary dysfunction at baseline, n (%)	5 (18%)	0 (0%)	2 (15%)	7 (15%)
Neurological dysfunction at baseline, n (%)	16 (57%)	2 (33%)	4 (31%)	22 (47%)
Infection, n (%)	24 (86%)	6 (100%)	8 (62%)	38 (81%)

Source: Statistical review team analysis based on d_pool.xlsx" dataset submitted in Applicant's IR response.

¹ Categorical variables presented as n (%)

² Pediatric defined as < 17 years of age

5.2.4.2. Response Analysis

In Study TMA-001, 17 of 28 patients (61%; 95% CI: 40.6, 78.5) achieved TMA response. The response in EAP Subgroup 1 was 68% (13/19), with 95% CI (43.4, 87.4). When combining adult patients from both studies, 26 of 41 adult patients (63%; 95% CI: 46.9, 77.9) had a response, and the overall combined analysis of all 47 patients showed a TMA response rate of 64% (95% CI: 48.5, 77.3). Detailed results for each population and the pooled total are presented in Table 5.

	TA-TMA Study (N = 28)	EAP Subgroup 1 (N=19)		Pooled Total Adults (N=41)	Pooled Total (N=47)
		Adult (N=13)	Pediatric (N=6)		
TMA response, n (%) 95% CI (Clopper–Pearson)	17/28 (61%) (40.6, 78.5)	9/13 (69%) (38.6, 90.9)	4/6 (67%) (22.3, 95.7)	26/41 (63%) (46.9, 77.9)	30/47 (64%) (48.5, 77.3)
Improvement in TMA markers	17/28 (61%)	9/13 (69%)	4/6 (67%)	26/41 (63%)	30/47 (64%)
Platelet count	14/23 (61%)	9/13 (69%)	4/6 (67%)	23/36 (64%)	27/42 (64%)
LDH	21/28 (75%)	11/13 (85%)	5/6 (83%)	32/41 (78%)	37/47 (79%)
Improvement in organ function	20/27 (74%)	11/13 (85%)	5/6 (83%)	31/40 (78%)	36/46 (78%)
Freedom from transfusion	12 /25 (48%)	9/13 (69%)	3/5 (60%)	21/38 (55%)	24/43 (56%)

Source: FDA analysis

The response rates from Study TMA-001 (TA-TMA Study) and the response rates for the adult patients in the EAP subgroup 1 are consistent. Due to differences in the dosing of narsoplimab, difference in use of concomitant therapies such as CNIs, between the two groups, no pooled data columns are included in the label.

The Applicant conducted sensitivity analyses using Bayesian methods in response to the Agency's information request (source: Applicant's response dated August 21, 2025).

Their statistical analyses yielded posterior mean estimates for response rates with corresponding 95% credible intervals (CrI) as follows:

- 1) TMA-001 + EAP subgroup 1 (N=47) showed a 64% response rate (95% CrI: 50% to 77%);
- 2) TMA-001 + adult EAP subset (N=41) showed a 63% response rate (95% CrI: 47% to 77%).

In Study TMA-001 and in EAP Subgroup 1, the point estimate and the entire 95% CrI exceeded the conservative literature-based threshold, with posterior probabilities greater than 0.9999. In the EAP Subgroup 1, this was true for both the adult only population and the population overall.

5.2.5. Conclusions Efficacy: Response Endpoint

During this review, after re-adjudication of the 5 patients whom the review team disagreed with the Applicant's assessment as responders during the review of the initial cycle, the Agency verified the Applicant's primary endpoint response rate of 61% (17/28) with a 95% CI of (40.6 to 78.5) from Study TMA-001.

Although the Applicant did not identify any new literature sources in this resubmission, after additional consideration, the review team concluded that calculating a response rate based on all patients in the NPTP group, including those from studies with less stringent response criteria than Study TMA-001, would likely overestimate an historic response rate, and therefore could

be considered as a benchmark for study TMA-001 to be measured against. The TMA-001 response rate of 61% is higher than the selected literature based historic control response rate 23.3% (15.1, 34.2) with non-overlapping confidence intervals. The Division concludes that there is a treatment effect of narsoplimab in patients with TA-TMA based on response rate.

The response rate in the EAP Subgroup 1 (68% [95% CI: 43.4, 87.4]) is consistent with that observed in Study TMA-001 and is internally consistent for pediatric and adult subgroups.

5.3. Survival Endpoints

Overall survival (OS) was defined as the time from first dose of narsoplimab to death. Patients who were alive at the time of analysis were censored at the date of last follow-up. Kaplan-Meier (KM) estimates were used to summarize OS for the overall population, as well as for adult and pediatric subgroups. Survival probabilities at 100 days and 1 year were estimated with 95% confidence intervals (CIs) using the log-log transformation.

5.3.1. Statistical Methods for Evaluating Survival, Study TMA-001 and EAP Subgroups

Overall survival was defined as the time from a specified index date to death, with multiple index dates considered, including time of first dose of narsoplimab, time of TMA diagnosis, and time of HSCT. Survival rates at day 100 and 1 year were estimated using the Kaplan-Meier method and the corresponding 95% confidence intervals were calculated using the log-log transformation. Results are presented for all considered index dates.

5.3.2. Study TMA-001

For the full analysis population in Study TMA-001 (N=28), the estimated survival probability was 73.4% (95% CI: 52.2, 86.4) at day 100 and 41.0% (95% CI: 21.9, 59.2) at 1 year from the date of TMA diagnosis.

Time to event endpoints are difficult to interpret in single-arm trials as lack of a concurrent control group introduces bias, making it hard to isolate the survival effect. Therefore, the survival results from Study TMA-001 are descriptive and were not used to make regulatory decision regarding the treatment effect of narsoplimab on survival.

5.3.3. EAP Subgroup 1

- Overall population (N=19): The estimated survival probability was 73.7% (95% CI: 47.9, 88.1) at 100 days and 73.7% (95% CI: 47.9, 88.1) at 1 year.

- Adults (N=13): Survival probability at 100 days was 76.9% (95% CI: 44.2, 91.9) and at 1 year 76.9% (95% CI: 44.2, 91.9).
- Pediatric patients (N=6): Survival probability at 100 days was 66.7% (95% CI: 19.5, 90.4) and at 1 year 66.7% (95% CI: 19.5, 90.4).

All the deaths occurred within 100 days of TMA diagnosis. For the Kaplan-Meier Estimates and Curves, please refer to the Appendix, Section 0.

5.3.4. EAP Subgroup 2

Survival outcome was analyzed for 100 days and 1-year from TA-TMA diagnosis and from first dose of narsoplimab. Results for all patients in the EAP Subgroup 2 and by age group (adult or pediatric) are summarized in Table 6.

The 100-day survival rate from first dose of narsoplimab for all EAP patients was 62.8% (95% CI: 55.3, 69.4) (with a 1-year survival from first dose of 49.6% (95% CI: 41, 57.6)).

Table 6. Efficacy Results: 100 day and 1 Year Survival, EAP Subgroup 2

Survival Rate (95% CI) ¹	Adult N=124 % (95% CI)	Pediatric ² N=97 % (95% CI)	Overall N=221 % (95% CI)
All Patients (N=221)			
100-day survival from TA-TMA diagnosis	64.5 (54.7, 72.8)	79.7 (69.9, 86.6)	71.5 (64.7, 77.2)
100-day survival from first dose	57.2 (46.9, 66.2)	69.9 (58.7, 78.7)	62.8 (55.3, 69.4)
1 year survival from TA-TMA diagnosis	49.6 (38.8, 59.5)	50.8 (37, 63)	50.6 (42.1, 58.4)
1 year survival from first dose	48 (37.1, 58.1)	51 (36.6, 63.6)	49.6 (41, 57.6)

Source: Statistical review team analysis based on "adtte" dataset for EAP Subgroup 2 patients

¹ Confidence intervals calculated using the log-log transformation method

² Pediatric defined as < 17 years of age

Refer to the Appendix Section 0 for the Kaplan-Meier curves for survival for the EAP group.

Several limitations should be considered when interpreting the survival results in the EAP datasets: the EAP was an uncontrolled observational study with voluntary data reporting, leading to substantial missing data (e.g., risk factors for TA-TMA), while TMA-001 followed rigorous standards; the EAP included heterogeneous populations (both allogeneic and autologous transplants, including patients with prior treatment failures) in different countries with variable clinical practices, whereas Study TMA-001 enrolled only patients with allogeneic HSCT; treatment administration was flexible in the EAP with physician-guided dosing compared to TMA-001's standardized protocol; and Study TMA-001 had enrollment period 2015-2019,

while the EAP spanned 2016 and onward potentially introducing temporal bias from evolving clinical practices and differences in prior or concomitant medications.

5.3.5. Survival Analysis: TMA-001/EAP Subgroups

Table 7 shows results of Day 100 survival and 1 year survival with the index date of time of first dose of narsoplimab as well as index dates from time of HSCT and time of TMA diagnosis for Study TMA-001 and EAP Subgroup 1 (N=47) and the pooled group for Study TMA-001/EAP Subgroup 1 as well as for the entire EAP group (n=221)².

Table 7. Summary of 100-day and 1 year survival by different index dates.

Index Date	Dataset	100-day survival % (95% CI)	1-year survival % (95% CI)
Time of first dose of Narsoplimab	TMA-001 (N=28)	61.7 (40.5, 77.3)	41.1 (22.1, 59.3)
	EAP Subgroup 1 (N=19)	73.7 (47.9, 88.1)	73.7 (47.9, 88.1)
	Pooled TMA-001 and EAP Subgroup 1 (N=47)	66.9 (51.2, 78.5)	55.2 (39.4, 68.4)
	EAP Subgroup 2 (N=221)	62.8 (55.3, 69.4)	49.6 (41.0, 57.6)
Time of TMA diagnosis	TMA-001 (N=28)	73.4 (52.2, 86.4)	41.0 (21.9, 59.2)
	EAP Subgroup 1 (N=19)	73.7 (47.9, 88.1)	73.7 (47.9, 88.1)
	Pooled TMA-001 and EAP Subgroup 1 (N=47)	73.7 (58.3, 84.1)	55.2 (39.4, 68.4)
	EAP Subgroup 2 (N=218) *	71.5 (64.7, 77.2)	50.6 (42.1, 58.4)
Time of HSCT	TMA-001 (N=28)	92.9 (74.3, 98.2)	57.9 (36.8, 74.2)
	EAP Subgroup 1 (N=19)	84.2 (58.7, 94.6)	73.7 (47.9, 88.1)
	Pooled TMA-001 and EAP Subgroup 1 (N=47)	89.4 (76.3, 95.4)	64.9 (49.1, 76.8)

Source: FDA analysis

The 95% confidence intervals were calculated using the log-log transformation method.

*Patients with missing index dates were excluded from the survival analysis.

² EAP Subgroup 2 could not be pooled with the TMA-001 or EAP Subgroup 1 due to lack of patient level data. Its separate analysis is included in this table for completeness.

5.3.6. External Control for Survival Endpoints, Kyoto Stem Cell Transplantation Group (KSCTG) registry

For an overview of the KSCTG registry and identification of patients for inclusion in the external control population, see Section 4.3.6

5.3.6.1. Survival Analysis Plan

The statistical analysis for external control comparison focused on the following:

- comparisons between patients from the pooled dataset of TMA-001 and EAP subset (N=47) to KSCTG confirmed TMA patients (N=121)
- comparisons between patients from TMA-001 (N=28) and KSCTG confirmed TMA patients (N=121)

Propensity score–based methods were used to adjust for potential imbalances between cohorts. The propensity score was estimated using logistic regression incorporating the following covariates:

- 1) Age (continuous variable)
 - 2) Sex (binary: 0 = female, 1 = male)
 - 3) Acute GVHD Grade 2-4 (binary: 0 = absent, 1 = present)
 - 4) Infection (binary: 0 = absent, 1 = present)
 - 5) Neurological dysfunction (binary: 0 = absent, 1 = present)
 - 6) Pulmonary dysfunction (binary: 0 = absent, 1 = present)
 - 7) Renal dysfunction (binary: 0 = absent, 1 = present)
 - 8) LDH ≥ 2 times ULN (binary: 0 = no, 1 = yes)
 - 9) Donor mismatch (binary: 0 = matched, 1 = mismatched)
 - 10) Donor relationship (binary: 0 = unrelated, 1 = related)
 - 11) Time from HSCT to TMA diagnosis (discrete variable, days)
- In the Applicant's analysis, the propensity score model only contained the first eight covariates listed above, where covariates 3 – 8 are the risk factors for high-risk TMA (Schoettler et al., 2023). In the Agency's analysis, three additional covariates were added in the propensity score model. Donor mismatch and donor relationship were included given their potential association with TA-TMA development. For time from HSCT to TA-TMA diagnosis, substantial differences were observed between cohorts, with treated patients having considerably later onset (TMA-001: mean 120.8 ± 108.8 days; EAP Subgroup 1: mean 141.6 ± 120.0 days) compared to KSCTG registry controls (mean 51.5 ± 58.7 days). These differences may indicate major differences such as disease patterns, severity, or underlying mechanisms. Therefore, time to TA-TMA diagnosis was included as a covariate to address this imbalance.

The Applicant utilized inverse probability of treatment weighting (IPTW) as the primary analytical approach. During the review, extreme propensity score values (approaching 0 and 1) were observed, which can lead to unstable weight estimates and increased variance. To address this concern and evaluate the robustness of treatment effect estimates, several sensitivity analyses were conducted:

- Propensity score matching (PSM): Both 1:1 and 1:2 matching strategies were implemented, with and without caliper restrictions.
- IPTW with truncation: Weights were truncated at the 1st and 99th percentiles (1% truncation) and at the 5th and 95th percentiles (5% truncation) to reduce the influence of extreme weights.
- Stabilized IPTW: Stabilized weights were calculated to improve the precision of effect estimates while maintaining the benefits of weighting.

These complementary approaches were implemented to evaluate the robustness of the treatment effect estimates and to mitigate bias due to residual covariate imbalance. Survival outcomes were analyzed using Cox proportional hazards regression on the matched dataset for PSM, and weighted Cox regression incorporating the IPW weights for the weighting analyses. Hazard ratios with corresponding 95% confidence intervals and p-values were reported, and Kaplan–Meier plots were generated to visually display survival distributions between groups.

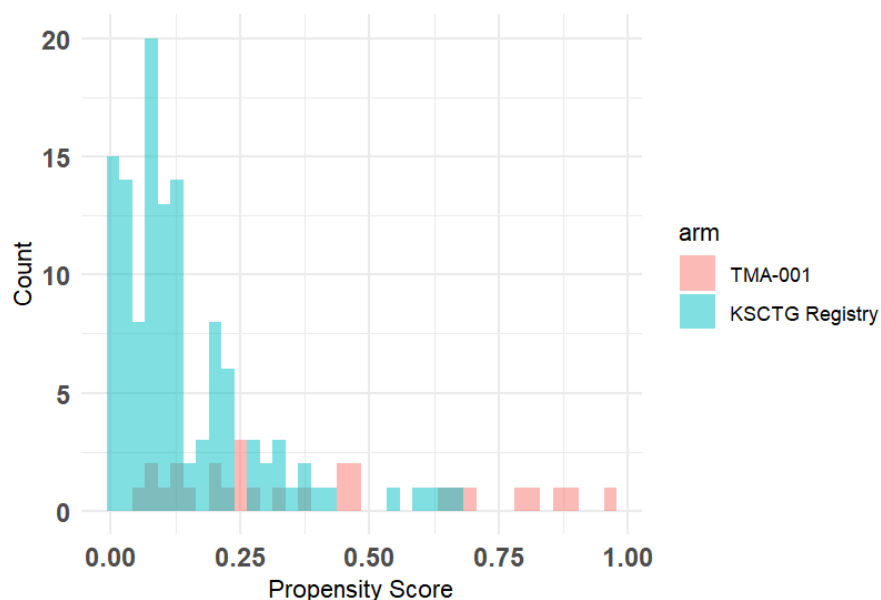
Overall survival was measured in days from the index date; patients alive at the time of analysis were censored at the last follow-up. For patients from study TMA-001 and EAP Subgroup 1 (Castelli et al.), the index date was defined as the first day of narsoplimab treatment. For patients in the KSCTG registry with TA-TMA, a date of first dose of narsoplimab was not applicable. The index date was therefore imputed as the date of TMA diagnosis plus the median time from TMA diagnosis to first dose of narsoplimab observed in the study TMA-001. Additional imputation methods were also applied to ensure the robustness of the final results.

5.3.6.2. Overall Survival Comparison TMA-001 and KTSCG

Results

This section presents the comparison of overall survival between patients from TMA-001 (N=28) and KSTCG confirmed TMA patients (N=121). The distributions of propensity scores are shown in Figure 2Error! Reference source not found.. There was low-to-moderate overlap overall, and a lack of common support was observed in parts of the propensity score distribution. Additionally, some propensity scores were at the extremes, which may indicate a potential violation of the positivity assumption. Similar findings were observed in a propensity analysis performed comparing OS between patients in the pooled TMA-001 and EAP Subgroup 1 dataset and KTSCG and can be found in Appendix, Section .

Figure 2: Distribution of propensity scores of TMA-001 and KSCTG Registry

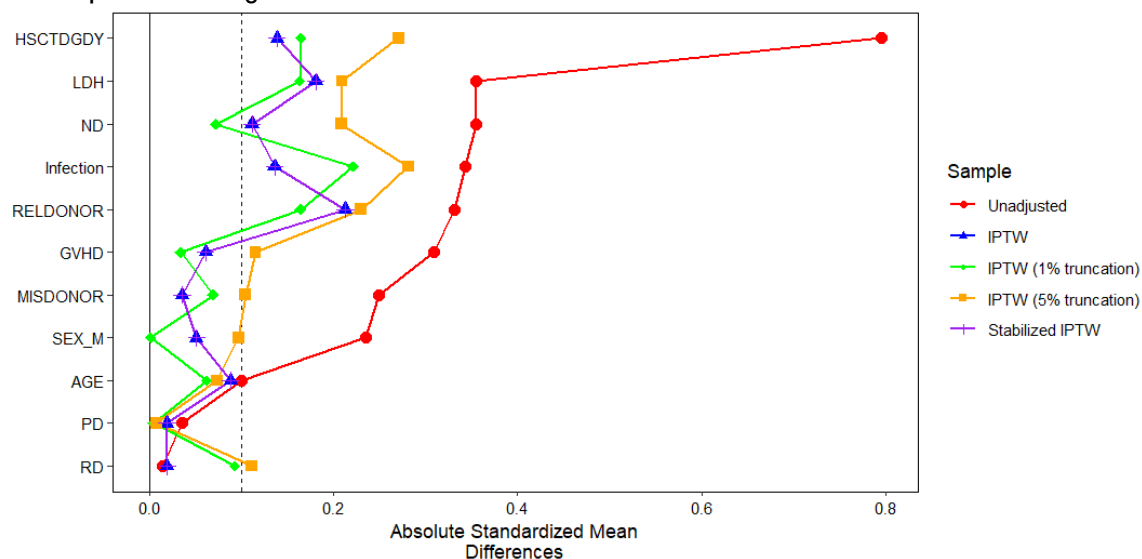


Source: FDA analysis

Standardized mean differences (SMDs) were used to assess covariate balance between groups. The SMD quantifies differences in means or proportions between the treated and external control groups relative to the pooled standard deviation. An absolute SMD less than 0.1 is generally considered to indicate adequate balance. Covariate balance plot for the IPTW-based methods is shown below in

Figure 3. While weighting improved balance for many covariates, a number of covariates still had absolute SMDs above the commonly used threshold of 0.1, such as time from HSCT to TMA diagnosis, neurological dysfunction, LDH ≥ 2 times ULN and infection, indicating some residual imbalance. These remaining imbalances should be considered when interpreting the adjusted results.

Figure 3: Covariate Balance Unadjusted and After IPTW Adjustment (TMA-001 vs KSCTG Registry)

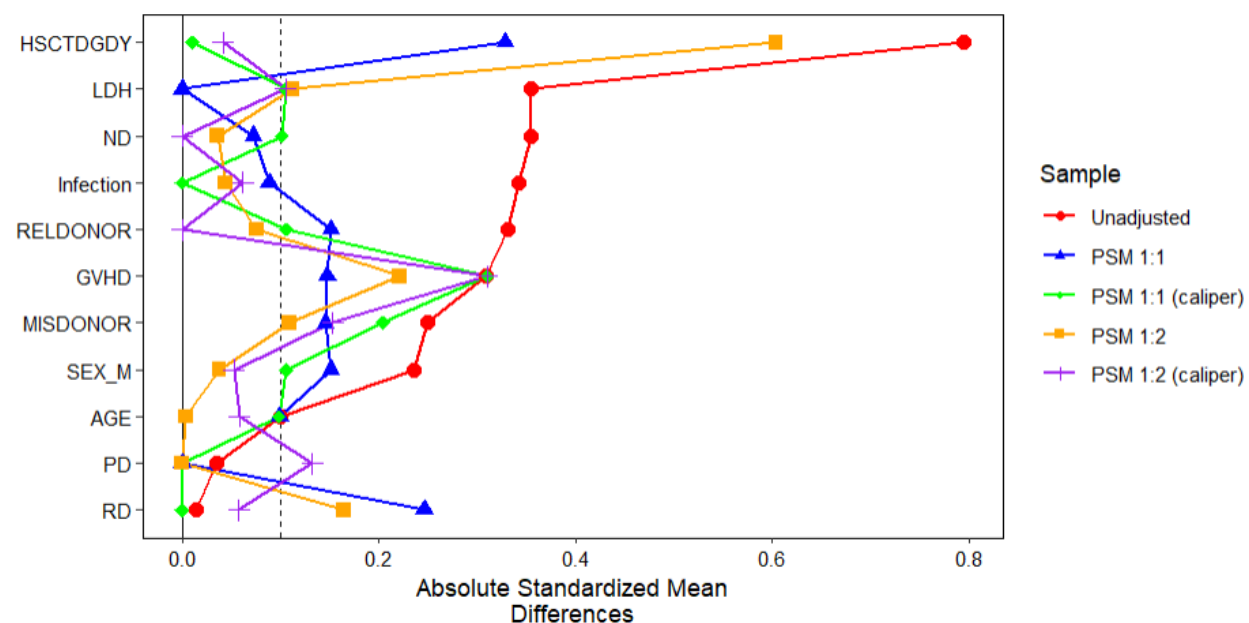


Source: FDA analysis.

Abbreviations: HSCTDGDY: Time from HSCT to TMA diagnosis; LDH: LDH ≥ 2 times ULN; ND: Neurological dysfunction; RELDONOR: Donor relationship; GVHD: Acute GVHD Grade 2-4; MISDONOR: Donor mismatch; PD: Pulmonary dysfunction; RD: Renal dysfunction.

Covariate balance for the PSM-based methods is shown in Figure 4. In general, propensity score matching with a caliper achieved better balance than matching without a caliper, particularly for time from HSCT to TMA diagnosis. However, applying a caliper restricts the set of matches and can result in exclusion of some patients from the treatment group, which results in fewer matched pairs available for analysis.

Figure 4: Covariate Balance Unadjusted and After PSM Adjustment (TMA-001 vs KSCTG Registry)

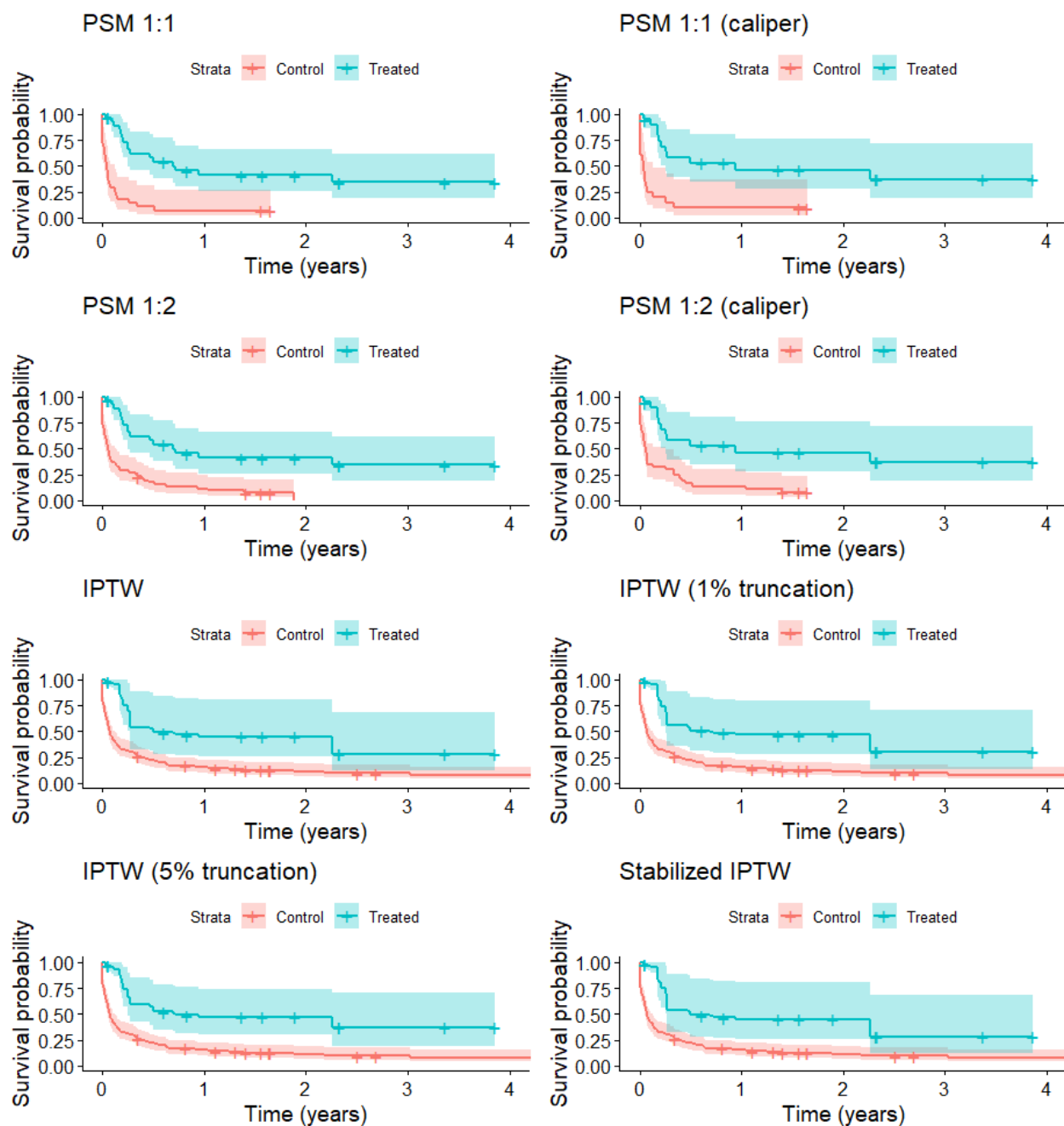


Source: FDA analysis.

Abbreviations: HSCTDGDY: Time from HSCT to TMA diagnosis; LDH: LDH ≥ 2 times ULN; ND: Neurological dysfunction; RELDONOR: Donor relationship; GVHD: Acute GVHD Grade 2-4; MISDONOR: Donor mismatch; PD: Pulmonary dysfunction; RD: Renal dysfunction.

Kaplan–Meier plots after applying IPTW and PSM methods are presented in Figure 5. Error! Reference source not found. For all analytic methods, the Kaplan–Meier curves suggested differences in observed survival between TMA-001 and the KSCTG registry, while slightly overlaps in the 95% confidence intervals were observed for some approaches.

Figure 5: Kaplan–Meier curves: TMA-001 vs KSCTG Registry



Source: FDA analysis

The hazard ratios for OS comparisons are presented in Table 8. Across all methods, the p-values were consistently very small (<0.001), indicating statistical significance. However, due to comparability issues between the groups (see below), these findings should be interpreted with caution.

Table 8. Hazard Ratios for Overall Survival: TMA-001 vs KSCTG registry

Method	Estimated hazard ratio	95% CI	P-value
PSM	0.22	0.11, 0.42	<0.001
PSM (caliper)	0.23	0.10, 0.51	<0.001
PSM 1:2	0.28	0.15, 0.50	<0.001
PSM 1:2 (caliper)	0.29	0.14, 0.59	<0.001
IPTW	0.35	0.20, 0.58	<0.001
IPTW (1% truncation)	0.33	0.20, 0.57	<0.001
IPTW (5% truncation)	0.32	0.19, 0.54	<0.001
Stabilized IPTW	0.38	0.23, 0.63	<0.001

Source: FDA analysis.

Note: IPTW methods were implemented using average treatment effect (ATE) weights.

Comparability Issues

There are several limitations with the registry identified by the clinical team, statistical team and the Division of Epidemiology 1 (DEP1) that limit the internal and external validity of the comparative analysis and limits the use of the KSTG registry. Key points from the DEPI-1 consult and the clinical and statistical team are summarized below. A detailed review from DEPI-1 can be found in DARRTS, dated December 15, 2025.

Lack of Patient Comparability

One of the major concerns for the external control study (KSTG registry) 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 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. 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.

- **Geographic Differences:** The narsoplimab-treated cohorts comprise patients from Study TMA-001, a global study and the EAP Subgroups 1 are derived from patients primarily in Italy (Castelli et al.), while the OS control group consists solely of Japanese registry patients. These geographical variations may introduce potential confounding due to differences in intrinsic or extrinsic factors (ICH E17), e.g. patient demographics, genetic backgrounds,

clinical practices, standard of care, and healthcare systems, thereby limiting the applicability of findings to the US patient population.

- **Small Sample Size:** The limited number of patients from Study TMA-001 with only 28 patients could limit the generalizability of the findings to a broader TA-TMA population .
- **Retrospective Analysis:** Results of study TMA-001 were already available before the consideration of using the KSCTG registry data as an external control.
- **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 hypothesis and in favor of the narsoplimab group.
- **Time from Transplant to TMA Diagnosis:** Earlier onset of TMA, which is associated with worse prognosis (Van Benschoten V et al., 2022), was more common in the KSCTG registry. The trial patients excluded those who developed TMA within three weeks following HSCT, while the KSCTG registry include such patients. In the KSCTG registry, 26% (32/121) patients had TMA onset within three weeks, with 6% (2/32) surviving beyond one year, compared to 26% (23/89) among patients with TMA onset beyond three weeks.
- **Missing Information:** Some patient-level data are missing from the registry, such as high-risk factors for TA-TMA, and components to determine TMA response.
- **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.
- **Propensity Score (PS) Considerations:** The propensity scores demonstrated only low to moderate overlap between the narsoplimab-treated and external control cohorts which could compromise the validity of the comparative analysis. Areas of limited common support and the presence of extreme propensity score values (near 0 or 1) also suggest potential challenges in achieving adequate matching and indicate that some patients may lack comparable counterparts in the opposite group,
- **Unmeasured Confounding:** Registry data may lack detailed information on important prognostic factors (e.g., patients' baseline status, such as LDH and transfusion requirement) that are systematically collected in clinical studies. Additionally, missing covariate information may introduce unmeasured confounding effect. Although the Applicant utilized the E-values to demonstrate that the impact of unmeasurable confounding is not a concern, given the other concerns, such as single registry and selection bias, the exact impact of unmeasurable confounding may not be ruled out.
- **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). 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).

- Stem Cell Source: The use of umbilical cord blood (UCB), which is associated with poorer outcomes (Lim YJ et al., 2022), was far more common in the KSCTG registry (39%, 47/121) than in the narsoplimab groups (2-7%).
- Performance Status: In the KSCTG registry, 24% (29/121) of patients had a poor performance score (≥ 2) with 0% surviving beyond one year, compared to a 29% (25/85) of those with better performance status surviving beyond one year.

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.
- Propensity Score Methodology: In the original submission, the Applicant failed to provide adequate documentation of the propensity score model diagnostics, including assessments of model fit, weight distributions, and covariate overlap. The effectiveness of weight truncation in such a small sample size is also uncertain.
- 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.

Although nominal statistical significances were observed in various analyses via different methods, the results should be interpreted with caution considering the aforementioned limitations and comparability issues.

5.3.7. Conclusion on Efficacy Overall Survival

In the absence of a reliable control arm, there is limited interpretability of the time-to-events survival endpoints from Study TMA-001. This remains true even with additional data from EAP Subgroups. Any analysis of EAP subgroup 2 is limited by lack of patient level data, missing data, heterogeneous population, and temporal disparity rendering the survival data uninterpretable.

Based on description of the limitations described in the section above, the selection of KSCTG as an external control is problematic and the results are inconclusive. In addition, the registry-based comparator for survival benchmark may introduce the potential for significant potential bias. Therefore, the KSTG registry as a comparator and survival data from the EAP and TMA-001 was not used for primary evidence for regulatory decision making.

The Day 100 survival (from first dose of narsoplimab) for patients from the EAP Subgroup 1 with patient level data and the Day 100 survival for the overall EAP group indicated directional consistency with the efficacy results from Study TMA-001 (Day 100 survival from first dose of narsoplimab). However, due to limitations with interpretation of single-arm survival data, the results can be considered only descriptive and exploratory. Further, as stated in the guideline from American Society for Transplantation and Cellular Therapy, published this year, “Overall survival from TA-TMA diagnosis alone is an insufficient endpoint to understand the impact of TA-TMA directed therapies as patients with TA-TMA may die of multiple etiologies including complications of GVHD, infections, or relapsed disease even after TA-TMA has resolved.” (Schoettler et al., 2025).

5.4. Pediatric Data

The sources of pediatric data for the use of narsoplimab is derived from the 6 patients (age range 5-15) described in EAP 1 group (Castelli et al). In terms of safety, FDA assessed 97 (6 from EAP 1 and 91 from EAP Subgroup 2) pediatric patients (defined as < 17 years of age) from the EAP.

In EAP 1 (Castelli et al) the baseline patient characteristics for the pediatric patients demonstrate that 100% of pediatric patients had an elevated LDH compared to 54% of adults. Both adult and pediatric patients had similar Grade II-IV acute GvHD. The percentage of renal, pulmonary and neurological dysfunction was similar in pediatric and adult patients. The rate of infection in pediatric patients was 100%, and 62% in adults. See Table 3 which presents demographics and baseline disease from 19 patients from EAP 1. The 6 pediatric patients had one criterion that met the high-risk TMA definition as defined by Schoettler et al.

In the EAP 1, pediatric patients had a longer exposure to narsoplimab and, therefore, likely a higher number of doses which was by investigator discretion (see Table 9. Duration of Exposure, Narsoplimab EAP). The Applicant confirms that the longer pediatric treatment duration was due to investigator-directed continuation of therapy after TA-TMA resolution, influenced by relapse prevention considerations.

Efficacy

TMA Response: In the EAP 1 subset (Castelli et al., 2023), 4 of 6 pediatric patients (66.7%, 95% CI: 22.3, 95.7) responded to narsoplimab treatment (see 5. Primary Endpoint, Response Rate, Pooled Analysis). The lower bound of 22.3% reflects the limitation of small sample size (N=6).

The response rate is consistent with the response rate observed in adults, in a high -risk population.

Survival rate at 100 days from first dose of narsoplimab was 69.9% (95% CI: 58.7, 78.7) and at 1 year, 51% (95% CI: 36.6, 63.6) for pediatric patients (N=97) in the EAP2 and the 6 pediatric subjects from EAP 1 (See Table 6. The mortality is high in patients with TA-TMA and 6-month overall survival rate is estimated to be approximately 18% in pediatric population (Jodele et al., 2024). In the pediatric population, Jodele et al. has reported that in high-risk pediatric patients with TA-TMA that did not receive complement inhibitors, OS at 1 year was 16.7% (Jodele et al., 2024). For pediatric patients, 1 year OS in TA-TMA after diagnosis is reported to be 1% in patients treated with therapeutic plasma exchange (Yang et al., 2023). The descriptive survival findings in the pediatric subgroup of EAP 2 and EAP 1 suggest a potential treatment effect, however no definitive conclusions regarding survival can be derived given limitations with survival data from the EAP datasets.

Safety

In the EAP, 97 pediatric patients (defined as < 16 years of age) were exposed to narsoplimab, in the EAP Subgroup 2 and EAP Subgroup 1. The youngest patient exposed to narsoplimab was nine months old. Pediatric patients with TA-TMA being treated with narsoplimab, had 35 (42.2 %) SAEs (see Table 13 in the Appendix). One pediatric patient died. Overall, the safety profile of narsoplimab in pediatric patients with TA-TMA was consistent with the adult patients with TA-TMA exposed to narsoplimab. Labeling should include Warnings and Precautions for serious infections. As with adults, the majority of SAEs were infectious in pediatric patients. The long-term safety of narsoplimab in pediatric patients with TA-TMA will continue to be reviewed through a PMR.

Conclusion

Pediatric and adult TA-TMA share similar underlying pathophysiology with similar characteristics such as endothelial damage and complement activation after HSCT with similar pattern of organ involvement, microangiopathic anemia.

There are differences in pediatric and adult patients in terms of the underlying diseases that necessitated HSCT, where adults usually undergo transplantation for malignant hematologic diseases and pediatric patients more frequently undergo transplantation for non-malignant diseases. Adults are often more likely to have comorbid conditions whereas pediatric patients often do not have baseline comorbidities, however the approach to treatment is similar for pediatric and adult patients with TA-TMA. The course of the disease is similar although there can be differences in baseline comorbidities, underlying disease and concomitant complications such as GVHD which can also impact outcomes.

In the 6 pediatric patients with subject level data available, the baseline disease characteristics and TMA response rates were consistent with what was observed in the adult population. Of

the 97 pediatric patients in the EAP, 89 were 2 years and older and there were no new safety signals were observed. Given the lack of available therapy for this rare disease with high mortality rate and the similar pathophysiology between adults and pediatric patients reasonable to consider partial extrapolation of efficacy and safety from the adult population to support the pediatric indication in pediatric patients age ≥ 2 with TA-TMA.

5.5.Overall Conclusions on Benefit

In Study TMA-001, there is a benefit of estimated TMA response observed in 17 of 28 patients (61%; 95% CI: 40.6, 78.5). No benefit on survival could be confirmed.

6. Safety Update

A thorough evaluation of safety of narsoplimab in patients with TA-TMA based on data from TMA-001 was performed as part of the review of the original BLA (see finalized review in DARRTS, loaded October 15, 2021). Serious and life-threatening infections have occurred in patients treated with narsoplimab and were reported in 36% (10/28) patients with TA-TMA in clinical trials in patients receiving narsoplimab. These included sepsis, viral infections, pneumonia, bacteremia, fungal infections, gastroenteritis, respiratory tract infections and urosepsis. The most common adverse reactions (incidence $>20\%$) are viral infections, sepsis, hemorrhage, diarrhea, vomiting, nausea, neutropenia, pyrexia, fatigue and hypokalemia.

Additional safety data from the EAP program was submitted with this resubmission. Analysis of this data did not identify any new or more serious safety signal not already identified the analysis of safety based on the data from TMA-001. Table 9 provides exposure information for the EAP population.

Table 9. Duration of Exposure, Narsoplimab EAP

	Pediatric Patients Age ≥ 2 and < 17 (N = 89)	Adult Patients Age ≥ 17 (N = 124)	Total (N = 213)
Total number of doses received			
N	89	124	213
Mean (SD)	26.1 (45.31)	11.4 (13.89)	17.5 (31.88)
Median	13	7	8
Min, Max	1, 302	1, 75	1, 302

Duration of treatment (weeks)			
N	89	123	212
Mean (SD)	14.96 (24.315)	7.16 (10.021)	10.43 (17.875)
Median	6.71	3.86	5.79
Min, Max	0.1, 141.4	0.1, 68.3	0.1, 141.4

Abbreviations: N, number of patients in treatment arm; SD, standard deviation

Source: Applicant's response to Information Request, July 31, 2025 and December 19, 2025.

Patients with TA-TMA in the EAP received narsoplimab for an average of 2.5 months. The duration of treatment in the safety database appears adequate to support approval in the context of this rare, serious disease. TA-TMA is not a chronic process and narsoplimab is discontinued when a patient achieves all of the response criteria and no longer requires therapy for TA-TMA. It is noted that the pediatric patients had a longer exposure to narsoplimab and, therefore likely a higher number of doses which was by investigator discretion. The Applicant confirms that the longer pediatric treatment duration was due to investigator-directed continuation of therapy after TA-TMA resolution, influenced by relapse prevention considerations.

In the EAP, the rate of serious adverse events (SAEs) was 46.2%. Serious adverse reactions included respiratory failure, multiple organ dysfunction syndrome, and polyserositis. Six (5.9%) deaths are listed as SAEs.

The most common serious adverse reactions were in the system organ class of 'Infections and Infestations', which is again similar to what was observed the TMA-001 study. Therefore, if the product were to be approved, serious infections should be included in the 'Warnings and Precautions' section of the USPI. Serious infections should also be further monitored through a postmarketing requirement.

See Table 12 and Table 13, in the Appendix for the total serious adverse events for the entire EAP group, and serious adverse events for the pediatric patients from the EAP, respectively.

7. Clinical Pharmacology

Although no new clinical pharmacology data was included in the BLA resubmission, this section includes a summary of assessment on dose and dosing frequency in adult and pediatric patients based on the additional clinical experience from the EAP and the need for supplemental dose

following plasma exchange. For clinical pharmacology assessment of the original BLA submission, refer to the Integrated Review in DARRTS (10/15/2021).

Dose and Dosing Frequency

The proposed narsoplimab dose and dosing regimen is 4 mg/kg, given as a 30-minute IV infusion (up to 370 mg per infusion) once weekly. This was the dose and dosing regimen studied in Study OMS721-TMA-001. As noted in the Integrated Review associated with the original BLA submission (DARRTS date: 10/15/2021), the Applicant selected a dose of 4 mg/kg based on the pharmacokinetic (PK) and pharmacodynamic (PD) results from Study OMS721-NHV-002 in healthy patients. This dose was expected to maintain C4d inhibition (marker for lectin pathway inhibition) greater than 80% for about 168 hours providing the basis for administering once weekly.

The efficacy and safety of narsoplimab 4 mg/kg administered once weekly has been demonstrated in OMS721-TMA-001. In the expanded access program (EAP), the Applicant evaluated a more frequent regimen of 4 mg/kg administered twice weekly due to the high-risk nature of patients typically enrolled under expanded access and further supported by the established safety profile from OMS721-TMA-001. Duration of dosing in OMS721-TMA-001 was 4 to 8 weeks. The duration and frequency of treatment administered to patients under the EAP varied and were determined by the treating physician based on the individual's clinical response. Median duration of dosing in the EAP was 5.7 weeks, and median number of doses was 9. The twice weekly regimen is supported by the efficacy and safety data published in EAP Subgroup 1 (Castelli *et al*), reviewed and confirmed by the Agency.

As OMS721-TMA-001 studied a once weekly regimen and the EAP employed a twice weekly regimen of narsoplimab, an information request was sent to understand the Applicant's approach to dosing and administration in the product's prescribing information. The Applicant clarified that once weekly administration is appropriate as the starting regimen, however, given inter-patient variability in disease severity and level of lectin pathway hyperactivation, increasing the frequency to twice weekly administration may be clinically justified in patients who do not respond adequately to narsoplimab treatment. Direct evidence showing improvement in patient response escalating from once weekly to twice weekly regimen is not available. However, from a PD perspective, a more frequent (e.g., twice weekly) dosing regimen is expected to maintain higher lectin pathway inhibition throughout the inter-dosing interval compared to once weekly regimen. It is also reassuring that the safety profile of a twice weekly regimen employed in the EAP is acceptable ensuring no additional safety risk to patients escalating to a more frequent regimen. Although the typical duration of treatment for TA-TMA is relatively shorter (<10 weeks), as patients are frequently monitored, it is still practically feasible to escalate the dosing frequency based on inadequate treatment response.

Therefore, based on the totality of data, narsoplimab can be initiated once weekly in patients with TA-TMA. The dosing frequency can be increased to twice weekly if there is no improvement in TA-TMA signs and symptoms.

While the proposed dose is narsoplimab 4 mg/kg (not to exceed 370 mg), patients in Study TMA-001 following amendment #10 received a flat dose of 370 mg once weekly if they weighed ≥ 50 kg. Only patients weighing < 50 kg received a body weight adjusted dose of 4 mg/kg once weekly. Similarly, in the EAP, patients weighing ≥ 50 kg received 370 mg twice weekly and patients weighing < 50 kg received 4 mg/kg twice weekly. As seen from Figure 11 in the Integrated Review associated with the original BLA submission, a flat dose of 370 mg results in higher exposure compared to the body weight adjusted dose of 4 mg/kg. As the safety of 370 mg in patients weighing ≥ 50 kg is demonstrated, the Agency recommends that the Applicant proposed dosing instructions i.e., 4 mg/kg (up to a maximum of 370 mg), be revised to recommend a flat dose of 370 mg in patients weighing ≥ 50 kg and 4 mg/kg in patients weighing < 50 kg.

Dosing in pediatric patients

No pediatric patients were enrolled in Study OMS721-TMA-001. Clinical experience in pediatric patients comes from the EAP. Eighty-six pediatric patients with TA-TMA were treated in the EAP and their age at the time of treatment is shown in Table 10 below.

Table 10. Pediatric patients in the EAP, < 16 years old

Age (at the time of narsoplimab treatment)	Count
< 1	3
1 to < 2	4
2 to < 6	24
6 to < 12	34
12 to < 16	21
Total	86

Source: Applicant's response to Information Requests, September 2025.

Out of 97 pediatric patients (< 17 years old) treated in EAP Subgroup 2, efficacy and safety data from 6 pediatric patients were included in EAP Subgroup 1. The efficacy and safety data in pediatric patients aligns with that observed in adults. The median age of the 6 pediatric patients is 11 years, ranging from 6 to 16 years. Narsoplimab was dosed at 4 mg/kg twice weekly, consistent with how adult patients with TA-TMA were dosed in the EAP. No PK or PD data is available from the pediatric patients treated in the EAP.

No PK or PD data was available from pediatric patients. In response to an information request, the Applicant simulated narsoplimab exposures in pediatric subjects using the adult population PK model. Of note, the adult population PK model including a body weight effect on clearance (exponent factor of 0.726) was reviewed by the Agency with the original BLA submission and found to be acceptable to characterize the observed adult PK data. The simulated PK data in pediatric subjects suggested comparable area under the curve (AUC) at steady state for subjects ≥ 2 years of age with either once weekly or twice weekly regimen of 4 mg/kg. Based on the general understanding of monoclonal antibody pharmacokinetics in pediatric population, the clearance on a per-kilogram basis is usually higher in pediatric patients compared to adults. As per expectation, the resulting narsoplimab exposures when dosed at the same 'mg/kg' dose in pediatric patients are not higher than what was observed in adults. The adult population PK model did not include allometric scaling on other PK parameters (e.g., volume of distribution), therefore the predicted concentration, particularly C_{max}, could be under predicted in young pediatric patients with low body weight and adds to the uncertainty in projecting exposures without any pediatric PK data in patients < 2 years of age. A post-marketing commitment is issued to collect PK and PD data in pediatric patients, including in patients $< \text{(b) (4)}$ years of age.

In summary, from a safety perspective the dose of 4 mg/kg seems appropriate in pediatric patients ≥ 2 years of age. With regard to efficacy, the appropriateness of the dose relies primarily on the efficacy evaluation from the EAP. As stated earlier, although the starting regimen is 4 mg/kg once weekly, patients including pediatric patients have the option to increase the frequency to twice weekly if there is no improvement in TA-TMA signs and symptoms.

Need for supplemental narsoplimab dose following plasma exchange (PE)

During the review of the original BLA submission, the clinical pharmacology review team evaluated (b) (4) a supplemental narsoplimab dose of 2 mg/kg to be administered up to 3 times weekly for patients who undergo plasma exchange (PE). Although 5 patients received supplemental doses of narsoplimab because of PE, the effect of PE on narsoplimab clearance (CL) and its exposure was not investigated in a dedicated clinical study or did the Applicant provide adequate justification for the selected supplemental dose of narsoplimab post-PE. Therefore, an information request was sent to the Applicant during the original BLA review to specifically assess the effect of PE as a time-varying, non-constant variable on CL via population PK analyses to accurately capture the transient nature of the intervention. In response, the Applicant conducted a comprehensive reanalysis by implementing a modified population PK model incorporating PE as a time-varying covariate across 36 documented PE events with a median duration of 1.45 hours. The Applicant's analysis estimated a 37% increase in narsoplimab clearance during PE events, representing a statistically significant improvement in model fit compared to the original model. The Applicant also showed that because of the transient nature of the intervention, the effect of PE on narsoplimab exposure was negligible and concluded that a supplemental dose following PE was not required. The Agency's review of the Applicant's analysis showed that the impact of PE on

narsoplimab CL is on an average 47% but with a wide 95% CI ranging from 24% to 124%. To improve the precision on the CL estimate, the Agency included a comment in the Complete Response Letter (CRL) to conduct a dedicated clinical study to methodically assess the effect of PE on narsoplimab clearance by collecting rich PK samples pre- and post-PE.

In the current BLA resubmission, no additional data to understand the effect of PE on narsoplimab CL/exposure was submitted. The EAP protocol also did not specify administration of supplemental doses following PE. Although any new data was not generated, the clinical pharmacology review team concludes that there may not be a need for a supplemental PE dose because (i) the duration of PE is short, (ii) despite limitations the transient nature of the intervention had negligible effect on narsoplimab exposures, (iii) supplemental doses were not administered in the EAP, and (iv) the current dosage and administration instructions in the label provides the option to increase the dosing frequency to twice weekly making the utility of a supplemental PE dose limited. Due to these considerations, a supplemental narsoplimab dose following PE is not required.

8. Chemistry, Manufacturing, and Controls (CMC)

Key points from the CMC consult review are briefly summarized here, the detailed, finalized primary review memo is in Panorama, dated 10/30/2025, and the quality executive summary can be found in DARRTS, dated 11/26/2025.

The CMC reviewer has concluded that the supported preparation and administration conditions are D5W saline administered with PVC contact materials (infusion bag and line) with a polyethersulfone (PES) in-line filter. Further, for pediatric patient with less than or equal to 10 kg (the total dose is 40 mg, around 2 years old) should be diluted to 0.8 mg/mL D5W by using polypropylene syringe and syringe pump since the dosing is small and maximal volume can be used as 50mL. The use of syringe pumps is also supported based on the stability data and dose preparation data (Table 6) in the IR response (SDN 103, received on October 1, 2025). For pediatric patients with more than or equal to 10 kg can be diluted between 0.8-8 mg/mL in D5W by regulator IV with PVC with in-line filter.

The suitability of preparation and administration conditions for narsoplimab will be further addressed in PMCs (see Section 8 below).

9. Plans for Pediatric Drug Development

Pediatric patients were included in the expanded access program (EAP) for narsoplimab. The indication statement will include pediatric patients down to 2 years old. The youngest patient in the EAP was 4 months of age. The efficacy and safety profile of the drug appear similar

between adult and pediatric patients. The review team expects the weight-based dosing to result in similar exposures and should not be higher than exposure in adults. In addition, a reportable PMR will be issued to establish a registry to characterize the long-term safety of narsoplimab in at least 50 adult and pediatric patients with TA-TMA.

10. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened to discuss this application. No issues were identified that would have benefitted from a public discussion with external experts.

11. Labeling Recommendations

11.1 Prescription Drug Labeling

Table 11. Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	FDA Revisions	Rationale for Revisions
Highlights of Prescribing Information	Product Title: Changed (b) (4) to “for intravenous use”. Adverse Reactions summary: Changed (b) (4) (b) (4) (b) (4) to “The most common adverse reactions (incidence >20% and independent of causality) are viral infections, sepsis, hemorrhage, diarrhea, vomiting, nausea, neutropenia, pyrexia, fatigue, and hypokalemia.”	Corrected route of administration per Product Title Guidance. Updated to remove promotional conclusion (b) (4) and list the most common ARs per Section 6.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	FDA Revisions	Rationale for Revisions
1 Indications and Usage	Added age groups for indicated population.	per the Pediatric Information Incorporated into Human Prescription Drug and Biological Products Guidance
2 Dosage and Administration	Reorganized entire section. Changed text to table for recommended dosage in Table 1 by weight category. Added 2.2 Important Preparation and Administration Instructions. Added 2.3 Preparation Instructions into an Intravenous Bag and 2.4 for Intravenous Syringe (for pediatric patients weighing <10 kg). Added 2.5 Storage and Administration.	Overall, text revised for clarity and content.
3 Dosage Forms and Strengths	Removed (b) (4).	(b) (4) is not part of the dosage form and not for inclusion in Section 3.
4 Contraindications	Added in subsection and included "none".	Required subsection.
5 Warnings and Precautions	5.1 Revised (b) (4) to Serious Infections. Deleted (b) (4), added description of serious and life-threatening infections, rate, types of infections observed, and mitigating strategies.	Warning describes serious infections, not all are systemic. (b) (4) is an ambiguous and uninformative statement.
6 Adverse Reactions	After heading 6, added a list of the Warnings and Precautions that are adverse reactions. 6.1 Revised text for	Per PLR Guidance. Per Adverse Reactions labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	FDA Revisions	Rationale for Revisions
	clarity, to provide the dose evaluated and exposure information. Added description of serious adverse reactions, including fatal, those that led to dosage interruptions. Added a table of all grade and grade ≥ 3 ARs from TA-TMA study. 6.2 Deleted (b) (4) and relocated (b) (4) (b) (4)	guidance. (b) (4)
7 Drug Interactions	No section proposed.	No change, optional section.
8 Use in Specific Populations	8.1, 8.2: Revised text to describe the insufficient available data on exposure of narsoplimab in pregnant women. Removed 8.3 as not relevant to this drug. 8.4 Revised text to reflect exposure in pediatric patients, basis of approval in pediatric patients and limitations in patients <2 years old. 8.5 Revised to provide actual numbers of geriatric patients studied.	Revised per PLLR guidance. Revised to reflect Pediatric Use Labeling Guidance. Per Geriatric Information in Human Prescription Drug and Biological Product Labeling.
10 Overdosage	Revised to remove statements (b) (4) (b) (4)	Per (b) (4)

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	FDA Revisions	Rationale for Revisions
		(b) (4)
11 Description	Revised to include the established pharmacologic class “mannan-binding lectin-associated serine protease 2 (MASP-2) inhibitor”, add molecular weight, and add source (produced in CHO cells). Added “preservative-free” and reordered inactive ingredients in alphabetical order.	Per 21 CFR 201.57(c)(12).
12 Clinical Pharmacology	12.1 MoA: Removed (b) (4) 12.2 PD: Revised for brevity and clarity. 12.3 PK Added a summary of the PK characteristics at beginning of the section. Replaced tradename with non-proprietary name. 12.6 Added Immunogenicity section.	Not relevant to this section. This section must summarize the established mechanism(s) of action. Per Immunogenicity Labeling Guidance.
13 Non-Clinical Toxicology	Replaced tradename with non-proprietary name. Added exposure level effects were noted in.	Per 21 CFR 201.57(c)(14).
14 Clinical Studies	Removed (b) (4) (b) (4)	(b) (4)

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	FDA Revisions	Rationale for Revisions
	Added patient baseline characteristics. (b) (4)	
15 References	None.	
16 How Supplied/Storage and Handling	Added text to describe visible liquid characteristics, NDC, “do not shake”.	Per 21CFR 201.57(c)(17).
17 Patient Counseling Information	Revised to be consistent with higher sections of labeling (specifically W&P). After this section, manufacturer information and US license added.	

Source: Associate Director of Labeling

12. Risk Evaluation and Mitigation Strategies (REMS)

Based on the available data, a risk evaluation and mitigation strategy is not necessary to ensure the benefits of narsoplimab in the high-risk TA-TMA population outweigh the risks.

Narsoplimab is part of the complement inhibitor class but has a different mechanism of action than other approved complement inhibitors. Certain approved complement inhibitors have a REMS due to their direct involvement in the alternative complement pathway which protects against encapsulated organism infections. Narsoplimab inhibits mannose binding protein-associated serine protease 2 (MASP-2) which is an enzyme in the lectin pathway of the complement system. The other two pathways of the complement system, classical and alternative, are not affected; and these two pathways are fully functional.

Inhibition of MASP-2 increases the risk of serious infections, but it is not clear how it increases the risk of infections from encapsulated bacteria. Infections with encapsulated organisms in patients with MASP-2 deficiency have not been a common finding (Garcia-Laorden et al., 2020). TA-TMA is an acute, potentially life-threatening complication that typically occurs early after transplant. It is expected that patients will be treated in an inpatient setting and narsoplimab is not intended as a chronic or long-term therapy. The standard of care for monitoring and managing serious infections for post-transplant patients would be similar to the management

of patients who are post-transplant, in general. Post-transplant patients are managed closely by a multidisciplinary team with hematology/oncology specialists who are knowledgeable about the risk of infections and management. This patient population is immunocompromised and at high risk of infection due to the recent transplant. The standard of care for post-transplant patients includes close monitoring for infections. Treatment with narsoplimab may increase the risk of serious infections; however, we do not anticipate a need for additional monitoring or changes to the standard of care. Patients who are candidates for transplant typically receive education on the risks and are expected to be knowledgeable about the infection risk and management. We do not anticipate additional mitigation strategies would be necessary beyond labeling to ensure prescribers are monitoring and managing serious infections

Based on our understanding of the disease state, duration of therapy, and anticipated prescribers and patient population, our assessment is that a REMS is not necessary to ensure the benefits of narsoplimab outweigh its risks.

13. Postmarketing Requirements and Commitments

Postmarketing requirement (PMR)

Narsoplimab 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. The long-term safety of patients who receive treatment with narsoplimab is unknown. The goal of a patient registry is to provide continued follow-up of patients to characterize the long-term safety of narsoplimab in patients with TA-TMA. 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. This 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.

4938-1 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 and laboratory data (i.e., CBC with differential and renal function tests), autoimmune disorders, concomitant medications, vital status, and cause of death for any fatalities.

Postmarketing commitments (PMCs)

No PK or PD data is available in pediatric patients who have been exposed to narsoplimab in the submitted clinical studies or compassionate use program. However, based on the general understanding of monoclonal antibody pharmacokinetics in pediatric population, the clearance on a per-kilogram basis is usually higher in pediatric patients compared to adults. Therefore, narsoplimab, a monoclonal antibody, when dosed at the same mg/kg dose in pediatric patients, the resulting exposures are not expected to be higher than what was observed in adults, at least down to 2 years of age. Below 2 years of age, there may be greater uncertainty in projecting exposures without any pediatric PK data due to maturation of clearance pathways. Therefore, from a safety perspective, the dose of 4 mg/kg seems appropriate in pediatric patients ≥ 2 years of age. However, evidence from a PK study in pediatric patients would further support pediatric dosing, particularly in patients < 2 years of age and provide data to lower the indicated age to < 2 years old, in the future.

4938-2 PMC:

Provide safety, pharmacokinetic (PK) and pharmacodynamic (PD) data in pediatric patients < 17 years of age treated with the recommended dosing regimen of narsoplimab for transplant-associated thrombotic microangiopathy (TA-TMA).

In-use compatibility studies were not conducted under worst-case conditions. Thus, there is residual risk that there are real-world conditions which may adversely impact product quality during routine preparation and administration in the clinic. To address this risk, we request the Applicant's commitment to conduct in-use compatibility studies under justified worst-case conditions (i.e., agitation, light exposure, duration of storage, administration volumes) and propose mitigations in the labeling, as necessary. The Applicant should investigate the root cause of visible and sub-visible particle formation. Identified visible and sub-visible particles should be adequately characterized to support conclusions that the preparation and administration conditions are appropriate and risks from sub-visible and visible particles are appropriately characterized. We also recommend that you evaluate additional preparation and administration conditions to determine compatibility with narsoplimab to allow for further flexibility in administration (i.e., product contact materials, narsoplimab dilutions, diluents, or filters). All incompatibilities should be thoroughly investigated to inform labeling.

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Draft Protocol Submission: 06/2026

Final Protocol Submission: 12/2026

Study/Trial Completion: 12/2032

Final Report Submission: 12/2033

4938-3 PMC:

Postmarketing commitment: Conduct a worst-case in-use stability study to evaluate the suitability of preparation and administration conditions for narsoplimab under clinically relevant conditions. The study should assess product stability under stressed conditions including but not limited to extended light exposure as mechanical stress from mixing as well as worst-case dilutions and volumes. All incompatibilities should be investigated to inform the labeling. Propose revisions to the labeling as appropriate.

Final Report Submission: 10/2026

4938-4 PMC:

Perform a reproducibility evaluation for size exclusion chromatography (SEC), cation exchange chromatography (CEX), and capillary electrophoresis (CE-SDS) reduced and non-reduced with appropriate stressed stability samples to support Vetter as a quality control testing site for narsoplimab stability samples.

Final Report Submission: 10/2026

4938-5 PMC:

Establish an appropriately justified drug product stability specification (b) (4) based on levels observed in clinical and commercial batches.

Final Report Submission: 03/2026

4938-6 PMC:

Complete a pending real-world shipping study for drug product transportation from the drug product manufacturing site to the drug product packaging and labeling facility and perform a real-world shipping study for drug product transportation from the drug product packaging and labeling facility to distribution centers and/or storage warehouses. The studies will be performed using representative commercial drug product lots under commercial shipping conditions and will include a total of three shipments, and the evaluation will include assessments for shipping temperature, integrity of the vials and/or packaging/labeling as well as product quality attributes from samples collected prior to and after shipment.

Final Report Submission: 12/2026

4938-7 PMC:

Conduct narsoplimab container closure integrity test (CCIT) validation with the (b) (4) container closure system used for the narsoplimab drug product, including assessments of sensitivity, intermediate precision, and robustness.

Final Report Submission: 01/2026

14. Appendices

14.1 Safety Tables

Table 12. Summary of Treatment-Emergent Serious Adverse Events by System Organ Class

System Organ Class and Preferred Term, Narsoplimab EAP

System Organ Class Preferred Term	Narsoplimab EAP (N=221) n (%)
TOTAL	102 (46.2)
Blood and lymphatic system disorders	14 (13.7)
Anemia	1 (0.1)
Disseminated intravascular coagulation	1 (0.1)
Febrile neutropenia	7 (6.9)
Hemolysis	1 (0.1)
Neutropenia	3 (2.9)
Thrombotic microangiopathy	3 (2.9)
Cardiac disorders	10 (9.8)
Cardiac arrest	4 (3.9)
Cardiac failure	1 (0.1)
Cardiotoxicity	1 (0.1)
Pericardial effusion	4 (3.9)
Right ventricular dysfunction	1 (0.1)
Gastrointestinal disorders	8 (7.8)
Food poisoning	1 (0.1)
Gastric hemorrhage	1 (0.1)
Gastrointestinal hemorrhage	1 (0.1)
Ileus	1 (0.1)

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Narsoplimab-wuug

System Organ Class Preferred Term	Narsoplimab EAP (N=221) n (%)
Intestinal perforation	2 (2)
Lower gastrointestinal hemorrhage	1 (1)
Esophagitis	1 (1)
General disorders and administration site conditions	23 (22.5)
Death	6 (5.9)
Disease progression	1 (1)
Generalized oedema	1 (1)
Multiple organ dysfunction syndrome	9 (8.8)
Polyserositis	9 (8.8)
Pyrexia	4 (3.9)
Sudden death	2 (2)
Hepatobiliary disorders	3 (2.9)
Hepatic failure	1 (1)
Hepatic hematoma	1 (1)
Veno-occlusive liver disease	1 (1)
Immune system disorders	2 (2)
Chronic graft versus host disease in lung	1 (1)
Graft versus host disease	1 (1)
Infections and infestations	34 (33.3)
Adenovirus infection	1 (1)
Bacterial sepsis	1 (1)
Candida sepsis	1 (1)
Clostridium difficile colitis	1 (1)
COVID-19	2 (1)
COVID-19 pneumonia	1 (1)
Cytomegalovirus infection reactivation	2 (2)
Device related bacteremia	1 (1)
Enterococcal bacteremia	1 (1)
Escherichia bacteremia	1 (1)
Fungemia	1 (1)
Fungal sepsis	1 (1)
Meningitis	1 (1)
Meningitis bacterial	1 (1)
Meningitis enterococcal	1 (1)
Norovirus infection	1 (1)
Osteomyelitis	1 (1)
Pneumonia	2 (2)
Pneumonia bacterial	1 (1)

CDER Clinical Review Template (CRT)

Version date: March 8, 2019

Clinical, Statistical, and Clinical Pharmacology Review

BLA 761152

Narsoplimab-wuug

System Organ Class Preferred Term	Narsoplimab EAP (N=221) n (%)
Pneumonia fungal	1 (1)
Pneumonia viral	1 (1)
Pseudomonal sepsis	1 (1)
Pseudomonas infection	1 (1)
Sepsis	8 (7.8)
Septic shock	8 (7.8)
Sinusitis	1 (1)
Staphylococcal abscess	1 (1)
Systemic candida	1 (1)
Upper respiratory tract infection	1 (1)
Urinary tract infection bacterial	1 (1)
Vascular device infection	1 (1)
Injury, poisoning, and procedural complications	3 (2.9)
Fall	1 (1)
Subdural hematoma	1 (1)
Transplant failure	1 (1)
Investigations	4 (3.9)
Alanine aminotransferase increased	1 (1)
Aspartate aminotransferase increased	1 (1)
Blood alkaline phosphatase increased	1 (1)
Respirovirus test positive	1 (1)
Troponin I increased	1 (1)
White blood cell count decreased	1 (1)
Metabolism and nutrition disorders	2 (2)
Dehydration	1 (1)
Hypernatremia	2 (2)
Musculoskeletal and connective tissue disorders	1 (1)
Muscular weakness	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2)
Leukemia	1 (1)
Myeloproliferative neoplasm	1 (1)
Nervous system disorders	9 (8.8)
Encephalopathy	2 (2)
Leukoencephalopathy	1 (1)
Posterior reversible encephalopathy syndrome	3 (2.9)
Seizure	1 (1)
Subdural hemorrhage	1 (1)
Uremic encephalopathy	1 (1)

CDER Clinical Review Template (CRT)

Version date: March 8, 2019

Clinical, Statistical, and Clinical Pharmacology Review

BLA 761152

Narsoplimab-wuug

System Organ Class Preferred Term	Narsoplimab EAP (N=221) n (%)
Psychiatric disorders	2 (2)
Confusional state	1 (1)
Mental status changes	1 (1)
Renal and urinary disorders	12 (11.8)
Acute kidney injury	5 (5)
Chronic kidney disease	1 (1)
Cystitis hemorrhagic	2 (2)
End stage renal disease	2 (2)
Renal failure	2 (2)
Tubulointerstitial nephritis	1 (1)
Respiratory, thoracic and mediastinal disorders	31 (30.4)
Acute respiratory distress syndrome	2 (2)
Acute respiratory failure	6 (5.9)
Aspiration	1 (1)
Dyspnea	1 (1)
Hypoxia	2 (2)
Idiopathic pneumonia syndrome	1 (1)
Pneumothorax	1 (1)
Pulmonary embolism	1 (1)
Pulmonary fibrosis	1 (1)
Pulmonary hemorrhage	1 (1)
Pulmonary hypertension	1 (1)
Pulmonary oedema	1 (1)
Respiratory distress	2 (2)
Respiratory failure	13 (12.7)
Vascular disorders	8 (7.8)
Deep vein thrombosis	1 (0.1)
Hemorrhagic infarction	1 (0.1)
Hypertension	1 (0.1)
Hypertensive crisis	1 (0.1)
Hypotension	4 (3.9)

Abbreviations: N, number of patients in treatment arm; n, number of patients of patients with adverse event
Source: Applicant's response to Information Request, July 31, 2025.

Safety in Pediatric Subset from EAP

Table 13 presents the SAEs in the pediatric EAP subgroup.

Table 13. Serious Adverse Events in the Pediatric EAP Patients, ≥ 2 years old and <17 years old.

System Organ Class Preferred Term	EAP, Exclusive of Castelli (N = 83) n (%)	Castelli (N = 6) n (%)	Total EAP (N = 89) n (%)
Any SAE	35 (42.2%)	2 (33.3%)	37 (41.6%)
Blood and lymphatic system disorders	4 (4.8%)	0	4 (4.5%)
Anemia	1 (1.2%)	0	1 (1.1%)
Disseminated intravascular coagulation	1 (1.2%)	0	1 (1.1%)
Febrile neutropenia	2 (2.4%)	0	2 (2.2%)
Thrombotic microangiopathy	1 (1.2%)	0	1 (1.1%)
Cardiac disorders	3 (3.6%)	0	3 (3.4%)
Cardiac arrest	1 (1.2%)	0	1 (1.1%)
Pericardial effusion	3 (3.6%)	0	3 (3.4%)
General disorders and administration site conditions	7 (8.4%)	0	7 (7.9%)
Death	1 (1.2%)	0	1 (1.1%)
Disease progression	1 (1.2%)	0	1 (1.1%)
Multiple organ dysfunction syndrome	4 (4.8%)	0	4 (4.5%)
Sudden death	1 (1.2%)	0	1 (1.1%)
Hepatobiliary disorders	0	1 (16.7%)	1 (1.1%)
Veno-occlusive liver disease	0	1 (16.7%)	1 (1.1%)
Immune system disorders	2 (2.4%)	0	2 (2.2%)
Acute graft versus host disease in intestine	1 (1.2%)	0	1 (1.1%)
Chronic graft versus host disease in lung	1 (1.2%)	0	1 (1.1%)
Infections and infestations	17 (20.5%)	0	17 (19.1%)
Adenovirus infection	1 (1.2%)	0	1 (1.1%)
Bacterial sepsis	1 (1.2%)	0	1 (1.1%)
COVID-19	1 (1.2%)	0	1 (1.1%)
COVID-19 pneumonia	1 (1.2%)	0	1 (1.1%)
Clostridium difficile colitis	1 (1.2%)	0	1 (1.1%)
Cytomegalovirus infection reactivation	1 (1.2%)	0	1 (1.1%)
Fungaemia	1 (1.2%)	0	1 (1.1%)
Fungal sepsis	1 (1.2%)	0	1 (1.1%)
Meningitis	1 (1.2%)	0	1 (1.1%)
Meningitis bacterial	1 (1.2%)	0	1 (1.1%)
Osteomyelitis	1 (1.2%)	0	1 (1.1%)

System Organ Class Preferred Term	EAP, Exclusive of Castelli (N = 83) n (%)	Castelli (N = 6) n (%)	Total EAP (N = 89) n (%)
Pneumonia	2 (2.4%)	0	2 (2.2%)
Pneumonia fungal	1 (1.2%)	0	1 (1.1%)
Pseudomonal sepsis	1 (1.2%)	0	1 (1.1%)
Sepsis	3 (3.6%)	0	3 (3.4%)
Septic shock	4 (4.8%)	0	4 (4.5%)
Sinusitis	1 (1.2%)	0	1 (1.1%)
Urinary tract infection bacterial	1 (1.2%)	0	1 (1.1%)
Vascular device infection	1 (1.2%)	0	1 (1.1%)
Investigations	1 (1.2%)	0	1 (1.1%)
White blood cell count decreased	1 (1.2%)	0	1 (1.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.2%)	0	1 (1.1%)
Leukemia	1 (1.2%)	0	1 (1.1%)
Nervous system disorders	1 (1.2%)	1 (16.7%)	2 (2.2%)
Leukoencephalopathy	0	1 (16.7%)	1 (1.1%)
Posterior reversible encephalopathy syndrome	1 (1.2%)	0	1 (1.1%)
Renal and urinary disorders	4 (4.8%)	0	4 (4.5%)
Acute kidney injury	2 (2.4%)	0	2 (2.2%)
Renal failure	1 (1.2%)	0	1 (1.1%)
Tubulointerstitial nephritis	1 (1.2%)	0	1 (1.1%)
Respiratory, thoracic and mediastinal disorders	12 (14.5%)	0	12 (13.5%)
Acute respiratory failure	3 (3.6%)	0	3 (3.4%)
Dyspnea	1 (1.2%)	0	1 (1.1%)
Hypoxia	1 (1.2%)	0	1 (1.1%)
Pneumothorax	1 (1.2%)	0	1 (1.1%)
Pulmonary fibrosis	1 (1.2%)	0	1 (1.1%)
Pulmonary hemorrhage	1 (1.2%)	0	1 (1.1%)
Pulmonary hypertension	1 (1.2%)	0	1 (1.1%)
Pulmonary oedema	1 (1.2%)	0	1 (1.1%)
Respiratory distress	1 (1.2%)	0	1 (1.1%)
Respiratory failure	4 (4.8%)	0	4 (4.5%)
Vascular disorders	2 (2.4%)	0	2 (2.2%)
Hypertension	1 (1.2%)	0	1 (1.1%)

System Organ Class Preferred Term	EAP, Exclusive of Castelli (N = 83) n (%)	Castelli (N = 6) n (%)	Total EAP (N = 89) n (%)
Hypertensive crisis	1 (1.2%)	0	1 (1.1%)

Abbreviations: N, number of patients in treatment arm; n, number of patients of patients with adverse event

Source: Applicant's response to Information Request, December 12, 2025.

14.2 Summary of Re-adjudication by Patient

- Patient (b) (6)

Original assessment:

The patient had a non-evaluable platelet response as the patient never engrafted platelets. During the initial review, there was insufficient evidence that the patient is a responder based on only two parameters of the response endpoint definition. In addition, cyclosporin was stopped 10 days prior to starting narsoplimab, and the review team could not completely exclude the possibility that the findings for the two other response parameters, an improvement in LDH and in serum creatinine, were attributable to cessation of cyclosporin.

Re-assessment:

The reviewer acknowledges that failure to engraft platelets in the post-transplant setting is well described as a serious complication and that initial review and adjudication of the patient as a non-responder may have been overly stringent. If a patient has not engrafted platelets and developed TA-TMA, a platelet count response would likely not be demonstrated with TA-TMA directed therapy in setting of platelet engraftment. The patient demonstrated a clear response in terms of a large magnitude of reduction in LDH (LDH decreased from 712 U/L to < 1.5 x upper limit of normal) and serum creatinine (creatinine decreased 1.68 mg/dL to 1.03mg/dL). While not part of the TMA response definition as defined in the protocol, the haptoglobin increase from undetectable to the normal range is evidence of a reduction of hemolysis, a key feature of TA-TMA.

With respect to the observed improvement in LDH and renal function potentially being due to discontinuing the cyclosporin 10 days prior to narsoplimab, it is possible that cyclosporin discontinuation improved renal function, as renal toxicity is well described with this drug. However, given the patient met the criteria for high-risk TMA as defined in protocol, it is unlikely that a substantial improvement in hemolytic markers such as LDH and haptoglobin would be attributed solely to stopping the CNI. As stated by Schoettler et al, patients with high-risk features should receive TA-TMA directed therapies (Schoettler et al., 2023). Further, there is recent literature and retrospective studies suggesting that outcomes are not improved with CNI withdrawal in patients with TA-TMA (Acosta-Medina et al, 2025).

Narsoplimab-wuug

The reviewer concludes there is sufficient evidence that this patient is a responder to narsoplimab based on improvement in LDH and decrease in creatinine in setting of failure to engraft platelets.

- Patient (b) (6)

Original assessment:

The patient did not meet renal inclusion criteria, and the baseline serum creatinine was trending down prior to narsoplimab administration; therefore, the effect of narsoplimab on the renal response could not be determined. The platelet response is non-evaluable as the patient had not engrafted platelets, and thus, the patient only met one response criteria, LDH.

Re-assessment:

This is another case in which the strict TMA response definition was problematic in determining response to narsoplimab, as the patient did not engraft platelets so this component could not be assessed.

The patient did not meet renal inclusion criteria at the time of study entry; however, it is notable that the patient did meet renal inclusion criteria at the time of TA-TMA diagnosis. In addition, the decline in renal function starts early, often with proteinuria, and the change in eGFR may not appear until further into the progression of the TMA. The improvement in renal function was likely due to withdrawal of sirolimus and tacrolimus (nephrotoxic agents); however, normalization of renal function occurred following administration of narsoplimab therapy. Further evidence of response to TA-TMA is supported by reductions in hemolytic markers of LDH and haptoglobin.

In considering the totality of the clinical picture, it appears that this patient had a response to narsoplimab based on improvement in renal function and reduction in LDH in setting of failure to engraft platelets.

- Patient (b) (6)

Original assessment:

The patient had a non-evaluable platelet response due to failure to engraft platelets. The LDH response was transient, and tacrolimus was stopped the same day as narsoplimab initiated so we cannot conclude that the LDH response or renal response was due to narsoplimab.

Re-assessment:

Consistent with similar line of reasoning as above, it is not unusual for this medically complex population to have platelet engraftment failure and therefore the entire clinical picture should be considered.

Narsoplimab-wuug

During a Type A meeting with the Sponsor on February 9, 2022 (DARRTS 3/16/2022), the Applicant clarified that the patient did not discontinue tacrolimus as stated in the patient narrative. The Applicant stated this was an error in the patient narrative and confirmed with documentation in the case report form that tacrolimus continued to be administered. Therefore, the intervention of administration of narsoplimab in setting of declining renal function provides evidence that the renal response was likely due to narsoplimab.

Further, while there were increases in LDH ($>1.5\times$ ULN) during this time period, upon review of the record, these lab values appear to be single values and not sustained. This patient also had multiple infections during the course of transplant and while receiving narsoplimab. When looking at the overall trend of LDH from time of administration of narsoplimab, the trend was downward, and the LDH response criterion was met.

It is the clinical reviewer's assessment based on the totality of data that the patient did respond to narsoplimab given the observed improvements in LDH and renal function in setting of failure to engraft platelets.

- Patient (b) (6)

Original assessment:

The patient did not meet renal inclusion criteria. The patient met platelet and LDH response criteria, but there was no evidence of clinical improvement, and thus, the patient did not meet response criteria. The patient also had a diagnosis of microangiopathic hemolytic anemia (MAHA) and a positive direct antiglobulin test (DAT) 80 days prior to finally meeting inclusion criteria of a negative DAT, calling into question as to whether this patient truly had DAT negative TA-TMA.

Re-assessment:

The patient did not have an evaluable organ function component of TA-TMA to assess response. However, response components of LDH and platelet count were met. As supportive evidence, hemoglobin also increased by approximately 2g/dL. While hemoglobin increase in the absence of transfusions was not a component of the response criteria it is evidence of reduction in hemolysis.

Despite the positive DAT, it does appear that the patient had a diagnosis of TA-TMA. Recent consensus diagnostic criteria for TA-TMA does not include a negative DAT, unlike some the previously proposed diagnostic criteria such as Cho et al., 2010 and Li et al., 2019 (Schoettler et al., 2023).

It is the reviewer's assessment that this patient responded to narsoplimab. While there was no evaluable "clinical" component, the patient clearly had a substantial reduction in hemolysis. In addition, the patient was receiving platelet transfusions at the time of TA-TMA diagnosis and achieved platelet transfusion independence following narsoplimab, which represents a clinical benefit.

- Patient (b) (6)

Original assessment:

The patient's neurological response could not be clearly attributed to a treatment effect of narsoplimab. Additionally, we could not conclude that the 4-week transfusion free interval was due to narsoplimab due to confounders. The patient did not meet three response criteria.

Re-assessment:

The patient met LDH and platelet count response criteria. Regarding the neurologic response, it is this reviewer's opinion that this is very difficult to interpret given the supportive care measures that were implemented to treat posterior reversible encephalopathy syndrome (PRES). However, the clinical reviewer does acknowledge that a 4-week transfusion free period did occur, and this was likely due to narsoplimab, as it occurred in the setting of decreased hemolysis after initiation of narsoplimab therapy. The other concern was this patient was not considered a responder by the Applicant until 103 days after narsoplimab treatment. However, the clinical reviewer acknowledges that underlying comorbidities likely contributed to inability to assess response prior to this timepoint.

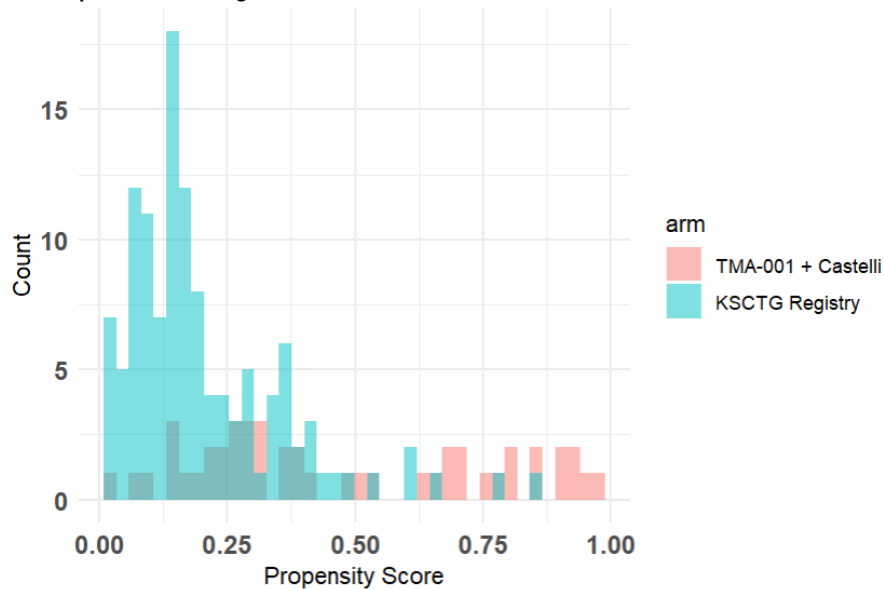
It is the clinical reviewer's assessment that the patient did have a response to narsoplimab.

14.3 Additional Survival Data

14.3.1 Propensity Score Comparison with pooled dataset

This subsection presents the comparison of patients from the pooled dataset of TMA-001 and EAP Subgroup (Castelli) (N=47) to KSTCG confirmed TMA patients (N=121). The distributions of propensity scores are shown in the following Figure 6. The patterns are similar to those reported in Section 7.2.2. There was partial overlap between the groups, and areas of limited common support were evident. In addition, some propensity scores were concentrated at the extremes, suggesting a potential violation of the positivity assumption.

Figure 6: Distribution of propensity scores of Pooled dataset and KSCTG Registry

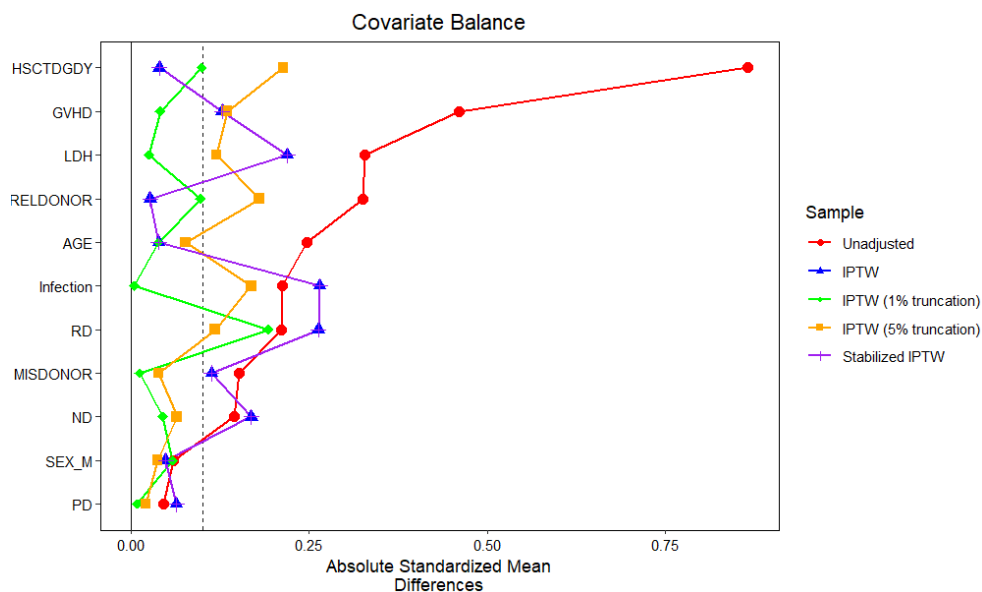


Covariate balance plots for the IPTW-based methods are shown in the following

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Figure 7. While weighting improved balance for many covariates, several still exhibited absolute standardized SMDs exceeding the commonly used threshold of 0.1. These residual imbalances should be taken into account when interpreting the adjusted results.

Figure 7: Covariate Balance Unadjusted and After IPTW Adjustment (Pooled dataset vs KSCTG Registry)



Source: FDA analysis.

Abbreviations: HSCTDGDY: Time from HSCT to TMA diagnosis; LDH: LDH ≥ 2 times ULN; ND: Neurological dysfunction; RELDONOR: Donor relationship; GVHD: Acute GVHD Grade 2-4; MISDONOR: Donor mismatch; PD: Pulmonary dysfunction; RD: Renal dysfunction.

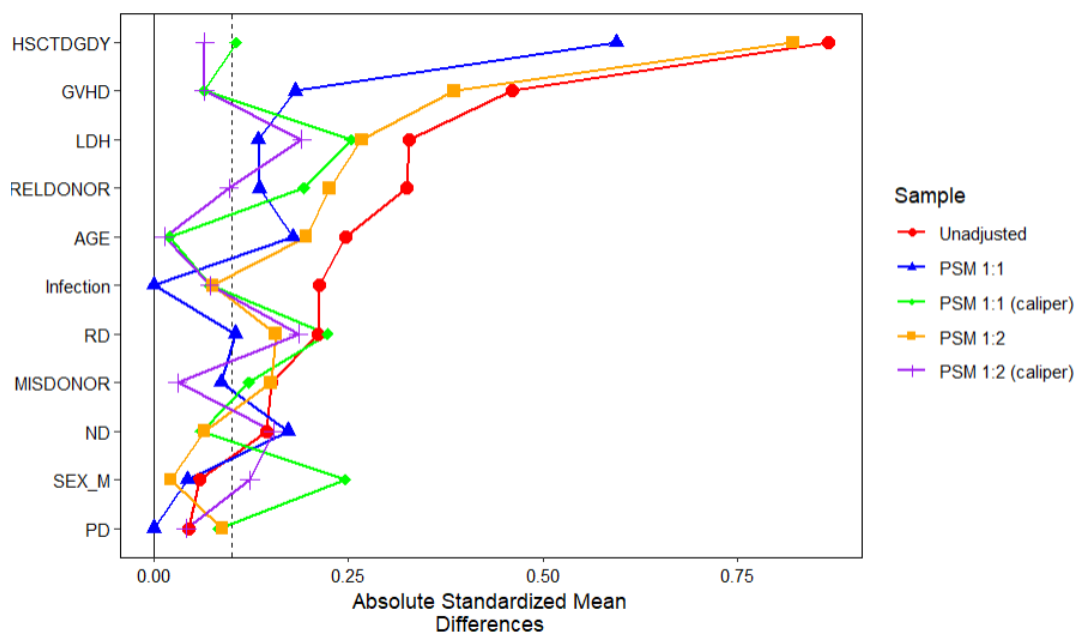
Covariate balance for the PSM-based methods is shown in

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Figure 8. The PSM methods without a caliper exhibited poor covariate balance, particularly for Time from HSCT to TMA diagnosis and GVHD. In contrast, the methods with a caliper generally performed better; although a few covariates had absolute SMDs that moderately exceeded the conventional threshold of 0.1. Nevertheless, applying a caliper reduced the number of matched pairs available for analysis.

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Figure 8: Covariate Balance Unadjusted and After PSM Adjustment (Pooled dataset vs KSCTG Registry)



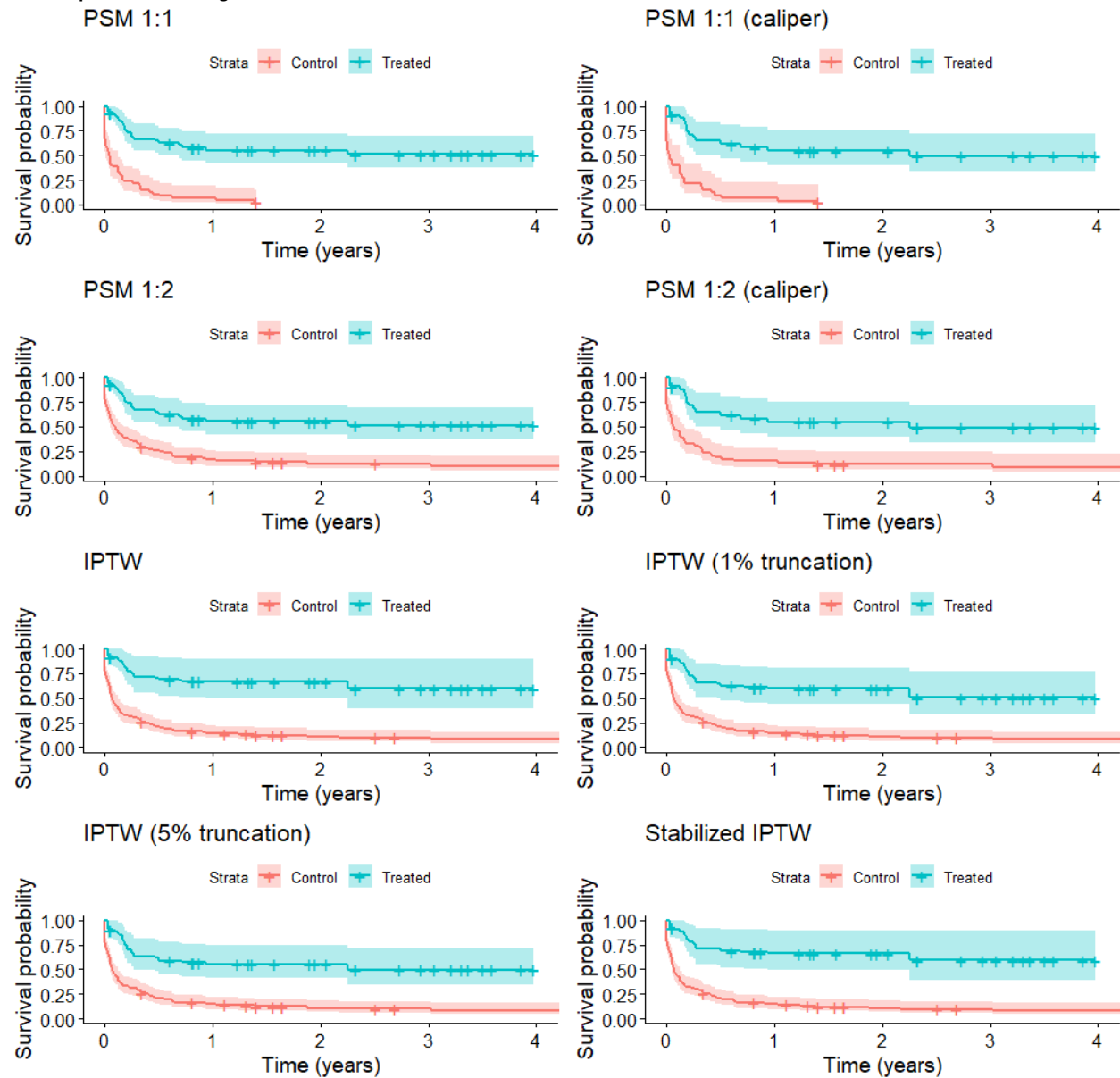
Source: FDA analysis.

Abbreviations: HSCTDGDY: Time from HSCT to TMA diagnosis; LDH: LDH ≥ 2 times ULN; ND: Neurological dysfunction; RELDONOR: Donor relationship; GVHD: Acute GVHD Grade 2-4; MISDONOR: Donor mismatch; PD: Pulmonary dysfunction; RD: Renal dysfunction.

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Figure 9. Across all the approaches, Kaplan–Meier curves showed separation between the treatment group and the external control cohort. These results reflect differences in observed survival outcomes across the methods applied.

Figure 9: Kaplan–Meier curves: Pooled dataset vs KSCTG Registry



The hazard ratios for OS comparisons are shown in Table 14. All methods yielded consistently very small p-values (<0.001), demonstrating robust nominally statistical significance. However, these findings should be interpreted with caution due to the issues and concerns discussed in Section 7.3.

Table 14. Hazard Ratios for Overall Survival: Pooled dataset vs KSCTG registry

Method	Estimated hazard ratio	95% CI	P-value
PSM	0.17	0.10, 0.30	<0.001

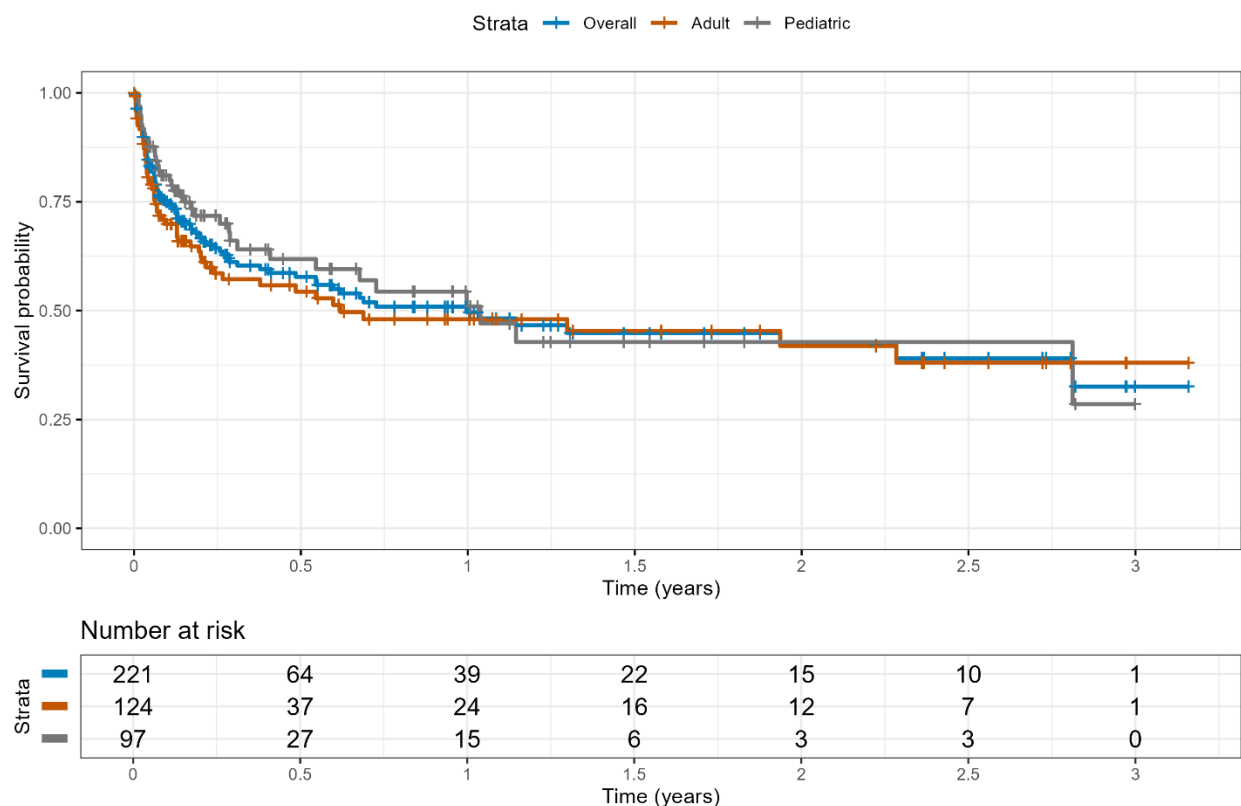
PSM (caliper)	0.17	0.09, 0.33	<0.001
PSM 1:2	0.29	0.18, 0.47	<0.001
PSM 1:2 (caliper)	0.28	0.15, 0.49	<0.001
IPTW	0.20	0.10, 0.41	<0.001
IPTW (1% truncation)	0.25	0.14, 0.43	<0.001
IPTW (5% truncation)	0.27	0.17, 0.44	<0.001
Stabilized IPTW	0.20	0.10, 0.42	<0.001

Source: FDA analysis.

Note: IPTW methods were implemented using average treatment effect (ATE) weights.

14.3.2 Kaplan-Meier Plots for OS in EAP

Figure 10: Kaplan-Meier Plots for Overall Survival, Narsoplimab EAP



Source: Statistical review team analysis based on adtte dataset

Note: Pediatric defined as < 17 years of age

14.4 Summary of Key Issues with the Original Submission

A summary of the key issues with the original submission is described in the Appendix

1. There were concerns regarding the conduct and efficacy analysis of TMA-001. Although TMA-001 had a protocol with inclusion and exclusion criteria and response criteria, the Applicant repeatedly issued waivers in order to enroll individual patients who did not meet the inclusion criteria and the lack of adherence to response criteria undermined the credibility of trial results. The trial enrolled 28 patients with HSCT-TMA. The review team discovered 11 patients who did not meet the entry criteria for whom waivers were granted. The Applicant concluded that the response rate based on the enrolled population was 17/28 (61%, 95% CI: 41, 79%). The review team independently reviewed each case in detail and concluded that there were 5 patients judged as responders by the Applicant who did not meet the response criteria. The FDA analysis of the response rate was 12/28 (43%) (95% CI 24% to 63%).
2. The primary analysis was to determine whether the study TMA-001 has demonstrated at least a 15% response rate of the study drug. The statistical assumptions in the protocol listed response rate of 15% for a non-treated group. However, they did not provide adequate justification for this assumed 15% response rate when the BLA was submitted.
3. Lack of confirmatory evidence. The Applicant submitted a mechanism of action (MOA) paper to provide further support regarding the mechanism of action of narsoplimab. There is sufficient literature to document the presence of MASP-2 and lectin components in TMA and HSCT-TMA. The Applicant also provided data based on in vitro and in vivo models of TMA demonstrating that narsoplimab mitigated complement deposition derived from the lectin/MASP2 pathway, reduced markers of endothelial cell injury and apoptosis, and delayed though did not prevent the onset of thromboses secondary to endothelial injury. Although there appears to be partial mitigation of C-activation and delay in thrombotic onset by narsoplimab in animal and in vitro models, the Applicant has not shown sufficient evidence that this is expected to translate into a measurable clinical benefit, either directly or indirectly.
4. The clinical pharmacology review team's assessment found no association between narsoplimab-wuug exposure or trough concentrations or the extent of complement component 4d (C4d) inhibition and the response to narsoplimab-wuug treatment in patients with HSCT-TMA. Almost all patients who did not respond to narsoplimab-wuug treatment had consistently comparable or higher exposure than patients who responded to treatment. Therefore, although related to the mechanism of action of the drug, the extent of C4d inhibition does not appear to be predictive of treatment response in HSCT-TMA patients.

14.5 Summary of Regulatory History

The following are summaries of the key regulatory interactions with the Sponsor from after the CRL to the submission of the response to clinical hold on XX date.

High level summaries from the meeting are described below, see finalized meeting minutes in DARRTS for further details.

Type A Meeting, February 9, 2022: Discussion of deficiencies of CRL and path forward

The Division acknowledged that they did not object to the proposed efficacy analysis during the IND stage of development, however, upon review of the application, significant efficacy review issues (including high proportion of patients not meeting inclusion/exclusion criteria, missing response data that introduced evaluation challenges, and significant issues with response interpretability), as described in the CRL were identified. These issues were determined to be too great, given the small number of patients evaluated.

The Division expressed concern regarding the robustness of the results of Study TMA-001 as the success of the trial hinged on a few patients with varying responses dependent upon different adjudications. The Agency reiterated concerns regarding the success threshold of 15% and concerns with the literature review to serve as an external control. The Agency also reiterated that the application lacked confirmatory evidence and the PD and PK data provided were not adequate.

Formal Dispute Resolution Request (FDRR) July 15, 2022.

The Applicant submitted a formal dispute resolution request (FDRR) to the Office of New Drugs(OND) on July 15, 2022. The appeal concerned the October 15, 2021, CRL issued by the Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN). On November 3, 2022, Peter Stein, MD, the deciding authority, issued a Formal Dispute Resolution Appeal Denied letter. In the letter, several paths forward were outlined. One approach would be to conduct a new trial—either randomized controlled or a single-arm trial using agreed upon responder criteria and compared to a well-matched historical control group and/or a pre-specified threshold based upon an independent literature assessment. Alternatively, the Applicant could consider a resubmission to address the CR deficiencies including results comparing response from Study TMA-001 to a threshold derived from an independent literature analysis and/or evidence of increased survival among patients from Study TMA-001 compared to an appropriate historical control group.

Post FDRR Meetings

- A Type B meeting was held on May 11, 2023 to discuss the Applicant's proposal for a resubmission which would include results comparing the response from Study OMS721-TMA-001 to a threshold derived from an independent literature analysis, as well as evidence of increased survival among patients from Study TMA-001 compared to an appropriate historical control group. In particular, the Applicant proposed to use data from

an independently conducted retrospective cohort study from the Kyoto Stem Cell Transplantation Group (KSCTG) for determination of survival estimates following TA-TMA diagnosis against which survival in OMS721-TMA-001 can be compared. The Division expressed concerns with this approach as highlighted in the Dispute Appeal Denial Letter, which noted survival results in the series reported by Matsui et al. (H Matsui, Y Arai et al. Blood Advances 4:2169-3179, 2020) with a <10% long-term survival in patients with TA-TMA appeared to be an outlier compared to other literature reports.

- Agency issued Written Responses on January 4, 2024, to provide feedback on the Applicant's resubmission proposal to provide evidence of efficacy based on the KSCTG registry to compared to survival data to Study TMA-001. In addition, the Applicant proposed to submit details from the single patient IND expanded access program and additional mechanistic information. The Agency expressed concerns with the Applicant's proposal in particular with comparability between the KSCTG registry patients and patients in Study TMA-001.
- A Type B face-to-face meeting was held with the Applicant on September 5, 2024 to discuss Omeros' proposal for resubmission of their BLA using the KSCTG registry as an external control group and using survival data from Omeros' EAP for mechanistic data as confirmatory evidence. The Division provided advice regarding the Applicant's proposal, stating that they were concerned the Applicants proposal for a resubmission may not be adequate to address the deficiencies outlined in the CRL without individual patient data and the limitations of using the real-world data for supporting the drug's efficacy.
- An Applicant-requested meeting took place on April 30, 2025. The Applicant received the acknowledgment letter for the resubmission of BLA 761152, which the Agency did not consider a complete response to the October 15, 2021 action letter, on April 28, 2025, and requested to meet with FDA to clarify the contents of the resubmission. The Applicant detailed which data was available for the KSCTG registry. The Applicant provided slides which stated: "We appreciate FDA's request for raw patient-level data, algorithms, and program codes that would permit the Agency to confirm which patients from the KSCTG registry (N = 2425) met diagnostic criteria for HSCT-TMA. Data necessary to verify or exclude a TA-TMA diagnosis are not collected or entered into the KSCTG registry. Omeros does not view the overall registry as germane to the external control in the BLA resubmission. The patients in the KSCTG registry who were diagnosed by their treating physician as having TA-TMA (N = 134) are the relevant population from which to begin the analysis of the external control." The Applicant also stated that "Additional data for the 134 patients, responding to nearly all of FDA's queries, have just been obtained and can be submitted shortly." The Agency stated that they would await the additional data and review once they were submitted.

14.6 Proposed consensus guidelines per Schoettler et al., 2023, for high-risk TA-TMA

Risk Stratification of TMA into Standard-Risk and High-Risk

Standard-Risk TMA	High-Risk TMA
Peak LDH <2 times ULN	Peak LDH >2 times ULN*
Spot rUPCR <1 mg/mg	Spot rUPCR ≥1 mg/mg
KDIGO stage I AKI	Any organ dysfunction developing in the setting of TMA except KDIGO stage I AKI (see Table 5)
Normal sC5b-9	Elevated sC5b-9 (> ULN)
	Concurrent acute GVHD grade II-IV*
	Concurrent systemic infection (bacterial or viral)*

KDIGO indicates Kidney Disease Improving Global Outcomes.
International Consensus Risk stratification is a modification of Jodele et al.¹, with additional risk factors indicated by an asterisk.

Source: Schoettler et al., 2023

14.7 Financial Disclosures

Financial disclosures for Study TMA-001 are detailed in the original review uploaded to DARRTS on October 15, 2021.

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Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number(s)	761152
Priority or standard	Priority
Submit date(s)	11/17/2020
Received date(s)	11/17/2020
PDUFA goal date	10/17/2021
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	See electronic stamp
Established/proper name	Narsoplimab-wuug
(Proposed) proprietary name	Yartemlea
Pharmacologic class	Complement inhibitor
Code name	OMS-721
Applicant	Omeros Corporation
Dosage form(s)/formulation(s)	Solution for injection
Dosing regimen	Intravenously once weekly (b) (4)
Applicant proposed indication(s)/ population(s)	Hematopoietic stem cell transplant-associated thrombotic microangiopathy
Proposed SNOMED indication	126729006 Thrombotic microangiopathy (disorder)
Regulatory action	Complete response
Approved dosage (if applicable)	N/A
Approved indication(s)/ population(s) (if applicable)	N/A
Approved SNOMED term for indication (if applicable)	N/A

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Glossary

ADA	antidrug antibody
ADAE	analysis dataset for adverse events
ADaM	analysis data model
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
AIHA	autoimmune hemolytic anemia
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AP	all patients (includes pharmacologically treated and nonpharmacologically treated)
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BSV	between subject variability
CCIT	container closure integrity test
CD	cluster of differentiation
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
$C_{\max}$	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSR	clinical study report
CV	coefficient of variation
DAH	diffuse alveolar hemorrhage
DAT	direct antiglobulin test
EBV	Epstein-Barr virus
EC_{50}	half maximal effective concentration
EFD	embryo-fetal development
ELISA	enzyme-linked immunosorbent assay
$E_{\max}$	maximum response
ETA	interindividual random effect
FAS	full analysis set
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
GBS	Guillain Barré syndrome
GD	gestation day

GI	gastrointestinal
GLP	good laboratory practice
GNP	glomerulopathy
GVHD	graft-versus-host disease
HIV-1	human immunodeficiency virus-1
HSCT	hematopoietic stem cell transplant
HSCT-TMA	hematopoietic stem cell transplant-associated thrombotic microangiopathy
HUS	hemolytic uremic syndrome
IC ₅₀	half maximal inhibitory concentration
ICU	intensive care unit
IND	investigational new drug
IR	information request
ISS	integrated summary of safety
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
K _D	dissociation equilibrium constant
K _m	Michaelis-Menten constant
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAC	membrane attack complex
MAGIC	Mount Sinai Acute GVHD International Consortium
MASP	mannan-binding lectin-associated serine protease
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRHD	maximum recommended human dosage
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NPTP	nonpharmacologically-treated patients
OFV	objective function value
OS	overall survival
PD	pharmacodynamic
PE	plasma exchange
PIND	pre-investigational new drug
PK	pharmacokinetic
PLT	plasma therapy
PRES	posterior reversible encephalopathy syndrome
Q	intercompartmental clearance
RRT	renal replacement therapy
SAE	serious adverse event
SC	subcutaneous(ly)
SDTM	study data tabulation model
SGE	special government employee
SVT	supraventricular tachycardia
TEAE	treatment-emergent adverse event

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TMA	thrombotic microangiopathy
T _{max}	time to maximum concentration
TMB	3,3',5,5'-tetramethylbenzidine
TTP	thrombotic thrombocytopenia purpura
ULN	upper limit of normal
USPI	United States Prescribing Information
V ₁	central volume of distribution
V ₂	peripheral volume of distribution
V _{max}	maximum elimination rate

I. Executive Summary

1. Summary of Regulatory Action

On November 17, 2020, Omeros Inc. submitted an original new drug application (NDA) for narsoplimab-wuug for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) based on data from an open-label, single arm phase 1/2 trial. 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. The proposed dosage of narsoplimab-wuug is 4 mg/kg administered as an intravenous infusion once a week (b) (4).

HSCT-TMA

HSCT-TMA occurs when endothelial injury, in the context of an allogeneic hematopoietic cell transplantation, causes microangiopathic anemia and platelet consumption, leading to microvascular thrombosis and fibrin deposition. HSCT-TMA may present with new onset or increasing proteinuria, hypertension, elevated serum creatinine and an increase in transfusion requirements with evidence of intravascular hemolysis. There is no consensus on a standardized diagnostic criterion, but most definitions include a combination of clinical and laboratory findings. The fatality rate of HSCT-TMA has been reported to be from 60-90% ([George et al. 2004](#)). HSCT-TMA is associated with increased morbidity from chronic kidney disease or other end organ dysfunction (i.e., pulmonary, gastrointestinal, neurological systems). The renal system is most frequently involved with acute kidney injury, chronic kidney disease, proteinuria, and hypertension. ([Laskin et al. 2011](#)). The use of high dose chemotherapy, radiation, calcineurin inhibitor (CNI) exposure, graft-versus-host disease (GVHD) and infections have all been reported as causative factors.

Current Treatment Options

There are no FDA approved products for the treatment of HSCT-TMA. The first line treatment of HSCT-TMA is generally limited to supportive therapy. Initial first line management has included withdrawal or minimization of CNIs (i.e., sirolimus, tacrolimus or both) as these agents have been implicated as risk factors although there is ongoing debate as to whether withdrawal is beneficial. Changing the immunosuppressive regimen is another important initial management step in patients with HSCT-TMA, but may take 1-2 weeks before an effect is observed. Additional measures include treatment of infections, GHVD and aggressive hypertension management.

Off-label medications such as rituximab*¹, defibrotide*² and complement inhibitors such as C5 inhibitors (ravulizumab³, eculizumab⁴)* have emerged as potential therapeutic agents in HSCT-TMA. There is no accepted pharmacodynamic marker to diagnose HSCT-TMA, or to assess prognosis/follow response to treatment, although several are being evaluated and used in clinical studies.

Study OMS-721-TMA-001 (Study TMA-001)

The Applicant conducted Study OMS721-TMA-001 (from here on referred to as Study TMA-001) in patients with HSCT-TMA. Study TMA-001 was originally designed as a 3-stage, open-label single-arm, ascending-dose-escalation study of narsoplimab-wuug evaluating patients with atypical hemolytic anemia (aHUS), TTP or HSCT-TMA. Stage 2 was a cohort expansion stage and Stage 3 was an optional extension of dosing for patients who completed stage 2. Enrollment of patients with TTP ended early as a treatment effect over standard of care was not observed, and enrollment of patients with aHUS was stopped early when a dedicated Phase 3 study was initiated for patients with aHUS.

Stage 2 of Study TMA-001 enrolled 28 patients with HSCT-TMA. Stage 2 of the trial consisted of a 4-week dosing period with optional extension of 4 additional weeks of dosing in Stage 3. Eligible patients were enrolled if they had a diagnosis of HSCT-TMA that persisted at least 2 weeks following modification or discontinuation of CNI treatment or at least 30 days after transplant with

¹ Rituximab is CD20-directed cytolytic antibody indicated for the treatment of adult patients with Non-Hodgkin's Lymphoma, adult patients with chronic lymphocytic leukemia, rheumatoid arthritis in combination with methotrexate in adult patients, granulomatosis with polyangiitis and microscopic polyangiitis in adult and pediatric patients 2 years of age and older, moderate to severe pemphigus vulgaris in adult patients.

² Defibrotide is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD). The mechanism of action has not been fully elucidated.

³ Ravulizumab is a complement inhibitor indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS).

⁴ Eculizumab is a complement inhibitor indicated for the treatment of patients with PNH, treatment of patients with aHUS, treatment of generalized myasthenia gravis in adult patients, treatment of neuromyelitis optica spectrum disorder in adult patients.

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platelet count <150,000/uL, evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > upper limit of normal (ULN), or haptoglobin < lower limit of normal), and renal dysfunction.

There was no internal control group.

Statistical Methods

The primary efficacy endpoint was the proportion of HSCT-TMA patients who responded to narsoplimab-wuug treatment. Treatment response was defined as both an improvement in TMA- associated laboratory markers (Requirement 1): platelet count and LDH, as well as improvement in clinical status (Requirement 2): either improvement in organ function (renal, pulmonary, GI or neurological) at any time point post-baseline during the study, or freedom of transfusion defined as no transfusions (RBC, platelet) for at least 4 weeks from the last transfusion except for patients who died within 4 weeks of the last transfusion. Improvement in organ function was determined by a clinical review of data by the local site investigators.

The primary analysis was to determine whether the study TMA-001 has demonstrated at least a 15% response rate of the study drug. The statistical assumptions in the protocol listed response rate of 15% for a non-treated group. However, they did not provide adequate justification for this assumed 15% response rate when the BLA was submitted. As noted above, there was no control group in the study; therefore, upon request, the Applicant submitted a literature-based review to justify the selected response rate from an external control group (see below).

Trial Conduct and Analyses of Efficacy

Although TMA-001 had a protocol with inclusion and exclusion criteria and response criteria, the Applicant repeatedly issued waivers in order to enroll individual patients who did not meet the inclusion criteria and the lack of adherence to response criteria undermined the credibility of trial results. The trial enrolled 28 patients with HSCT-TMA. The review team discovered 11 patients who did not meet the entry criteria for whom waivers were granted. The Applicant concluded that the response rate based on the enrolled population was 17/28 (61%, 95% CI 41, 79%). The review team independently reviewed each case in detail and concluded that there were 5 patients judged as responders by the Applicant who did not meet the response criteria. The FDA analysis of the response rate was 12/28 (43%) (95% CI 24% to 63%).

Literature-Based Historical Data of Untreated HSCT-TMA

The Applicant conducted a literature review based on publications from 2000 to 2020 to provide relevant clinical data on HSCT-TMA patients with the attempt to include similar risk factors and inclusion/exclusion criteria to those in pivotal Study TMA-001 to estimate

the response rate in patients not treated with narsoplimab, i.e., to provide justification for the 15% efficacy threshold for Study TMA-001. The clinical and statistical review teams identified a number of limitations to the use of the proposed literature based historical data to establish the response threshold. The limitations are outlined in the review. One hundred and seventy patients were identified for the final analysis for a historical control response rate of 32% (95% CI 26%, 40%). Although limitations exist in this exercise, at a minimum we can state that the chosen 15% appears too low and not supported by the literature review.

Mechanistic Evidence

The Applicant submitted a mechanism of action (MOA) paper to provide further support regarding the mechanism of action of narsoplimab. There is sufficient literature to document the presence of MASP-2 and lectin components in TMA and HSCT-TMA. The Applicant also provided data based on in vitro and in vivo models of TMA demonstrating that narsoplimab mitigated complement deposition derived from the lectin/MASP2 pathway, reduced markers of endothelial cell injury and apoptosis, and delayed though did not prevent the onset of thromboses secondary to endothelial injury. Although there appears to be partial mitigation of C-activation and delay in thrombotic onset by narsoplimab in animal and in vitro models, the Applicant has not shown sufficient evidence that this is expected to translate into a measurable clinical benefit, either directly or indirectly. It is possible that narsoplimab-wuug's inhibition of the lectin pathway is not sufficient to alter the outcome in HSCT-TMA in a sufficient magnitude to demonstrate clinical benefit.

Exposure-Response

The clinical pharmacology review team's assessment found no association between narsoplimab-wuug exposure or trough concentrations or the extent of complement component 4d (C4d) inhibition and the response to narsoplimab-wuug treatment in patients with HSCT-TMA. Almost all patients who did not respond to narsoplimab-wuug treatment had consistently comparable or higher exposure than patients who responded to treatment. Therefore, although related to the mechanism of action of the drug, the extent of C4d inhibition does not appear to be predictive of treatment response in HSCT-TMA patients.

Conclusions on Effectiveness

The FDA review team concludes that the data presented in BLA 761152 fail to demonstrate substantial evidence of effectiveness for narsoplimab-wuug for the treatment of HSCT-TMA. This conclusion is primarily based on the lack of at least one "adequate and well-controlled" trial. In addition, there is insufficient mechanistic evidence that narsoplimab-wuug will have the purported effect. It is also notable that, although we have limited confidence in the estimated response rate of 32% from the literature review, this percentage falls within the 95% confidence interval for the FDA's calculated response rate of 43% (95% CI 24% to 63%) not supporting a treatment effect.

To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation" (21 CFR 314.126(a)). This is the basis for the statutory requirement that approval be based on adequate and well-controlled investigations, as well as the basis for FDA's regulations describing the characteristics of such investigations (i.e., design elements that are generally intended to minimize bias and permit a valid comparison with a control to provide a quantitative assessment of drug effect).

There are certain circumstances when one adequate and well-controlled clinical investigation with compelling results, supported by additional data from the natural history of the disease could support an application. However, Study TMA-001 is a single arm uncontrolled study and the lack of a concurrent control prevents differentiation of the treatment effect from the confounding therapies, competing risks, and durability of response in patients with HSCT related TMA. The Applicant has not provided sufficient evidence for a reliable responder rate in an untreated group. The Applicant has not provided substantial evidence of effectiveness to support approval.

Safety

The safety database is limited given rarity of disease and small sample size. Observed serious adverse events included infections occurring in 36% of patients but given the lack of a control arm, the level of certainty for casual association between drug exposure and risk difficult to determine. If a clinical benefit of the treatment can be established for narsoplimab for the proposed indication, the risks, e.g., infections, can be adequately addressed in the product labeling.

Path Forward

Additional data will be needed to demonstrate efficacy of narsoplimab in HSCT-TMA. Possible options include:

If a reliable responder rate in a comparator group could be worked out, that might allow for retaining the current approach (threshold analysis). The Applicant could explore alternative external data (e.g. registries) to establish a responder rate. The Applicant would need to increase the total number of evaluable patients in TMA-001 so that the analysis isn't entirely post hoc, for example, to 50 as we stated in the minutes to the January 29, 2019 meeting (see last paragraph of response of FDA to Question 2).

Alternatively, the Applicant could conduct at least one randomized control trial to demonstrate the effectiveness of narsoplimab-wuug for the treatment of HSCT-TMA.

The Applicant will also need to provide confirmatory evidence; what this evidence will consist of can be discussed in a post action meeting. Of note, if the current trial that Omeros is now running in HUS were to be successful, that data might be used as confirmatory evidence for HSCT TMA.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	HSCT-TMA is a challenging complication of HSCT associated with significant morbidity and mortality. The complex pathophysiology and multiple contributing factors converges on final pathway involving endothelial cell injury and complement activation. Risk factors leading to endothelial damage include calcineurin inhibitors (CNIs), chemotherapy graft-versus-host disease (GVHD), total body irradiation and complement abnormalities. The gold standard for diagnosis is based on characteristic histological tissue findings however, bleeding risk often limits the ability to obtain tissue diagnosis. of Tthe lack of a consensus definition for diagnostic criteria and limited therapeutic options have contributed to challenges in describing incidence, severity, and defining a response. There are consistent reports that HSCT-TMA negatively impacts nonrelapse mortality and overall survival of hematologic malignancies. The clinical presentation ranges from mild, self-limited disease to multi-organ failure and death with involvement of the kidneys, gastrointestinal tract, central nervous system, heart, lung and serosal surfaces. Risk factors for HSCT-TMA include factors associated with HSCT, such as human leukocyte antigen (HLA)-mismatch, infections, GVHD, calcineurin inhibitors, high dose chemotherapy and radiation.	HSCT-TMA is a rare, serious life-threatening complication of HSCT in which endothelial injury and complement over activation results in microangiopathic hemolytic anemia,thrombocytopenia, and microvascular thrombosis. Patients are at high risk for significant morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are no FDA approved therapies for the treatment of HSCT-TMA. Management can be difficult and includes supportive therapies to include removing the insulting agent, transfusion support, and treating concurrent conditions such as GVHD and infections. While often considered as an initial step in management, modification and/or discontinuation of CNIs and/or sirolimus may not be effective as there is no clear evidence that discontinuation of these agents provide a benefit to patients with HSCT-TMA. The role of total plasma exchange in HSCT-TMA remains unclear and is often not beneficial. Off-label therapies such as defibrotide and rituximab have demonstrated variable response rates and have an unclear impact on mortality. Other complement inhibitors such as C5 inhibitors are currently being investigated and frequently used off-label in treatment of HSCT-TMA.	There is an unmet clinical need for an effective approved therapy for patients with HSCT-TMA.
Benefit	- In a single-arm, open-label Study TMA-001, 28 patients with HSCT-TMA received narsoplimab-wuug every week for 4 to 8 weeks. - In the FDA analysis 12/28 (43%) (95% CI 24% to 63%) responded to narsoplimab-wuug therapy defined by an improvement in platelets, reduction lactate dehydrogenase (LDH) and clinical improvement. The sponsor had intended to demonstrate at least a 15% response rate (based on expert opinion of the probable response rate in an untreated group). A literature review intended to support the selection of 15% was not adequate from a methodologic standpoint, however. It is also notable that, although we have limited confidence in the estimated response rate of 32% from the literature review, this percentage falls within the 95% confidence interval for the FDA's calculated response rate and thus, study data do not support a treatment effect.	The clinical benefit of narsoplimab-wuug cannot be determined from Study TMA-001.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	- Primary safety results included 28 patients with HSCT-TMA 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 narsopolimab. Serious adverse reactions in $>5\%$ of patients who received narsoplimab-wuug included, acute kidney injury, confusional state, acute respiratory failure, neutropenic sepsis, septic shock, pulmonary edema and vomiting. - Fatal adverse reactions occurred in 7% of patients, including neutropenic sepsis, and septic shock. - Dosage interruptions due to an adverse reaction occurred in 7% of patients who received narsoplimab-wuug included Escherichia sepsis, pyrexia, pulmonary alveolar hemorrhage, and acute myocardial infarction. - Serious infections occurred in 10/28 (36%) of patients. Neutropenic sepsis and septic shock occurred in two patients with HSCT-TMA. The following was reported in one patient; bacteremia, Escherichia sepsis, fungal infection, gastroenteritis, infection, viral pneumonia, viral respiratory tract infection, urosepsis, and pneumonia. - One patient with aHUS in clinical trials had a treatment-emergent adverse event (TEAE) of granulomatous orchitis.	The safety database is limited, as would be expected given the size of the affected population. The risks of narsoplimab-wuug could be sufficiently addressed through the Warnings and Precautions in the United States Prescribing Information (USPI). To minimize risk, labeling should include Warnings and Precautions for serious infections and the risk of tuberculosis. The risk of serious infections will be further assessed in a postmarketing requirement (PMR) should the product be approved, and can be negotiated in next review cycle.

2.2. Conclusions Regarding Benefit-Risk

HSCT-TMA is a rare disease that occurs post hematopoietic stem cell transplantation associated with high morbidity and mortality. There are no FDA available therapies and usual treatment is supportive care, modification of calcineurin inhibitors and off-label use of complement inhibitors. The nature of the benefit, size of treatment effect and clinical benefit of treatment effect cannot be determined based on the data submitted in this application. The safety database is limited given rarity of disease and small sample size. The therapeutic context in which this drug would be used is a condition for which there is high mortality with no available therapies. Observed serious adverse events included infections occurring in 36% of patients but given the lack of a control arm, the level of

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certainty for casual association between drug exposure and risk difficult to determine. If a clinical benefit of the treatment can be established for narsoplimab for the proposed indication, the risks, e.g., infections, can be adequately addressed in the product labeling to support informed individual benefit-risk assessments by patients and providers However, at this time no conclusion regarding benefit-risk can be determined as efficacy cannot be established for this product.

II. Interdisciplinary Assessment

3. Introduction

Product Introduction

Narsoplimab-wuug (proprietary name, YARTEMLEA), a new molecular entity (NME), 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.

The Applicant proposes the following indication: the treatment of patients with HSCT-TMA

The proposed dosing regimen is to administer narsoplimab-wuug 4 mg/kg once weekly, given as a 30-minute intravenous (IV) infusion (up to a maximum of 370 mg per infusion) (b) (4)

(U) (4)

Disease Background

Hematopoietic stem cell transplantation-associated thrombotic microangiopathy (HSCT-TMA) is a serious multisystem complication of transplant that is associated with significant morbidity and mortality. Milder forms of HSCT-TMA can result in an increased risk of long-term complications such as chronic kidney disease, while whereas severe forms are associated with mortality rates of 60-90% or even higher % or more ([Khosla et al. 2018](#); [Epperla et al. 2020](#)). HSCT-TMA is characterized by thrombocytopenia, Coombs-negative hemolysis (elevated lactate dehydrogenase, decreased haptoglobin, anemia), presences of schistocytes, and often renal injury or other organ involvement ([Elsallabi et al. 2016](#)). Extra- renal manifestations include central nervous system (convulsions, encephalopathy, drowsiness), cardiovascular complications (cardiomyopathy, myocarditis), and pulmonary and gastrointestinal involvement. It remains unclear if the high mortality rate is due to HSCT-TMA or a reflection of the severity of illness in patients with HSCT-TMA, unrelated to the etiology ([Schoettler et al. 2020](#)).

The true incidence of HSCT-TMA following allogeneic transplant is not known at as it is difficult to calculate given the lack of consensus on diagnostic criteria; studies have estimated the incidence anywhere from 0% to 64% ([Khosla et al. 2018](#)). One study cited an incidence of 8.2% in a comprehensive literature review published in 2004 based on 5423 allotransplant patients ([George et al. 2004](#)). A more recent review of nearly 2000 adult patients with HSCT identified 13% as having definite TMA ([Postalcioglu et al. 2018](#)).

Diagnosis is particular also challenging not only because of the complex and critically ill patient population, with but due to lack of a universally accepted diagnostic criteria. The diagnosis is difficult due to confounding complications such as graft-versus-host disease (GVHD), which can closely resemble certain aspects of HSCT-TMA ([Khosla et al. 2018](#)). Biopsy with clinical criteria can yield a definitive diagnosis, but many patients cannot undergo invasive procedures

without a high risk of bleeding or other complications ([Khosla et al. 2018](#)). Histologic features in the kidney include thickened capillary walls, occluded vascular lumen and endothelial cell separation ([Elsallabi et al. 2016](#)). Common features of HSCT-TMA include the presences of

schistocytes, elevated lactate dehydrogenase (LDH), decreased haptoglobin, renal or neurologic dysfunction, thrombocytopenia and anemia.

It is critical to differentiate HSCT-TMA from other TMA disorders such hemolytic uremic syndrome (HUS) and thrombotic TTP, in addition to disseminated intravascular coagulation and Coombs-positive hemolytic anemia. To aid in this, typically patients with a diagnosis HSCT-TMA are found to have a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity level >10%, normal coagulation studies and a negative direct antiglobulin test. Proteinuria and terminal complement activation were recently reported to be markers of poor prognosis in children and young adults with HSCT-TMA ([Jodele et al. 2014](#)). More recently it has been proposed to include elevated serum C5b-9 levels to the diagnostic criteria, in addition to hypertension and proteinuria as early clinical markers of HSCT-TMA ([Khosla et al. 2018](#)).

The pathophysiology of HSCT-TMA is complex and continues to evolve as it is investigated. Fundamental to the pathophysiology of HSCT-TMA is endothelial dysfunction ([Khosla et al. 2018](#)). Inflammatory cytokines result in endothelial damage and the activation of platelets as well as other coagulation factors, this in turn leads to thrombosis and fibrin deposition in the microvasculature of organs with subsequent end organ damage ([Kim et al. 2015](#)). Complement dysregulation has more recently been recognized as an important component of HSCT-TMA pathophysiology ([Kim et al. 2015](#)). Neutrophil extracellular traps (NETs) have also been implicated as a biomarker in HSCT-TMA ([Arai et al. 2013](#)).

Risk factors for HSCT-TMA include unrelated donor, human leukocyte antigen mismatch, high-dose chemotherapy, radiation therapy, immunosuppression agents (calcineurin inhibitors and newer mammalian target of rapamycin (mTOR) inhibitors such as sirolimus), advanced age, female sex, GVHD and infections ([Kim et al. 2015](#); [Elsallabi et al. 2016](#)).

The majority of cases present 20 to 100 days following transplant, although rare cases up to 2 years have been reported ([Jodele et al. 2014](#))([Gavrilaki et al. 2017](#); [Khosla et al. 2018](#)).

Current Therapy Options

There are no FDA-approved therapies for HSCT-TMA. Response rates to supportive care and off-label therapies are variable and range from 25% to 93%, with lower response rates attributed to plasma therapy and higher response rates seen with complement therapies ([Young et al. 2021](#)). The first-line management of HSCT-TMA is to provide supportive care which includes minimizing the insult that is causing endothelial damage, this may be an effective treatment strategy in patients with mild-moderate forms of HSCT-TMA ([Rosenthal 2016](#)). This approach includes treating infections and/or GVHD and hypertension management ([Jodele et al. 2015](#); [Khosla et al. 2018](#)). In addition, reduction or withdrawal of calcineurin inhibitors (CNIs) may be considered an initial step in HSCT-TMA management ([Ho et al. 2005](#); [Khosla et al. 2018](#)). Sometimes an effective approach is to change the immunosuppression from a CNI to an

alternative agent. Patients may not be responsive to withdrawal or modification of immunosuppressants and there is the potential to increase the risk of developing or worsening GVHD ([Elsallabi et al. 2016](#); [Li et al. 2019](#); [Epperla et al. 2020](#)).

Therapeutic plasma exchange (TPE), an established treatment for TTP, is not generally considered to be as beneficial ([Khosla et al. 2018](#)) for patients with HSCT-TMA. TPE may be more effective when initiated early or when there is factor H autoantibodies ([Khosla et al. 2018](#); [Young et al. 2021](#)). TPE is also associated with significant risks such as infection, hemorrhage, thrombosis, hypoxia, hypotension, serum sickness and anaphylaxis ([Khosla et al. 2018](#)).

There are several unapproved therapies that are used for the treatment of HSCT-TMA with varying response rates.

Response Rates to Unapproved Therapies

Response rates to supportive care and off-label therapies are variable and are reported to range from 25% to 93%, with lower response rates attributed to plasma therapy and higher response rates seen with complement therapies ([Young et al. 2021](#)) with the caveat that responses described in literature are frequently based on retrospective studies, use different response definitions and do not control for biases.

Rituximab, an anti-cluster of differentiation 20 (CD20) monoclonal antibody has also been used as monotherapy or in combination with other therapies such as TPE or defibrotide ([Jodele et al. 2015](#)). Jodele et al demonstrated a 67% response rate with rituximab with or without plasma exchange in 6 patients although this was single arm trial and prospective randomized trials needed. Rituximab is associated with adverse reactions including; infusion related reactions, peripheral edema and hypertension, as well as less common but serious adverse reactions such as hepatitis B virus reactivation and progressive multifocal leukoencephalopathy ([Kim et al. 2015](#)).

Defibrotide, a polydeoxyribonucleotide salt, has also been used for HSCT-TMA, with response rates ranging from 61-76% (monotherapy or in combinations with other therapies), although prospective studies are still needed ([Young et al. 2021](#)).

Other complement inhibitors are being investigated as therapeutic options. More recently, eculizumab, a C5 inhibitor, has been reported to be successful at resolving HSCT-TMA in 67-92% of patients in case reports and small studies to include pediatric population ([Khosla et al. 2018](#)). Many of the dosing regimens with C5 inhibitors in HSCT-TMA is guided by measuring CH50 and adjusting dosing schedule to maintain an adequately suppressed CH50 level. Larger, multi-institutional, controlled studies are need to better evaluate the use of C5 inhibitors in patients with HSCT-TMA. Reported case series have indicated a possible role for daclizumab and vincristine as well ([Elsallabi et al. 2016](#)).

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Determination of Response Rate: Appliant's vs. FDA's analysis

3.1.1.2. External Literature-Based Validation of Non-Treated Response Rate.

3.1.1.3. Subject Matter Expert Analysis

3.1.1.4. Duration of Response Between Responders and Nonresponders

3.1.1.5. Pediatric Indication

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Infections Were the Most Common TEAE Reported in Patients With HSCT-TMA

3.1.2.2. Based on the Mechanism of Action of Narsoplimab-wuug of Inhibition of MASP-2, Narsoplimab-wuug May Increase Risk of Tuberculosis Infections

3.1.2.3. Additional Analysis Conducted to Try to Determine if Narsoplimab-wuug Caused Drug Induced Liver Injury

3.1.2.4. Second Most Common TEAE (FMQ) Was Hemorrhage

3.1.2.5. Autoimmunity Has Rarely Been Associated With MASP-2 Deficiency; Given That Narsoplimab-wuug Inhibits MASP-2, There Is a Theoretical Risk of Autoimmunity

3.2. Approach to the Review

This is a joint review. Sarabdeep Singh and Yeh-Fong Chen focused on the data supporting efficacy. The Clinical Data Scientist team (Xin Gao and Jinzhong Liu) focused on the data supporting safety and efficacy. Carrie Diamond and Tanya Wroblewski focused on the data supporting safety and efficacy. Carrie Diamond and Tanya Wroblewski independently reviewed the cases and readjudicated responses based on response criteria. Pedro DelValle, Bo Lee, Geeta Negi reviewed the nonclinical toxicology studies, and LaiMing Lee and Sudharshan Hariharan reviewed the clinical pharmacology data. [Table 3](#) provides an overview of the clinical trials submitted in support of the efficacy and/or safety determinations for narsoplimab-wuug.

Table 3. Clinical Trials Submitted¹ in Support of Efficacy and Safety Determinations

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized/Actual Enrolled	Number of Trial Sites
OMS721-TMA-001	Patients diagnosed with HSCT-TMA, aHUS and TTP	Control Type: No treatment concurrent (single-arm) Randomization: No randomization (single-arm) Blinding: Open-label Biomarkers: No biomarkers Innovative design features: None	Drug: Narsoplimab-wuug Dose: 0.675 mg/kg, 2 mg/kg, 4 mg/kg, 370 mg, IV, 400 mg IV Number treated: 58 Duration: up to 24 weeks. Poland specific amendment: 52 weeks for aHUS	Primary: improvement in TMA markers and clinical improvement. Safety. Secondary: survival, laboratory measures, duration of response, transfusion requirements, PK, PD and immunogenicity	Planned: 60 Actual: 58 (28 with HSCT-TMA)	Centers: 27 Countries: 12

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized/Actual Enrolled	Number of Trial Sites
OMS721-HUS-002	Patients with plasma therapy-resistant/responsive aHUS	Control Type: No treatment concurrent (single-arm) Randomization: No randomization (single-arm) Blinding: Open-label Biomarkers: No biomarkers Innovative design features: None	Drug: Narsoplimab-wuug Dose: 370 mg IV followed by 150 mg SC Number treated: 6 Duration (quantity and units): 104 weeks	Primary: effectiveness evaluation based on platelet count change from baseline Secondary: safety and tolerability assessment, TMA response, eGFR measures, hematological normalization, EQ-5D-5L measure, changes in serum creatinine, LDH, and haptoglobin, PK measures, PD measures, ADA response	Planned: 80 Actual: 6 (ongoing)	Centers: 2 Countries: 2

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized/Actual Enrolled	Number of Trial Sites
OMS721-GNP-001	Patients with IgA/membranous nephropathy; lupus nephritis; or C3 glomerulopathy	Control Type: Placebo concurrent or No treatment concurrent (single-arm)	Drug: Narsoplimab-wuug	Primary: safety and tolerability assessment, PD measures Secondary: effectiveness assessment based on proteinuria and urine albumin/creatinine, PK measures, PD measures, ADA	Planned: 54	Centers: 1
		Randomization: Standard randomization or No randomization (single-arm)	Dose: 4 mg/kg, 370 mg, IV, 150 mg SC		Actual: 29 (ongoing)	Countries: 7
		Blinding: Double-blind or Open-label	Number treated: 29			
		Biomarkers: No biomarkers	Duration (quantity and units): 12 wks + potential 12 wks Open label			
		Innovative design features: None				
OMS721-IGA-001	Patients with IgA nephropathy	Control Type: Placebo	Drug: Narsoplimab-wuug	Primary: proteinuria assessed by 24-hour urine protein excretion (UPE) in g/day at 36 weeks from baseline Secondary: effectiveness assessment based on proteinuria, durability, renal function, safety, tolerability, PK measures, PD measures, immunogenicity	Planned: 450	Centers: 57
		Randomization: Standard randomization	Dose: 370 mg, IV		Actual: 55 (ongoing)	Countries: 13
		Blinding: Double-blind	Number randomized: 55			
		Biomarkers: No biomarkers	Duration (quantity and units): 12 wks + potential 6 wks extended treatment and/or retreatment			
		Innovative design features: None				

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized/Actual Enrolled	Number of Trial Sites
OMS721-NHV-001	Healthy male	Control Type: Placebo concurrent	Drug: Narsoplimab-wuug	Primary: safety assessment and PK parameter measures Secondary: PD measures, ADA	Planned: 50	Centers: 1
		Randomization: Standard randomization	Dose: <2 mg/kg IV or SC, 400 mg IV		Actual: 41	Countries: 1
		Blinding: Double-blind	Number treated: 41			
		Biomarkers: No biomarkers	Duration (quantity and units): Single dose			
		Innovative design features: None				
OMS721-NHV-002	Healthy	Control Type: Placebo concurrent	Drug: Narsoplimab-wuug:	Primary: safety assessment, PK parameter measures Secondary: PD measures, ADA response, changes in MBL, MASP-2 and IgG	Planned: 88	Centers: 4
		Randomization: Standard randomization	Dose: 2 mg/kg IV, 4 mg/kg IV, >4 mg/kg SC, 2-4 mg/kg SC		Actual: 90	Countries: 2
		Blinding: Double-blind	Number treated: 90			
		Biomarkers: No biomarkers	Duration (quantity and units): Up to 6 weeks			
		Innovative design features: None				

¹Source: Clinical data analyst, Clinical Study Report and adsl.xpt

Abbreviations: ADA, antidrug antibody; aHUS, atypical hemolytic uremic syndrome; eGFR, estimated glomerular filtrations rate; IgA, immunoglobulin A; IgG, immunoglobulin G; IV, intravenous(ly); LDH, lactate dehydrogenase; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; wks, weeks

4. Patient Experience Data

There were no patient experience data submitted for the Phase 2 Study TMA-001, in patients with HSCT-TMA.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Complement Inhibitor
Mechanism of action	Mannan-binding lectin-associated serine protease-2 (MASP-2) is a key enzyme for the activation of the lectin pathway of complement, which leads to cleavage of complement components C2 and C4, followed by C3 and C5 activation and formation of the membrane attack complex (MAC). OMS721 selectively blocks MASP-2 and inhibits the lectin pathway of complement activation, which is postulated to reduce prothrombotic responses in thrombotic microangiopathy.
Active moieties	OMS721 is a human IgG4 monoclonal antibody directed against MASP-2.
QT prolongation	Not applicable since narsoplimab-wuug is a mAb
	General Information
Bioanalysis	Concentrations of narsoplimab-wuug in human serum were determined using a validated ELISA method at the Bioanalytical Laboratory of (b) (4). The method included ELISA plates coated with MASP-2A, mouse antihuman IgG4 HRP conjugated antibodies, and TMB as the detection substrate. The method validation is acceptable per FDA's Bioanalytical Method Validation Guidance.
Healthy subjects versus patients	Clearance (CL) in healthy subjects who received IV narsoplimab-wuug 4 mg/kg once weekly for 6 weeks was 0.128 L/h and is similar to the CL of 0.122 L/h in HSCT-TMA patients who received IV narsoplimab-wuug 4 mg/kg or 370 mg once weekly for up to 8 weeks.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	In healthy subjects, PK parameters (mean (%CV)) following multiple dosing IV narsoplimab-wuug 4 mg/kg are presented below: AUC: 2314 (27.3) mcg.h/mL C _{max} : 36.9 (18.2) mcg/mL CL: 0.128 (32) L/h
Range of effective dosage(s) or exposure	Narsoplimab-wuug 4 mg/kg capped to 370 mg results in exposure that results in >80% inhibition of C4d through the interdosing interval. However, it is not clear if C4d inhibition is reflective of clinical response.

BLA 761152
Narsoplimab-wuug

Characteristic	Drug Information
Maximally tolerated dosage or exposure	A maximum tolerated dose (MTD) was not identified in any of the clinical studies. The Applicant selected 4 mg/kg for evaluation in HSCT-TMA patients in Study TMA-001 based upon mean trough C4d inhibition of approximately 80%.
Dosage proportionality	In healthy subjects who received IV narsoplimab-wuug 2 mg/kg and 4 mg/kg once weekly for 6 weeks, there was a less than dose proportional increase in C _{max} and AUC _{0-tau}
Accumulation	Mean (range): 1.31 (1.02 - 1.75)
Time to achieve steady-state	Time to steady-state: 15 days (after three once weekly IV dosing of 4 mg/kg narsoplimab-wuug).
Bridge between to-be-marketed and clinical trial formulations	The proposed product is narsoplimab-wuug injection for infusion, 185 mg/mL, which is the same product and formulation used in the safety and efficacy Study TMA-001.
Absorption	
Bioavailability	100% (IV infusion)
T _{max}	Median (range): 0.5 (0.5 – 0.5) h
Food effect (fed/fasted) Geometric least square mean and 90% CI	Not applicable as the administration route is by IV infusion.
Distribution	
Volume of distribution	V _z =36.5 L
Plasma protein binding	Narsoplimab-wuug, a monoclonal antibody administered by IV infusion, is expected to be limited to the vascular and interstitial space.
Drug as substrate of transporters	Narsoplimab-wuug, a monoclonal antibody, is not expected to be a substrate of transporters.
Elimination	
Mass balance results	No mass balance study was conducted.
Clearance	Mean (%CV): 0.128 (32) L/h
Half-life	198 h
Metabolic pathway(s)	Narsoplimab-wuug, a monoclonal antibody, is expected to be metabolized into small peptides and amino acids via nonspecific proteolytic degradation.
Primary excretion pathways (% dosage)	Elimination of narsoplimab-wuug via renal excretion is expected to be insignificant.
Intrinsic Factors and Specific Populations	
Body weight	The clearance of narsoplimab-wuug is affected by body weight; therefore, weight-based dosing of 4 mg/kg is recommended. However, there is a dose cap of 370 mg. A weight-based dosing and dose cap will provide comparable steady-state exposure across all body weight ranges.
Age	Age did not affect narsoplimab-wuug exposure based upon popPK analysis.
Renal impairment	Not applicable as renal excretion of narsoplimab-wuug is expected to be insignificant.
Hepatic impairment	Not applicable as hepatic metabolism is not mechanism for narsoplimab-wuug elimination.

BLA 761152
Narsoplimab-wuug

Characteristic	Drug Information
Drug Interaction Liability (drug as perpetrator)	
Inhibition/induction of metabolism	Narsoplimab-wuug, a monoclonal antibody, is not expected to be an inhibitor or inducer of CYP enzymes.
Inhibition/induction of transporter systems	Narsoplimab-wuug, a monoclonal antibody, is not expected to be an inhibitor or inducer of transporters.
Immunogenicity (if applicable)	
Bioanalysis	Anti-Narsoplimab-wuug antibodies were measured by electrochemiluminescence immunoassay (ECLIA) via C4d on mannan-coated beads.
Incidence	Two of 6 (33%) healthy subjects who received IV narsoplimab-wuug 4 mg/kg once weekly for 6 weeks developed antidrug antibodies. Narsoplimab-wuug exposure (AUC_{0-last}) was 50% lower (1810 vs. 2781 mcg.h/mL) in the 2 subjects with ADA. In HSCT-TMA patients who received IV narsoplimab-wuug 4 mg/kg or 370 mg once weekly for up to 8 weeks, 2 of 28 (7%) developed antidrug antibodies. One of the 2 HSCT-TMA patients developed neutralizing antibodies.
Clinical impact	Compared to HSCT-TMA patients without antidrug antibodies, total clearance (CL_{total}) was greater in HSCT-TMA patients with antidrug antibodies. Based upon popPK V_{max} was 143% higher in patients with ADA, and is predicted to result in 22% lower AUC_{ss} and 52% lower $C_{min,ss}$. The patient who developed neutralizing antibody was a treatment responder.

Abbreviations: ADA, antidrug antibody; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly); mAb, monoclonal antibody; MASP-2, mannan-binding lectin-associated serine protease; PK, pharmacokinetic; popPK, population pharmacokinetics; TMB, 3,3',5,5'-tetramethylbenzidine

5.1. Nonclinical Assessment of Potential Effectiveness

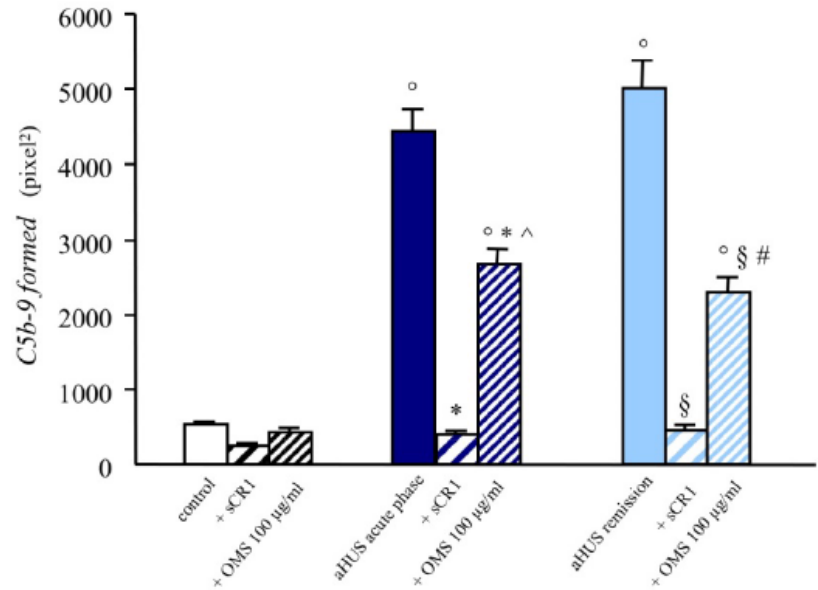
Summary: Narsoplimab is specific for MASP-2 and selectively blocks lectin-initiated complement activation. The lectin pathway contributes to complement (C) activation and thrombus formation in defined in vitro and in vivo models of endothelial injury, which presumably reflect key elements of TMAs. Narsoplimab inhibits this contribution, but other C-activation pathways are also contributory; thus, vascular occlusion appears delayed, but occlusion still occurred in the murine model of TMA.

Background: OMS721 (narsoplimab) binds MASP-2 with a K_D of 62-73pM and selectively inhibits the lectin pathway of complement (IC_{50} 2.5nM). Specificity for the lectin pathway was evaluated by demonstrating a dose-dependent inhibition of lectin-dependent membrane attack complex (MAC) deposition with an IC_{50} of 1nM without significant inhibition of the alternative- or classical pathway-induced MAC deposition up to 100nM. In vivo studies in healthy animals demonstrated that OMS721 has a pharmacokinetic-pharmacodynamic (PK-PD) relationship with eventual saturation of lectin-dependent C4 and C3 activation.

Key pharmacodynamic effects of OMS721 were evaluated in an ex vivo model of aHUS and an in vivo mouse model of TMA. In the ex vivo aHUS study, serum from patients with aHUS (during the acute phase of the disease and at remission) was incubated with activated human microvascular endothelial cells in vitro in the presence and absence of OMS721.

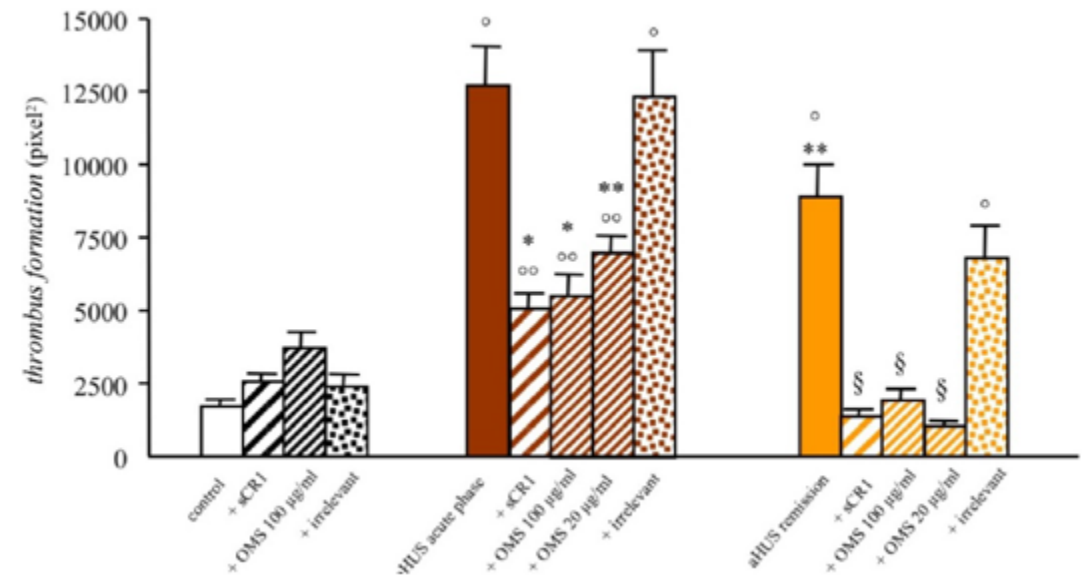
OMS721 partially reduced C5b-9 deposition (range 40% - 54%; [Figure 1](#)) and reduced platelet adherence (range 57% - 79%; [Figure 2](#)) on the surface of microvascular endothelial cells at the timepoint measured upon exposure to serum of patients with aHUS both in the acute phase and in remission. Of note, [Figure 2](#) indicates that the pan-complement inhibitor sCR1 abrogated C5b-9 deposition whereas narsoplimab exhibited partial inhibition, demonstrating that complement pathways other than lectin substantially contribute to C5b-9 deposition induced by aHUS serum.

Figure 1. Effect of Narsoplimab and a Pan-Complement Inhibitor on aHUS Serum-Induced C5b-9 Deposition on Activated Human Microvascular Endothelial Cells



Source: Excerpted from the Applicant's submission
aHUS = atypical hemolytic uremic syndrome; C5b-9 = complement component 5b-9;
sCR1 = soluble complement receptor 1; control = normal healthy volunteer serum
Data are mean $\pm$ standard error
° P<0.0001 vs. control; *P<0.0001 vs. aHUS acute phase untreated; ^P <0.0001 vs. aHUS acute phase+sCR1
§ P<0.0001 vs. aHUS remission phase untreated; #P<0.0001 vs. aHUS remission phase+sCR

Figure 2. Effect of Complement Inhibitors on aHUS Serum-Induced Thrombus Formation (Platelet Adherence) on ADP-Activated HMEC1



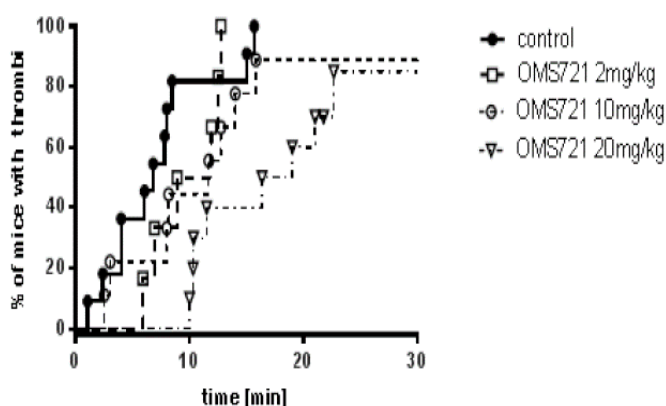
Source: Excerpted and revised from the Applicant's submission
Data are mean $\pm$ SE.
° P<0.0001; °° P<0.01 vs. control; * P<0.0001; ** P<0.01 vs. aHUS acute phase untreated; § P<0.0001 vs. aHUS remission phase untreated
Abbreviations: ADP, adenosine 5'-diphosphate; aHUS, atypical hemolytic uremic syndrome; HMEC-1, human microvascular endothelial cells 1. 'Irrelevant' = nonspecific antibody

In vivo efficacy of OMS721 was assessed in a mouse model of TMA in which localized thrombosis was induced by photo-activation of fluorescein isothiocyanate-labeled dextran in the microvasculature of the cremaster muscle of C57Bl/6 mice.

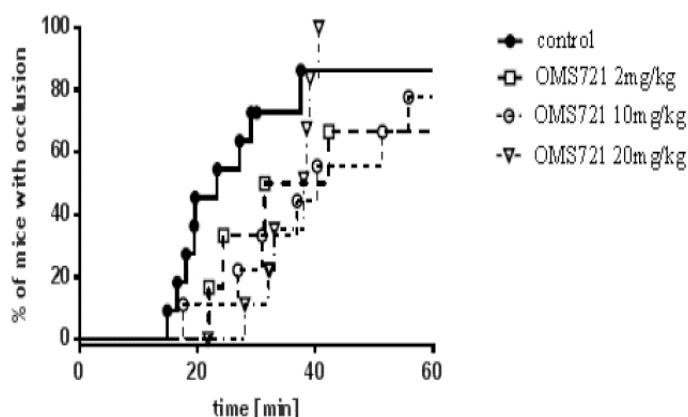
Administering OMS721 one hour before induction of thrombosis delayed the initiation of thrombus formation and the time to complete vessel occlusion, demonstrating a contribution of the lectin complement pathway to the thrombotic response to injury ([Figure 3](#)). However, over time, thrombus formation still occurred in a similar percentage of mice regardless of treatment, suggesting that pathways in addition to lectin C activation contribute to and eventually result in microvascular thrombosis.

Figure 3. OMS721 Delays Onset of Thrombus Formation (top panel) and Microvascular Occlusion (bottom panel) in the Mouse Model of FITC-Dextran-Induced TMA

Kaplan-Meier Plot showing percentage of mice with thrombus as a function of time in FITC-Dextran induced thrombotic microangiopathy



Kaplan-Meier Plot showing percentage of mice with microvascular occlusion as a function of time in FITC-Dextran induced thrombotic microangiopathy



Source: Excerpted from the Applicant's submission

Abbreviation: FITC, fluorescein isothiocyanate

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. Study TMA-001

The proposed narsoplimab-wuug dose and dosing regimen is 4 mg/kg, given as a 30-minute IV infusion (up to 370 mg per infusion) once weekly. The clinical studies to support the proposed dose and dosing regimen include a multiple, dose-escalation study (OMS721-NHV-002) in healthy subjects and a small safety and efficacy study (TMA-001) in HSCT-TMA patients.

The Applicant conducted a multiple dose escalation study (OMS721-NHV-002) in healthy male and female subjects to assess the PK, PD, and safety of narsoplimab-wuug IV and SC. The study included assessment of C4d inhibition, a pharmacodynamic marker of the lectin pathway that the Applicant hypothesized would be representative of clinical efficacy. After the first IV infusion of narsoplimab-wuug 4 mg/kg, maximum inhibition of C4d was approximately 95% at 6 hours after the start of infusion and was sustained above 80% from 48 to 312 h after the last dose. With narsoplimab-wuug 2 mg/kg, C4d inhibition above 80% was maintained from 2 to 48 h after the first dose. The ex-vivo assay of C4d inhibition was used to justify the selection of a maximum dose of 4 mg/kg IV dosing in the Phase 2 studies as it was expected to maintain mean lectin pathway inhibition >80% for about 168 hours, the proposed dosing interval.

Evaluation of inhibition by narsoplimab-wuug of the lectin-pathway of complement activation, and specifically the lectin-mediated complement component 4d (C4d) formation, is not an unreasonable approach to dose selection; however, it is important to note that there are no available biomarkers known to predict treatment response in HSCT-TMA.

The Applicant conducted Study TMA-001, which was initially a proof-of-concept, dose-finding study in patients with HSCT-TMA, but then was submitted as the ‘pivotal’ safety and efficacy study for the proposed indication. In stage 1 of Study TMA-001, narsoplimab-wuug was administered to patients in 3 cohorts (Cohorts 1, 2, and 3), with dose escalation by cohort (0.67 mg/kg, 2 mg/kg, and 4 mg/kg, respectively) in order to identify the optimal dosing regimen. After enrollment and dosing at each dose level, a safety review by the clinical study monitoring team was conducted to determine whether dose escalation should proceed. In Stage 2 of the Core Study (refers to data collected under protocol versions prior to Amendment 11.1), the dose selected in the first stage (4 mg/kg) was administered to patients by disease etiology (aHUS alone in Cohort 4; TTP or HSCT-TMA in Cohort 5). Patients enrolled in Stages 2 and 3 prior to Amendment 10 (Appendix [III.15](#)) received narsoplimab-wuug 4 mg/kg. As of Amendment 10 of the protocol, newly enrolled patients received a fixed narsoplimab-wuug dose of 370 mg. Preliminary PK evaluation suggested that clearance (CL) was not affected by body weight. In the Core Study, patients in Stage 2 could proceed to Stage 3 based on the patients’ response to therapy, safety, and tolerability.

The review team’s assessment found no association between narsoplimab-wuug exposure or trough concentrations or the extent of C4d inhibition and the response to narsoplimab-wuug treatment in patients with HSCT-TMA. Almost all non-responders to narsoplimab-wuug treatment had consistently comparable or higher exposure than patients who responded to

treatment, with trough narsoplimab-wuug concentrations consistently above IC80 for C4d inhibition in majority of non-responders ([Figure 34](#), Section [14.3.4](#)). Conversely, amongst the treatment responders, many patients had trough narsoplimab-wuug concentrations just above IC₅₀ for C4d inhibition.

Therefore, although related to the mechanism of action of the drug, the extent of C4d inhibition does not appear to be predictive of treatment response in HSCT-TMA patients at the studied dosage.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Study OMS-721-TMA-001 (TMA-001)

Overview and Objectives

To support the proposed indication, the Applicant conducted Study 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.”

Study TMA-001 was originally designed to provide preliminary information on the safety and efficacy of narsoplimab-wuug for the treatment of TMAs (aHUS, TTP, or HSCT-TMA). Based on preliminary results, the study was modified to support the indication for treatment of HSCT-TMA with narsoplimab-wuug.

Primary Objective (HSCT-TMA):

The coprimary objectives of this study were to:

- Assess the safety and tolerability of multiple-dose administration of narsoplimab-wuug in patients with TMA, including patients with HSCT-TMA, aHUS, and TTP
- Evaluate the efficacy of narsoplimab-wuug in patients with HSCT-TMA by response. Response is defined as meeting both of the following criteria:
 - Improvement in TMA laboratory markers of platelet count and LDH
 - Improvement in clinical status (explained in detail below)

Secondary Objectives (HSCT-TMA):

- 100-day survival
- Overall survival
- Platelet count change from baseline
- Lactate Dehydrogenase (LDH) change from baseline
- Haptoglobin change from baseline

- Hemoglobin change from baseline
- Duration of response (defined as the time between the first date a response is achieved and the first date the platelet count decreases by more than 50% from the maximum and LDH increases to >150% of the upper limit of normal).
- Creatinine change from baseline in patients who had no reason other than HSCT-TMA for creatinine elevation
- Freedom from platelet transfusion in patients who received at least 1 platelet transfusion within 2 weeks of the first narsoplimab-wuug dose
- Freedom from red blood cell (RBC) transfusion in patients who received at least 1 RBC transfusion within 2 weeks of the first narsoplimab-wuug dose
- The PK of multiple-dose administration of narsoplimab-wuug (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The PD of multiple-dose administration of narsoplimab-wuug (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The immunogenicity of multiple-dose administration of narsoplimab-wuug (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)

Study Design

Study TMA-001) is a Phase 2, open-label, uncontrolled, 3-stage ascending-dose-escalation study in patients with TMA, specifically aHUS, TTP, and HSCT-TMA. The study design described below will focus on HSCT-TMA patients which is used to support the HSCT-TMA indication for narsoplimab-wuug.

In Stage 1 of the study, narsoplimab-wuug was administered to 3 cohorts (Cohort 1, Cohort 2, and Cohort 3), with dose escalation by cohorts. Each patient in stage 1 received 4 weekly doses of narsoplimab-wuug. In Stage 2 of the study, the dose selected in the first stage (4 mg/kg IV) was administered to expanded cohorts. Prior to Amendment 10, patients in Stage 2 with HSCT-TMA received 4 weekly doses (See [Table 115](#) for details on protocol amendments). Patients in Stage 2 who demonstrated improvement in TMA signs during their initial treatment period were eligible for Stage 3, which provided an additional 4 weekly doses in patients with HSCT-TMA. Dosing and administration of narsoplimab-wuug is described in [Table 6](#). Design schema of Stage 1, 2, and 3 (HSCT-TMA patients only) are shown in Figures [4](#), [5](#), and [6](#) below. Standard treatments were continued on study.

Table 6. Study TMA-001 Treatment Stages and Cohorts

Stage, Cohort	Number of Patients Planned	OMS721 Dose
1, Cohort 1	3	0.675 mg/kg IV weekly x 4
1, Cohort 2	3	2.0 mg/kg IV weekly x 4
1, Cohort 3	3	4.0 mg/kg IV weekly x 4
2, Cohort 4 ^a	40 (aHUS)	4.0 mg/kg IV weekly x 12
3, Cohort 4 ^a	≤ 40 (aHUS)	4.0 mg/kg IV weekly x 12
2 ^b , Cohort 5	40 (TTP ^c /HSCT-TMA)	4.0 mg/kg or 370 mg IV weekly x 4
3 ^b , Cohort 5	≤40 (TTP ^c /HSCT-TMA)	4.0 mg/kg or 370 mg IV weekly x 4

Source: Applicant's TMA-001 Protocol

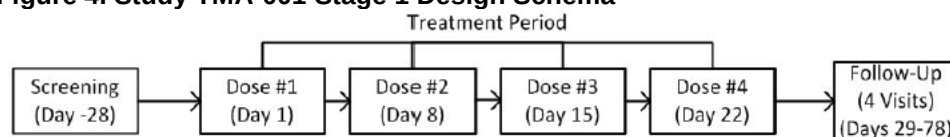
^a As of Amendment 10, Cohort 4 was closed.

^b Doses for Stage 2 and Stage 3 were determined from Stage 1 PK, PD, and safety results. After Stage 1, this was 4 mg/kg. As of Amendment 10 of this protocol, the dose for HSCT-TMA patients was 370 mg IV weekly x 4. Any patients in the middle of treatment at the time of this protocol amendment remained on their original dose.

^c As of Amendment 10 of this protocol, enrollment of TTP patients was closed.

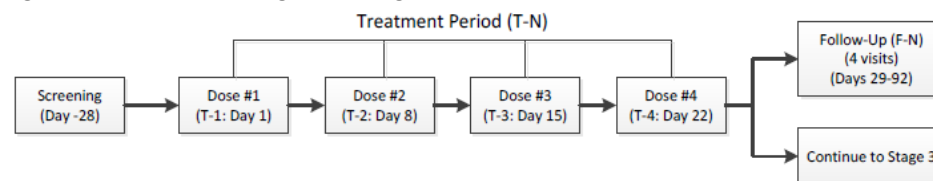
Abbreviations: aHUS, atypical hemolytic uremic syndrome; HSCT-TMA, hematopoietic stem cell transplant-thrombotic microangiopathy; IV, intravenous(ly); TTP, thrombotic thrombocytopenic purpura

Figure 4. Study TMA-001 Stage 1 Design Schema



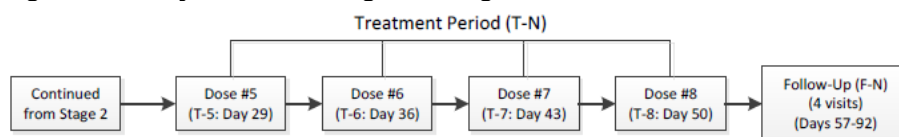
Source: Applicant's TMA-001 protocol

Figure 5. TMA-001 Stage 2 Design Schema



Source: Applicant's TMA-001 protocol

Figure 6. Study TMA-001 Stage 3 Design Schema



Source: Applicant's TMA-001 protocol

The protocol for Study TMA-001 underwent 12 amendments; description of all amendments is listed in [Table 112](#). Amendment 10 discontinued enrollment of patients with aHUS and TTP and changed the dose of narsoplimab-wuug from 4 mg/kg IV to a fixed dose of 370 mg IV for patients with HSCT-TMA. Enrollment was closed for aHUS patients because a Phase 3 study was opened for aHUS patients (Study OMS721-HUS-002). Enrollment was closed for TTP patients because there was no apparent benefit of narsoplimab-wuug over standard of care. Amendment 11.1 provided for retrospective collection of additional data from patients with HSCT-TMA, including changes to the primary and secondary objectives to focus on HSCT-TMA, and defined criteria by which to determine clinical response to treatment. As of

amendment 11.1, 28 subjects had been enrolled. The additional data collected included patient demographics, baseline conditions, donor characteristics, the transplant procedure, concomitant medications, TMA-related laboratory measures, transfusions, transplant complications, and outcomes. Data were collected from medical records from the time of transplant conditioning through the last available patient contact with the site or up to 2 years (104 weeks) after the first narsoplimab-wuug dose, whichever was earlier.

Data collected under protocol versions prior to Amendment 11.1 (the Core Study) are referred to as Core Data. Collection of the additional data defined in Amendment 11.1 is referred to as additional data collection (ADC). Not all data were available in the ADC due to the retrospective collection from medical records. Clinical sites or third-party vendors unaffiliated with Omeros then reviewed the site medical record of each patient and entered the data as available.

Reviewer Comment

The retrospective data collection of additional data from patients with HST-TMA occurred after all 28 patients were enrolled. Ideally, response criteria should be pre-defined.

6.2.1.1. Key Inclusion and Exclusion Criteria for HSCT-TMA Patients

Inclusion Criteria

- Age ≥ 18 years at screening
- Patients with persistent HSCT-TMA were defined as having 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 $< 150,000/\mu\text{L}$
 - Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH $>$ upper limit of normal (ULN), or haptoglobin $<$ LLN)
 - Renal dysfunction (doubling of serum creatinine from pretransplant)
- No clinically apparent alternative explanation for thrombocytopenia and anemia.
- If sexually active and of childbearing potential, must have agreed to practice a highly effective method of birth control until the end of the study

Exclusion Criteria

- Had eculizumab therapy within 3 months prior to screening
- Had Shiga toxin-producing *Escherichia coli*-induced HUS
- Had a positive direct Coombs test
- Had an active systemic bacterial or fungal infection requiring antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care was allowed)

- Had a poor prognosis with a life expectancy of less than 3 months in the opinion of the Investigator
- Were pregnant or lactating
- Had received treatment with an investigational drug or device within 4 weeks prior to screening
- Had abnormal liver function tests defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times ULN

Clinical reviewer comment

The Applicant also submitted patient narratives to better characterize the HSCT-TMA population. The inclusion and exclusion criteria define a HSCT-TMA patient population with evaluable endpoints.

6.2.1.2. Study Endpoints

Primary Endpoint

The primary efficacy endpoint was the proportion of HSCT-TMA patients who responded to narsoplimab-wuug treatment. Treatment response was defined as a patient with HSCT-TMA who demonstrated both an improvement in laboratory TMA markers (Requirement 1; platelet count and LDH) as well as improvement in clinical status (Requirement 2; either improvement in organ function or freedom from transfusion) at any time point post baseline during the study.

Requirement 1: Improvement in laboratory TMA markers

- Improvement in platelet count
 - For patients with baseline platelet count $\leq 20,000/\mu\text{L}$: tripling of baseline platelet count AND postbaseline platelet count $> 30,000/\mu\text{L}$ AND no platelet transfusions 2 days before and on the day of the platelet count collection
 - For patients with baseline platelet count $> 20,000/\mu\text{L}$: increase in platelet count $\geq 50\%$ AND postbaseline platelet count $> 75,000/\mu\text{L}$ AND no platelet transfusions 2 days before and on the day of the platelet count collection
- Improvement in LDH is defined as LDH < 1.5 times ULN

Requirement 2: Improvement in clinical status OR freedom from transfusion

- Improvement in organ function
 - Improvement in renal function as evidenced by any of the following: 1) a reduction of creatinine $> 40\%$; 2) creatinine $< \text{ULN}$ and reduction of creatinine $> 20\%$; or 3) discontinuation of renal replacement therapy (RRT)
 - Improvement in pulmonary function as evidenced by either of the following criteria: 1) extubation and discontinuation of ventilator support; or 2) discontinuation of noninvasive mechanical ventilation (continuous positive pressure ventilation).

- Improvement in neurological function as evidenced by either of the following criteria:
 - 1) improvement in reversible neurological conditions (e.g., cessation of seizures); or
 - 2) stabilization of irreversible neurological conditions (e.g., stability of neurological deficits following stroke without further deterioration or subsequent strokes). The neurological deficits considered for improvement were limited to stroke, seizures, posterior reversible encephalopathy syndrome (PRES), and weakness.
- Improvement in gastrointestinal function (gastrointestinal HSCT-TMA requires diagnosis by tissue biopsy) as measured by improvement in the gastrointestinal staging in the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria
- Freedom from transfusion defined as no transfusions for at least 4 weeks from the last transfusion

Secondary Endpoints

- 100-day survival, from the date of TMA diagnosis
- Overall survival, from the date of TMA diagnosis
- Freedom from platelet transfusion defined as no platelet transfusions for at least 4 weeks following the last platelet transfusion except for patients who died within 4 weeks of the last platelet transfusion (only evaluated in patients who had platelet transfusions in the 2 weeks prior to or on the first narsoplimab-wuug dose date)
- Freedom from RBC transfusion defined as no RBC transfusions for at least 4 weeks following the last RBC transfusion except for patients who died within 4 weeks of the last RBC transfusion (only evaluated in patients who had RBC transfusions in the 2 weeks prior to or on the first narsoplimab-wuug dose date)
- Change from baseline in platelet count (postbaseline platelet counts without platelet transfusions 2 days before and on the day of the platelet count collection were used) over time using central laboratory values
- Change from baseline in LDH over time using central laboratory values
- Change from baseline in haptoglobin over time using central laboratory values
- Change from baseline in hemoglobin (postbaseline hemoglobin without RBC and whole blood transfusions 6 days before and on the day of the hemoglobin collection were used) over time using central laboratory values
- Change from baseline in creatinine over time in patients who had no reason other than HSCT-TMA for creatinine elevation using central laboratory values
- Duration of response, defined as the number of days from the first response date to the first relapse date

Clinical reviewer comment

A Type A meeting with the Applicant occurred on May 2, 2019, in which endpoints were discussed. The Agency and Applicant reached agreement on response based on LDH and

transfusion freedom. The Agency pointed out concerns regarding interpretation of magnitude of platelet improvement and renal improvement. These components were later agreed to after correspondence with the Applicant in written communication on July 9, 2019. The Agency commented that there may be some overlap (i.e., presence of both TMA and GVHD) and that the Applicant will need to address this in narratives and discussions for each patient. In a Type A meeting on January 6, 2020 the Agency stated the evaluation of weakness is difficult in patients with multiple comorbidities and who require intensive care treatment. There may be multiple causes for a patient's weakness therefore the Agency did not agree with the assessment of weakness to assess neurological improvement. In addition, The Agency stated improvement in confusion, agitation, headache will be difficult to assess given multitude of contributing factors to these signs and symptoms.

Statistical Analysis Plan

Sample Size Determination

The sample size for each cohort (aHUS, and HSCT TMA/TTP) was determined by comparison to the total sample size of uncontrolled Phase 2 studies that provided sufficient data for approval of eculizumab for the treatment of aHUS. The Applicant stated that 28 patients are adequate because of the orphan disease status. The Applicant stated that it was expected that approximately 28 HSCT-TMA patients enrolled with observed response rate of 50%, results in the exact 95% CI 30.6%, 69.4%.

Reviewer Comment

There was no pre-agreement between the Agency and the Applicant that 28 patients was an adequate sample size.

Control

Study TMA-001 is a single arm study, neither concurrent control nor historical control was utilized.

Reviewer comment

During the development of narsoplimab-wuug the possibility of establishing a historical control was discussed, and the Agency pointed out potential barriers with this approach. A single-arm trial based on response endpoint could possibly provide sufficient magnitude of treatment effect and be acceptable to support the biologics license application (BLA) submission given the rarity of HSCT-TMA and the high risk for poor outcomes in a population with no approved therapies. The Agency also agreed with the modification of the primary endpoint in Amendment 11.1 in order to assess response in patients with HSCT-TMA and the additional data collection.

Randomization

This was a single arm trial with no randomization required.

Interim Analysis

No interim analysis was planned.

Missing Data

Non-responder imputation was used to handle missing data for the binary efficacy endpoints. Time-weighted average analysis and repeated measure model was used to analyze the continuous secondary efficacy endpoints over time.

The TMA diagnosis date must have had at least the month and the year. If the day was missing, the day was be imputed as 1.

For patients whose death dates were incomplete, if only the day of the death date was missing, the day was imputed as the first day of the month. If either the month or the year of the death date was missing, the death date was not imputed, and the overall survival was censored at the last known date of alive in the database. For patients who were alive, overall survival was censored at the last known date of alive in the database.

Primary Efficacy Analysis

Efficacy analyses were performed for the full analysis set (FAS) population and the Per-protocol Patient Set (PPS) population. The FAS population included all HSCT-TMA patients who received any amount of study drug. The PPS population included all HSCT-TMA patients who received at least 4 weeks of study treatment (treatment period was greater than or equal to 28 days).

Analysis of the primary efficacy endpoint used a non-responder imputation to impute missing or incomplete data. The number and percent of responders were summarized with an exact 95% CI (Clopper-Pearson) by dose and total for the FAS and PPS populations. If the lower bound of the exact 95% CI was greater than 15%, the sponsor determined that there was sufficient evidence to demonstrate efficacy of narsoplimab-wuug in the target patient population.

Statistical reviewer comment

In the original BLA submission, the Applicant did not provide an adequate justification for the chosen 15% response rate in patients with HSCT-TMA. The Agency recommended that the Applicant conduct a literature search to justify 15% response rate (see Section [6.2.2](#) below).

Subgroup Analysis

- Subgroup analyses for the following subgroups was performed for the FAS population:
 - Age (<65, ≥65 years)
 - Gender (Male or Female)
 - GVHD (Yes or No)
 - Significant infection (Yes or No)

- Graft failure or non-engraftment (Yes or No)
- Female-to-male transplant (Yes or No)
- Multiple organ TMA involvement (Yes or No)
- Mismatched donor (Yes or No)
- Baseline platelet counts ($<20,000$ or $\geq 20,000$ platelets/ μL)
- Renal dysfunction at baseline (Creatinine $>$ ULN or spot urine protein $\geq 2+$ or >30 mg/dL; Yes or No)
- Any transfusions within the 2 weeks prior to or on the first OMS721 dose date (Yes or No)
- A completer analysis was performed using the patients with non-missing responses only. The exact 95% CI for the completer response rate was provided for the FAS population by dose.
- Two alternative definitions of response were analyzed:
 - The first alternative response was defined as achieving an improvement in TMA markers and an improvement in renal function. The number and percent of the patients achieving the first alternative response was summarized with an exact 95% CI by dose for the FAS population.
 - The second alternative response was defined as the same as the primary endpoint by excluding the neurological function. The number and percent of the patients achieving the second alternative response were summarized with an exact 95% CI by dose for the FAS population.

Secondary Efficacy Analyses

The following secondary efficacy endpoints were proposed:

- 100-day Survival: The 100-day survival status was determined as a binary variable. A patient achieved a 100-day survival if the overall survival from the date of HSCT-TMA diagnosis of the patient would have been greater than or equal to 100 days. If the 100-day survival status of a patient was unknown (i.e., censored before 100 days), this patient would have been considered to have died prior to 100 days. The 100-day survival rate was estimated with an exact 95% CI by dose for the FAS population.
- Overall Survival: Overall survival was calculated from the date of HSCT-TMA diagnosis. For patients who were alive, their overall survival was censored at the last known date of alive in the database. Overall survival was analyzed using Kaplan Meier method by dose for the FAS population. Median overall survival and its 95% CI was estimated by dose.
- Duration of Response: Duration of response was defined as the number of days from the first response date to the first relapse date (first relapse date – first response date +1). Duration of response was censored at the last platelet or LDH collection date if relapse did not occur during the study. Kaplan-Meier analysis of the duration of response was

performed for the patients who achieved a response by dose for the FAS population.
Median duration of response was presented with 95% CI.

Patient Disposition

Disposition data for patients with HSCT-TMA are provided in [Table 7](#). A total of 8 patients (28.6%) discontinued study drug. In the Core Study, 15 patients (53.6%) discontinued the study, and 13 (46.4%) patients completed the study. All 13 patients responded to study drug. Three patients withdrew for nonstudy-related reasons (“Other” in [Table 7](#)) following treatment completion and each responded to study drug. Ten patients (35.7%) remained alive through the last site contact for ADC. No patients remained on treatment.

Table 7. TMA-001 HSCT-TMA Patient Disposition in Study

Disposition	4 mg/kg (N=24) n (%)	370 mg (N=4) n (%)	Total (N=28) n (%)
Completed treatment	17 (70.8%)	3 (75%)	20 (71.4%)
Discontinued study drug	7 (29.2%)	1 (25%)	8 (28.6%)
Reason for study drug discontinuation			
Physician decision	4 (16.7%)	0	4 (14.3%)
Withdrawal by subject	3 (12.5%)	0	3 (10.7%)
Adverse event	0	1 (25%)	1 (3.6%)
Other	0	0	0
Pregnancy	0	0	0
Protocol deviation/protocol violation	0	0	0
Completed core study	10 (41.7%)	3 (75%)	13 (46.4%)
Discontinued core study	14 (58.3%)	1 (25%)	15 (53.6%)
Reason for core study discontinuation			
Death	5 (20.8%)	1 (25%)	6 (21.4%)
Withdrawal by subject	4 (16.7%)	0	4 (14.3%)
Other	3 (12.5%)	0	3 (10.7%)
Physician decision	2 (8.3%)	0	2 (7.1%)
Adverse event	0	0	0
Lost to follow-up	0	0	0
Sponsor request	0	0	0
Alive at last site contact	8 (33.3%)	2 (50%)	10 (35.7%)

Source: Page 17 of the summary report

Patient noncompliance with protocol is categorized as Protocol Deviation/Protocol Violation. Source: adapted from t1-01a-dispa (date: September 28, 2020 9:48 AM) with updates to row titles.

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy. Prohibited concomitant therapy is categorized as Other.

The three patients who withdrew from the study included logistical difficulty attending follow-up visits, enrollment in an unrelated clinical study, continuation of narsoplimab-wuug treatment under compassionate use without entering the follow-up period. The two patients who discontinued by physician decision were withdrawn to receive eculizumab treatment and subsequently died due to progression of underlying malignancy.

Demographic Characteristic and Baseline Characteristics

Demographics summary and some baseline characteristics of patients are provided in [Table 8](#). Most patients were male (20 patients, 71%) and white (17 patients, 61%). There were no marked

differences in baseline weight or body mass index between patients who received a fixed dose of 370 mg and those who received the target weight-based dose of 4 mg/kg although all patients receiving the fixed dose were male.

Median time to TMA diagnosis after transplant was 73.5 days (range: 21 to 436 days). Twenty-five patients (89%) received transfusions within 2 weeks prior to treatment with narsoplimab-wuug. Five patients (18%) received prior plasma therapy.

Table 8. TMA-001 HSCT-TMA Patient Demographics and Baseline Characteristics in Study

Demographics/Baseline Characteristics	4 mg/kg (N=24) n (%)	370 mg (N=4) n (%)	Total (N=28) n (%)
Age (yr)			
n	24	4	28
Mean (SD)	49.54 (12.09)	38.5 (18.30)	47.96 (13.32)
Median	49	33	48
Min, max	22, 68	23, 65	22, 68
Sex, n (%)			
Male	16 (67%)	4 (100%)	20 (71%)
Female	8 (33%)	0	8 (29%)
Ethnicity, n (%)			
Hispanic or Latino	1 (4%)	1 (25%)	2 (7%)
Not Hispanic or Latino	23 (96%)	3 (75%)	26 (93%)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	6 (25%)	1 (25%)	7 (25%)
Black or African American	2 (8%)	0	2 (7%)
Native Hawaiian or other Pacific Islander	1 (4%)	0	1 (4%)
White	15 (63%)	2 (50%)	17 (61%)
Other	0	1 (25%)	1 (4%)
Childbearing potential, n (%)			
Yes	3 (13%)	0	3 (11%)
No	5 (21%)	0	5 (18%)
Not applicable	16 (67%)	4 (100%)	20 (71%)
Baseline weight (kg)			
n	24	4	28
Mean (SD)	75.99 (22.55)	68.93 (14.65)	74.98 (21.52)
Median	69	70.5	69
Min, max	51, 134.1	51.7, 83	51, 134.1
Baseline BMI (kg/m ²)			
n	23	4	27
Mean (SD)	25.89 (6.08)	22.53 (4.14)	25.39 (5.90)
Median	23.70	22.62	23.70
Min, max	16.7, 42.3	18.1, 26.8	16.7, 42.3

Source: Page 19 of the summary report

Abbreviations: BMI, body mass index; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; max, maximum; min, minimum; SD, standard deviation; yr, years

Characteristics related to the transplant procedure (both patient and donor associated) or transplant complications are presented in [Table 9](#). At least 50% of the population had each of GVHD, significant infection, multiple organ involvement, baseline renal dysfunction, and/or baseline neurological dysfunction. The enrolled population was at high risk for poor outcomes and fairly representative of the general HSCT-TMA population.

Table 9. HSCT History of HSCT-TMA Patients (Safety Population)

HSCT History	4 mg/kg (N=24) n (%)	370 mg (N=4) n (%)	Total (N=28) n (%)
Time from HSCT to Day 1 (days)			
n	24	4	28
Mean (SD)	135.8 (109.81)	203 (90.54)	145.4 (108.43)
Median	101	215.5	119
Min, Max	33, 444	82, 299	33, 444
Graft-versus-host disease, n (%)			
Yes	17 (70.8%)	2 (50%)	19 (67.9%)
No	7 (29.2%)	2 (50%)	9 (32.1%)
Significant infection, n (%)			
Yes	21 (87.5%)	3 (75%)	24 (85.7%)
No	3 (12.5%)	1 (25%)	4 (14.3%)
Refractory primary disease or primary disease relapse, n (%)			
Yes	5 (20.8%)	1 (25%)	6 (21.4%)
No	19 (79.2%)	3 (75%)	22 (78.6%)
Graft failure or non-engraftment, n (%)			
No	24 (100%)	4 (100%)	28 (100%)
Female-to-male transplant, n (%)			
Yes	6 (25%)	1 (25%)	7 (25%)
No	18 (75%)	3 (75%)	21 (75%)
Multiple organ TMA involvement, n (%)			
Yes	11 (45.8%)	3 (75%)	14 (50%)
No	13 (54.2%)	1 (25%)	14 (50%)
Mismatched donor, n (%)			
Yes	9 (37.5%)	1 (25%)	10 (35.7%)
No	15 (62.5%)	3 (75%)	18 (64.3%)
Related donor, n (%)			
Yes	10 (41.7%)	2 (50%)	12 (42.9%)
No	14 (58.3%)	2 (50%)	16 (57.1%)
Renal dysfunction at baseline, n (%)			
Yes	17 (70.8%)	4 (100%)	21 (75%)
No	7 (29.2%)	0	7 (25%)
Pulmonary dysfunction at baseline, n (%)			
Yes	5 (20.8%)	0	5 (17.9%)
No	19 (79.2%)	4 (100%)	23 (82.1%)
Neurological dysfunction at baseline, n (%)			
Yes	14 (58.3%)	2 (50%)	16 (57.1%)
No	10 (41.7%)	2 (50%)	12 (42.9%)
Gastrointestinal dysfunction at baseline, n (%)			
Yes	1 (4.2%)	0	1 (3.6%)
No	23 (95.8%)	4 (100%)	27 (96.4%)
Cell source, n (%)			
Bone marrow	5 (20.8%)	1 (25%)	6 (21.4%)
Peripheral blood stem cells	16 (66.7%)	3 (75%)	19 (67.9%)
Umbilical cord blood	2 (8.3%)	0	2 (7.1%)
Patient pretransplant blood type, n (%)			
A	10 (41.7%)	1 (25%)	11 (39.3%)
AB	1 (4.2%)	1 (25%)	2 (7.1%)
B	0	1 (25%)	1 (3.6%)
O	13 (54.2%)	1 (25%)	14 (50%)

	4 mg/kg (N=24) n (%)	370 mg (N=4) n (%)	Total (N=28) n (%)
HSCT History			
Patient pretransplant Rh factor, n (%)			
Negative	2 (8.3%)	0	2 (7.1%)
Positive	22 (91.7%)	4 (100%)	26 (92.9%)
Cytomegalovirus antibody status, n (%)			
Negative	4 (16.7%)	0	4 (14.3%)
Positive	20 (83.3%)	4 (100%)	24 (85.7%)
Number of donors, n (%)			
1	22 (91.7%)	4 (100%)	26 (92.9%)
2	2 (8.3%)	0	2 (7.1%)
Donor 1 relatedness to patient, n (%)			
Parent	1 (4.2%)	0	1 (3.6%)
Sibling	9 (37.5%)	2 (50%)	11 (39.3%)
Unrelated	14 (58.3%)	2 (50%)	16 (57.1%)
Donor 2 relatedness to patient ^a , n (%)			
Unrelated	2 (100%)	0	2 (100%)

Source: Page 20 of the summary report

^a Percentages are based on the number of patients with 2 donors.

Abbreviations: HSCT, hematopoietic stem cell transplant; HSCT-TMA, hematopoietic stem cell transplant- associated thrombotic microangiopathy; max, maximum; min, minimum; SD, standard deviation; TMA, thrombotic microangiopathy.

Efficacy Results-Primary Endpoint

In the FAS, the Applicant's results showed that 17 of 28 patients with HSCT-TMA (61%) responded to narsoplimab-wuug treatment ([Table 10](#)), and the 95% CI for response was 40.6% to 78.5%. This response rate was statistically superior to the protocol-specified response rate in this high-risk population of 15% ($p < 0.0001$). As a reminder the PPS population include all HSCT-TMA patients who received at least 4 weeks of study treatment (treatment period is greater than or equal to 28 days). The Applicant's results based on PPS appear to support their findings based on FAS population.

Within this overall composite response endpoint, the Applicant's results suggest that each of the 3 contributing clinical measures showed improvement in the FAS: 17 of 28 patients (61%) showed improvement in both platelet count and LDH. However, FDA's evaluation showed that 12 of 28 patients (43%) had improvement in both platelet count and LDH; 20 of 27 patients (74%) had improvement in at least one organ function; 12 of 25 patients (48%) experienced freedom from RBC and/or platelet transfusion after narsoplimab-wuug treatment (see [Table 10](#)). The clinical team could not conclude a treatment effect for the overall composite endpoint nor for the individual parameters below, see Section [6.3.1](#) for further details.

Table 10. Summary of Response for Patients With HSCT-TMA

Number of Patients/Number of Evaluable Patients (%)	Full Analysis Set (Applicant's Results) (N=28)	Full Analysis Set (FDA Estimation) (N=28)	Per Protocol Set (N=23)
Responders [exact 95% CI] ^a	17/28 (61%) [40.6%, 78.5%]	12/28 (43%) [24.4%, 62.8%]	17/23 (74%) [51.6%, 89.8%]
Improvement in TMA markers ^b	17/28 (61%)		17/23 (74%)
Platelet count ^c	14/23 (61%)		13/19 (68%)
LDH	21/28 (75%)	16/28 (57%)	19/23 (83%)
Improvement in organ function ^d	20/27 (74%)		17/22 (77%)
Improvement in renal function	18/27 (67%)		15/22 (68%)
Improvement in pulmonary function ^e	NA		NA
Improvement in neurological function	3/6 (50%)		3/6 (50%)
Improvement in gastrointestinal function	1/1 (100%)		1/1 (100%)
Freedom from transfusion	12/25 (48%)		11/20 (55%)

Source: FDA reviewer

^a Responder is defined as achieving improvement in TMA markers and either improvement in any organ function or freedom from transfusion. Patients whose response cannot be determined are considered non-responders. Clopper Pearson (Exact) 95% confidence interval for the response rate is given in square brackets.

^b Improvement in TMA markers is defined as achieving improvement in both platelet count and LDH or in just LDH if patients were not included in platelet count analysis due to never engrafting.

^c Five patients never achieved platelet engraftment and were not included in platelet count analysis.

^d Improvement in organ function is defined as achieving improvement in at least one of the organ functions.

^e No patient is evaluable for the pulmonary function improvement.

Abbreviations: CI, confidence interval; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; LDH, lactate dehydrogenase; NA, not applicable; TMA, thrombotic microangiopathy.

A detailed summary of the Applicant's results for improvement in platelet count and LDH in patients treated with narsoplimab-wuug is provided in [Table 11](#) for both FAS and PPS. In particular, improvement in platelet count was assessed in patients relative to their baseline platelet count. The Applicant's results demonstrated that in patients with very low baseline platelet counts (20,000 or lower), 3 of 6 patients (50%) showed improvement (defined as a platelet count at any time point that was greater than 30,000 and at least 3-fold above baseline platelet levels); In patients with baseline platelet counts over 20,000, 11 out of 17 patients (65%) showed improvement (defined as a platelet count at any time point that was greater than 75,000 and 1.5-fold or more above baseline platelet levels). Twenty-one (75%) of the patients showed improvement in LDH (defined as an LDH <1.5 times the ULN). There was an overall improvement in TMA markers in 17 patients (61%).

Table 11. Applicant's Results (Confirmed by FDA) - Improvement in TMA Markers for HSCT-TMA

Type of Improvement	Full Analysis Set (N=28)	Per-Protocol Set (N=23)
	n/m ^d (%)	n/m ^d (%)
Improvement in TMA markers ^a	17/28 (61%)	17/23 (74%)
Improvement in platelet count	14/23 (61%)	13/19 (68%)
For baseline ≤20,000 ^b	3/6 (50%)	3/5 (60%)
≥3x baseline and no platelet transfusion ^c	3/6 (50%)	3/5 (60%)
>30,000 and no platelet transfusion ^c	4/6 (67%)	4/5 (80%)
For baseline >20,000 ^b	11/17 (65%)	10/14 (71%)
≥1.5x baseline and no platelet transfusion ^c	12/17 (71%)	11/14 (79%)
>75,000 and no platelet transfusion ^c	11/17 (65%)	10/14 (71%)
Improvement in LDH	21/28 (75%)	19/23 (83%)
LDH <1.5x upper limit of normal	21/28 (75%)	19/23 (83%)

Source: Page 26 of the summary report, t2-04a-improve-tmaa (date: September 28, 2020 9:48 AM) and t2-04b-improve-tmab (date: September 28, 2020 9:48 AM)

^a Improvement in TMA markers is defined as achieving improvement in both platelet count and LDH or in just LDH if patients were not included in platelet count analysis due to failure of platelet engraftment.

^b Improvement in platelet count is defined as achieving both criteria from the same platelet count. Each of these two criteria is summarized separately.

^c No platelet transfusions 2 days before and on the day of the platelet count collection.

^d m is the number of patients who are evaluable for the corresponding criterion.

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy

Reviewer Comment

The protocol stated that if a patient is not evaluable for a response criterion due to confounding factors, the non-evaluable response criterion will not be included in the determination of responder. Evaluability of each response criterion will be determined by a clinical review of relevant data. The review team did not agree with this allowance which is further discussed in Section 6.3.1.

A detailed summary of the Applicant's results for improvement in organ function in all patients (FAS) with HSCT- TMA and in the PPS is provided in [Table 12](#). As seen from the table, the Applicant reported that twenty of 27 patients (74%) experienced improvement in at least 1 organ function in the FAS with the majority evaluated on the basis of renal function (27/28 patients, 96.4%). Eighteen of the 27 patients (67%) showed improvement in renal function, with 10 patients (37%) showing a reduction of creatinine levels of greater than 40%, and 15 patients (56%) recorded creatinine levels less than the ULN and reduction of creatinine >20%. Of the 6 patients with neurologic dysfunction at baseline, 3 patients (50%) showed improvement in evaluable neurologic function. These improvements were all in reversible neurological conditions, and there was no stabilization of irreversible conditions. Improvements in organ function in the PPS were generally similar to those in the FAS. with 17 of 22 patients (77%) experiencing an improvement in organ function.

Table 12. Applicant's Results - Improvement in Organ Function for HSCT-TMA or Transfusion Freedom

Type of Improvement	Full Analysis Set (N=28) n/m ^e (%)	Per-Protocol Set (N=23) n/m ^e (%)
Improvement in organ function ^a	20/27 (74%)	17/22 (77%)
Improvement in renal function ^b	18/27 (67%)	15/22 (68%)
Reduction of creatinine >40%	10/27 (37%)	9/22 (41%)
Creatinine < ULN and reduction of creatinine >20%	15/27 (56%)	13/22 (59%)
Discontinuation of renal replacement therapy	0/1 (0%)	0/22 (0%)
Improvement in pulmonary function ^c	NA	NA
Extubation and discontinuation of ventilator support	NA	NA
Discontinuation of noninvasive mechanical ventilation	NA	NA
Improvement in neurological function ^d	3/6 (50%)	3/6 (50%)
Improvement in reversible neurological conditions	3/6 (50%)	3/6 (50%)
Stabilization of irreversible neurological conditions	0/6 (0%)	0/6 (0%)
Improvement in gastrointestinal function	1/1 (100%)	1/1 (100%)
Improvement of at least 1 grade in MAGIC GI criteria	1/1 (100%)	1/1 (100%)

Freedom From Transfusion

Freedom from transfusion ^f	12/25 (48%) [27.8%,68.7%]	11/20 (55%) [31.5%,76.9%]
Freedom from platelet transfusion ^g	8/18 (44%) [21.5%,69.2%]	7/13 (54%) [25.1%,80.8%]
Freedom from RBC transfusion ^h	11/22 (50%) [28.2%,71.8%]	10/19 (53%) [28.9%,75.6%]

Source: adapted from Page 27 of the summary report - t2-05a-improve-organa (date: September 28, 2020 9:48 AM) and t2-05b-improve-organb (date: September 28, 2020 9:48 AM).

Abbreviations: GI, gastrointestinal; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; MAGIC, Mount Sinai GVHD International Consortium; NA, not applicable; ULN, upper limit of normal

^a Improvement in organ function is defined as achieving improvement in at least one organ function.

^b Improvement in renal function is defined as achieving at least one of the criteria.

^c Improvement in pulmonary function is defined as achieving either criteria. No patients were evaluable for pulmonary function.

^d Improvement in neurological function is defined as achieving either criteria.

^{ee} is the number of patients who are evaluable for the corresponding criterion.

^f No transfusions for at least 4 weeks from the last transfusion except for patients who died within 4 weeks of the last transfusion; only evaluated in patients who received transfusions within the 2 weeks prior to or on the first narsoplimab-wuug dose date.

^g No platelet transfusions for at least 4 weeks following the last platelet transfusion except for patients who died within 4 weeks of the last platelet transfusion; only evaluated in patients who had platelet transfusions in the 2 weeks prior to or on the first narsoplimab-wuug dose date

^h No RBC transfusions for at least 4 weeks following the last RBC transfusion except for patients who died within 4 weeks of the last RBC transfusion; only evaluated in patients who had RBC transfusions in the 2 weeks prior to or on the first narsoplimab-wuug dose date

Abbreviations: CI, confidence interval; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; RBC, red blood cell

is the number of patients who are evaluable for the corresponding criterion.

The Applicant's results showed that there were 25 patients in the FAS who had required an RBC or platelet transfusion in the 2 weeks leading up to study entry. Of these patients, 12 (48%) experienced freedom from transfusion for a consecutive 4-week period after narsoplimab-wuug treatment. The patients showing freedom from transfusion were made up of 8 of 18 patients (44%) who had required platelet transfusion and 11 of 22 (50%) patients who had required RBC transfusion prior to narsoplimab-wuug treatment. Results in the PPS were generally similar to those in the FAS, with 11 of 20 patients (55%) experiencing freedom from transfusion.

Subgroup Analyses

[Table 13](#) provides the Applicant's results for response rate by subgroups defined by patient characteristics, transplant characteristics, and the presence or absence of transplant complications.

Table 13. Applicant's Results - Subgroup Analysis of Response for HSCT-TMA (Full Analysis Set Population)

Subgroup	4 mg/kg (N=24) n/m ^b (%)	370 mg (N=4) n/m ^b (%)	Total (N=28) n/m ^b (%)
Responders by subgroup ^a			
Age (years)			
<65	12/21 (57%)	2/3 (67%)	14/24 (58%)
≥65	2/3 (67%)	1/1 (100%)	3/4 (75%)
Sex			
Male	10/16 (63%)	3/4 (75%)	13/20 (65%)
Female	4/8 (50%)	-	4/8 (50%)
Acute graft-versus-host disease n (%)			
Yes	10/17 (59%)	2/2 (100%)	12/19 (63%)
No	4/7 (57%)	1/2 (50%)	5/9 (56%)
Significant infection n (%)			
Yes	13/21 (62%)	2/3 (67%)	15/24 (63%)
No	1/3 (33%)	1/1 (100%)	2/4 (50%)
Multiple organ TMA involvement n (%)			
Yes	6/11 (55%)	3/3 (100%)	9/14 (64%)
No	8/13 (62%)	0/1	8/14 (57%)
Mismatched donor n (%)			
Yes	5/9 (56%)	1/1 (100%)	6/10 (60%)
No	9/15 (60%)	2/3 (67%)	11/18 (61%)
Baseline platelet counts (10E ⁹ /L)			
≤20	5/9 (56%)	1/1 (100%)	6/10 (60%)
>20	9/15 (60%)	2/3 (67%)	11/18 (61%)
Renal dysfunction at baseline n (%)			
Yes	9/17 (53%)	3/4 (75%)	12/21 (57%)
No	5/7 (71%)	-	5/7 (71%)
Pulmonary dysfunction at baseline n (%)			
Yes	2/5 (40%)	-	2/5 (40%)
No	12/19 (63%)	3/4 (75%)	15/23 (65%)
Neurological dysfunction at baseline n (%)			
Yes	8/14 (57%)	2/2 (100%)	10/16 (63%)
No	6/10 (60%)	1/2 (50%)	7/12 (58%)
Gastrointestinal dysfunction at baseline n (%)			
Yes	1/1 (100%)	-	1/1 (100%)
No	13/23 (57%)	3/4 (75%)	16/27 (59%)
Transfusions within two weeks prior to or on the date of first narsoplimab-wuug dose n (%)			
Yes	12/22 (55%)	2/3 (67%)	14/25 (56%)
No	2/2 (100%)	1/1 (100%)	3/3 (100%)

Source: Page 29 of the summary report

^a responder is defined as achieving improvement in TMA markers and either improvement in organ functions or freedom from transfusion. Patients whose response cannot be determined are considered nonresponders.

^b m is the number of patients in the corresponding subgroup.

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; TMA, thrombotic microangiopathy

Sensitivity Analyses

No response status was missing. Therefore, the analysis with non-missing responses was identical to the primary analysis. For TMA markers and renal function only, the FDA's analysis results showed that 12 of 28 (43% with 95% CI, 24.5% to 62.8%) patients in the FAS responded to treatment.

Efficacy Results-Secondary and Other Relevant Endpoints

100-Day and Overall Survival

A summary of 100-day survival and overall survival (OS) following narsoplimab-wuug treatment in the FAS, PPS, and treatment responders from the FAS is shown in [Table 14](#). Survival days were calculated from the day of TMA diagnosis. At Day 100 after HSCT-TMA diagnosis, 19 patients (68%) remained alive in the FAS, and the median OS was 274 days. For the PPS, the 100-day survival rate was 83%, and the median OS was 361 days. Among patients who responded to narsoplimab-wuug treatment, 100-day survival rate was 94% while OS was not estimable.

Table 14. FDA Results - Overall Survival and 100-Day Survival for HSCT-TMA

Overall Survival/ 100-Day Survival	Full Analysis Set (N=28)
Overall survival ^a	
Number of deaths (%)	16 (57%)
Median survival (days) (95% CI) ^b	274 (103, NE)
Min, max ^c	33, 1424+
100-day survival ^d	
Number of patients (%)	19 (68%)
95% CI ^e	(47.6%, 84.1%)

Source: FDA reviewer

a Overall survival is date of death – date of HSCT-TMA diagnosis +1. Overall survival of an alive patient is censored at the last known date of alive in the database.

b Median survival is estimated by Kaplan-Meier method. 95% confidence interval for median survival is calculated using complementary log-log transformation.

c "+" indicates censoring

d A patient achieves a 100-day survival if the overall survival is greater than or equal to 100 days. If the 100-day survival status is unknown, the patient will be considered to have died prior to 100 days.

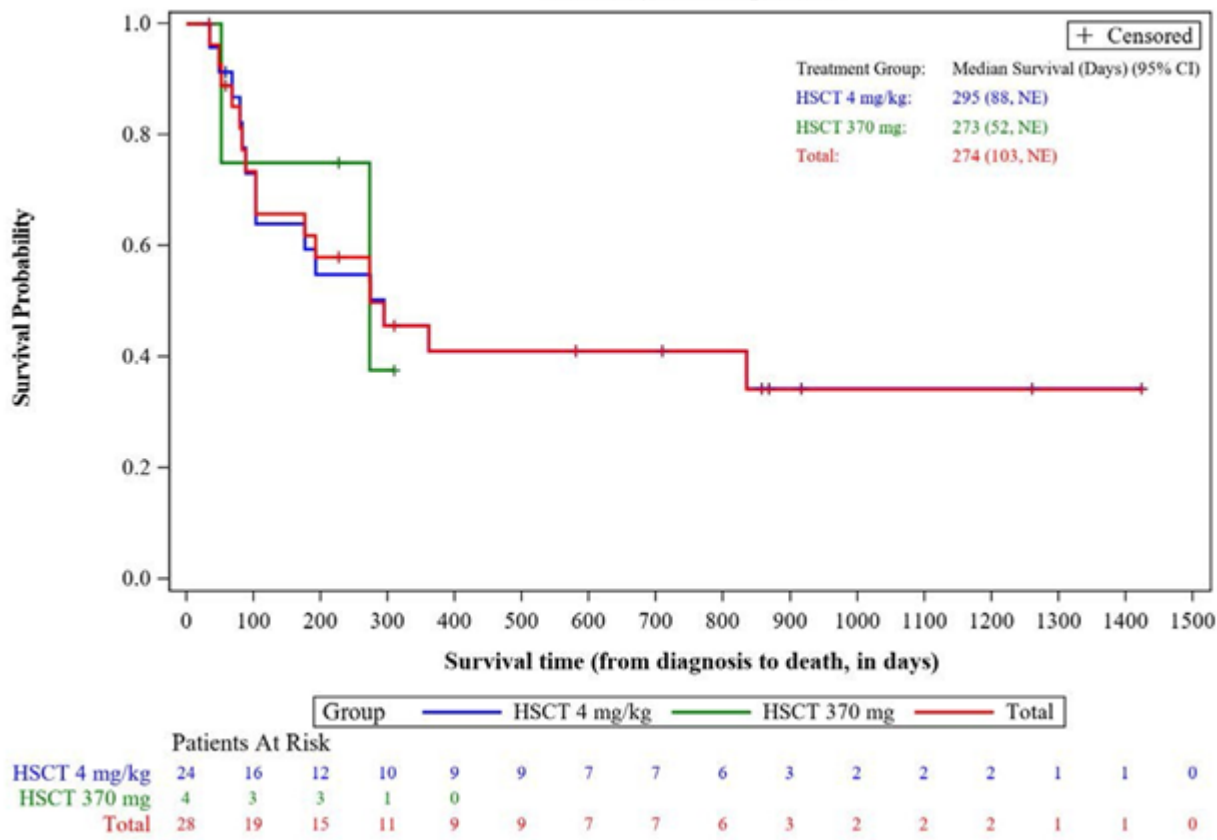
e Exact 95% confidence interval for proportion.

Abbreviations: CI, confidence interval; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; max, maximum; min, minimum; NE, not estimable

Overall Survival

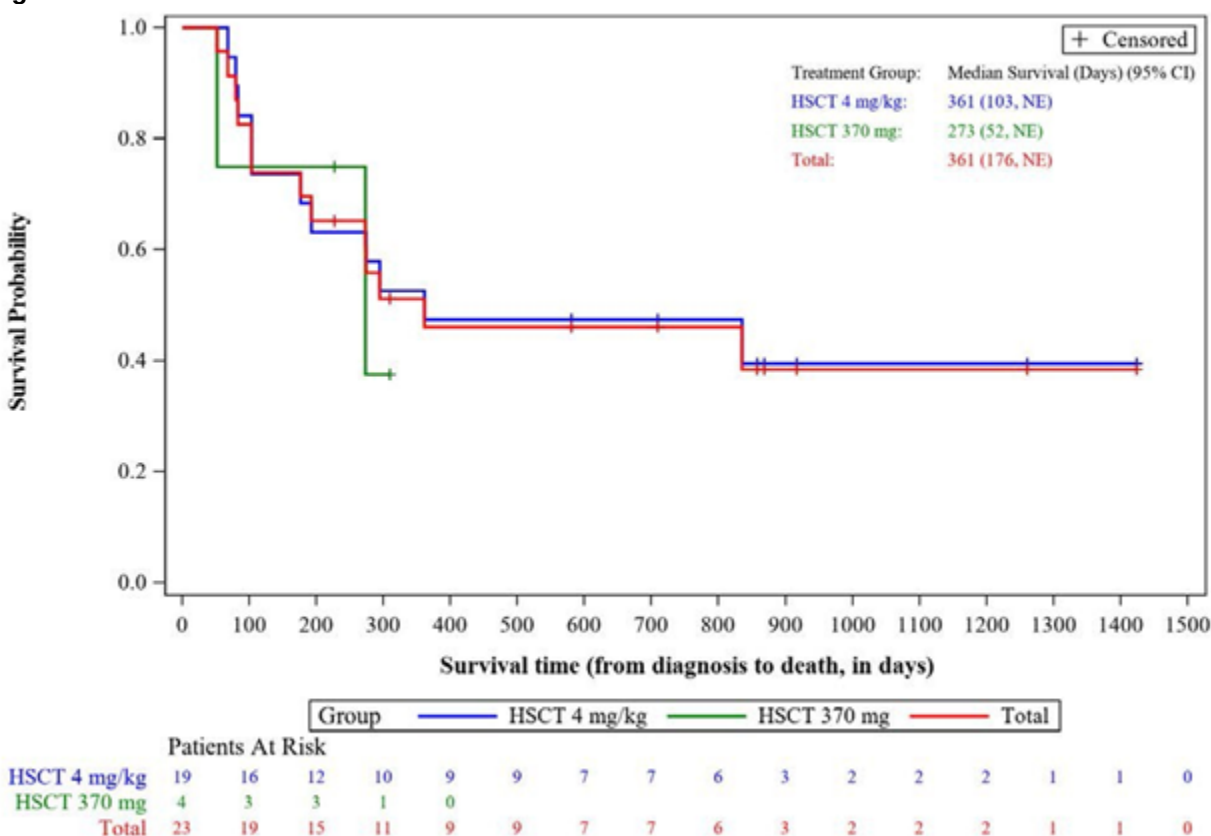
Overall survival over time in the FAS and PPS is provided in Kaplan-Meier plots in Figures [7](#) and [8](#).

Figure 7. Overall Survival Over Time in the FAS



Source: Page 32 of the summary report
Abbreviations: CI, confidence interval; FAS, full analysis set; HSCT, hematopoietic stem cell transplant; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; NE, not estimable; PPS, per-protocol population

Figure 8. Overall Survival Over Time in the PPS



Source: Page 33 of the summary report

Abbreviations: CI, confidence interval; FAS, full analysis set; HSCT, hematopoietic stem cell transplant; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; NE, not estimable; PPS, per-protocol population

Clinical reviewer comment

The definition of 100-day survival was defined as survival 100 days after diagnosis of HSCT-TMA and the definition of overall survival was survival after diagnosis of HSCT-TMA. In the transplant setting there are different definitions of survival as well as different definitions used in the literature. In the transplantation setting, 100-day survival is often defined as survival 100 days after the transplantation date (Day 0) and overall survival is defined as survival after date of transplantation. Therefore, it is difficult to interpret any survival data due to differences in definitions and lack of adequate control.

Durability and Duration of Response

Table 15 provides a summary of durability (no relapse) and duration of response for the FAS population based on the FDA analyses. Out of 12 responders, 9 were without relapse. Median duration of response was 617 days (95% CI: 185,822 days).

Table 15. Duration of Response

Duration of Response^a	4 mg/kg (N=24)	370 mg (N=4)	Total (N=28)
Number of responders	10	2	12
Number of responders without relapse (%) ^b	8 (80%)	1 (50%)	9 (75%)
Median duration of response (days) ^c	655	185	617
95% CI for median duration of response ^d	206.0,822.0	NA	185.0,822.0
Min, max ^e	18, 823+	174, 185+	18, 823+

Source: FDA reviewer

^a Duration of response is defined as first relapse date – first response date +1. Duration of response is censored at the last platelet or lactate dehydrogenase collection date if relapse does not occur during the study.

^b Relapse is defined as having a platelet count greater than 50% decrease from the maximum platelet count and a lactate dehydrogenase greater than 1.5 times the upper limit of normal. Percentage is based on the number of responders.

^c Median duration of response is estimated by Kaplan-Meier method. Only the responders are included in the analysis.

^d 95% confidence interval for median duration of response using complementary log-log transformation.

^e "+" indicates censoring.

Abbreviations: CI, confidence interval; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; max, maximum; min, minimum

Reviewer comment

There is a wide range in durability of response which makes it difficult to describe durability. Further discussion on durability of response is addressed in Section [6.3](#) Key Review Issues Relevant to Efficacy.

Change from baseline in selected laboratory tests

The change from baseline for platelets, LDH and haptoglobin were evaluated.

Table 16. Change From Baseline for Platelets, LDH, and Haptoglobin

Parameters	Baseline	Change From Baseline
Platelet count		
N	28	22
Mean (SD)	34 (22)	29.5 (36.2)
Median	26	17
Min, max	6, 80	-33, 94
LDH count		
N	28	28
Mean (SD)	581 (230)	-111.9 (203.2)
Median	559	-106.7
Min, max	237, 1140	-446, 373
Haptoglobin (mg/dL)		
N	27	27
Mean (SD)	21.2 (29.7)	67.7 (69.5)
Median	2.9	57.3
Min, max	3, 95	-37, 242
Hemoglobin (g/dL)		
N	27	22
Mean (SD)	8.8 (1.21)	0.38 (1.22)
Median	8.9	0.42
Min, max	5.8, 11.5	-1.5, 2.6

Source: FDA Analysis

Abbreviations: LDH, lactate dehydrogenase; SD, standard deviation

Overall, the magnitude of change from baseline in hemoglobin, platelet and LDH was marginal. The mean change in baseline for haptoglobin demonstrated the most robust response of the

hematological parameters. Without a control group, the magnitude of change in laboratory values is difficult to interpret. The clinical benefit cannot be determined. Please also see Section [6.3](#) on Key Review Issues.

Data Quality and Integrity

Materials reviewed include the protocol, statistical analysis plan, and study report for this study. Data of this submission, provided with study data tabulation model (SDTM) and analysis data model (ADaM) formats, are acceptable. The Applicant also provided clear definition file for datasets and, reviewer guide and detailed analysis SAS programs for assisting review.

Statistical reviewer comment

Appropriate materials were provided to replicate the Applicant trial results.

6.2.2. Historical Literature Review

6.2.2.1. Design, Literature Historical Review

During the review of the application, FDA requested additional data to justify the 15% response rate in untreated patients to further evaluate the clinical benefit of narsoplimab-wuug in patients with HSCT-TMA to serve as a control group for OMS-TMA-00. The Applicant submitted the literature based historical control on April 23, 2021. Because of the extent of the additional review required, a major amendment was issued on May 19, 2021, extending the user fee goal date by 3 months.

Objectives: Describe the natural history of HSCT-TMA in adult patients following allogeneic transplant.

- Describe the demographic and baseline characteristics of adult patients with HSCT-TMA reported in the literature
- Describe the literature-reported frequency of HSCT-TMA improvement/resolution in the following adult patient populations:
 - All reported patients except those noted to have received treatment with eculizumab and/or defibrotide (AP group)
 - All reported patients in the AP group except those noted to have received any pharmacological treatment (nonpharmacologically treated patients, or NPTP). These excluded therapies: rituximab, vincristine, pravastatin, recombinant thrombomodulin, etanercept, prednisone, mycophenolate mofetil, cyclosporin, imatinib, doxycycline, limaprost. (NPTP group)

Reviewer comment

The withdrawal or change in calcineurin inhibitors as initial management was not characterized or described. This is a limitation of the data because CNI discontinuation is a common step in TMA management.

- Describe the literature-reported 100- day survival following HSCT-TMA diagnosis in the following adult patient populations:
 - All reported patients except those noted to have received treatment with eculizumab and/or defibrotide group (AP group)
 - All reported patients except those noted to have received any pharmacological treatment (NPTP group as above)
- Describe the impact of the following risk factors on the improvements/resolution of HSCT-TMA and 100- day survival following HSCT-TMA diagnosis:
 - Co-existing GVHD
 - Co-existing infection
 - Co-existing neurological findings
 - Co-existing pulmonary complications
 - Co-existing renal dysfunction
 - Co-existing gastrointestinal complications
 - Relapsed or persistent underlying malignancy
- Compare the response and 100-day survival rates in the literature- based patient groups to the response and 100-day survival rates observed with narsoplimab-wuug in Study TMA-001.

6.2.2.2. Eligibility Criteria, Literature Historical Control

The study included patients from the published literature (dated year 2000 and later) only if the met all of the following criteria:

- Age >18 reported in the article
- Diagnosis of HSCT-TMA following allogeneic HSCT
- Identifiable patient-level data
- Data including (i) any variable of the primary response variable (platelet count, lactate dehydrogenase, organ function or transfusions) used in Study TMA-001 or (ii) report of response and at least 1 risk factor present in the narsoplimab-wuug pivotal trial patients (i.e., GVHD, neurological dysfunction, infection, pulmonary dysfunction, renal dysfunction, gastrointestinal dysfunction, relapse, or persistence of underlying malignancy)

Exclusion

- Patients from the published literature were excluded from the study if they had received eculizumab and/or defibrotide therapy.

Data Sources

- The study procedures were limited to review of the published English-language literature generated through a PubMed search.

Methods

The following was used to conduct the literature review:

- Criteria for publication selection were:
 - Reports of adult patients receiving allogeneic transplants
 - Reports with patient level data including (i) any component of the primary response endpoint used in the narsoplimab-wuug pivotal trial or (ii) report of response and at least 1 risk factor present in the narsoplimab-wuug pivotal trial patients
 - Publication after 2000

- A PubMed search was conducted of the following terms:
 - “Thrombotic microangiopathy” and “stem cell
 - “Transplant-associated thrombotic microangiopathy”
 - “Cancer associated thrombotic microangiopathy

- All unique, English-language articles that met the criteria above were collected.

Primary review of each full publication not abstracts was conducted by at least 2 independent reviewers with medical backgrounds. All articles identified by either reviewer were forward for secondary review by different individuals.

Working independently, 2 physicians performed a secondary review of publications identified in the primary review to confirm correct inclusion of publications in the literature review. Inclusion of publications was based on meeting the criteria for publication selection. A third physician adjudicated any differences.

All relevant data were extracted by one of the secondary review physicians compiled. A medical writer conducted a quality control review on all extracted data against all publications passing the secondary review.

All articles identified in the primary review but rejected in the review were provided. secondary

Operational definitions of the response components from Study TMA-001 and criteria for improvement in the literature patients are:

Platelet Count

Evidence of platelet count improvement was considered a positive platelet count response in the literature patients. Platelet count improvement due to platelet transfusions were not considered a platelet count response in the literature patients.

LDH

Evidence of lactate dehydrogenase improvement was considered a positive LDH response in literature patients

Renal Function

Evidence of creatinine improvement or cessation of RRT was considered a positive renal function response in the literature patients.

Neurological Function

Improvement in gastrointestinal function was defined as any improvement in gastrointestinal function or bleeding reported in the literature patients.

Transfusion Burden

Transfusion freedom was defined as a report in the literature of transfusion freedom in a patient previously receiving transfusions.

Risk Factor Definition

Any of the risk factors of graft-versus-host disease (GVHD), infection, relapse or persistence of underlying malignancy and organ dysfunctions were defined as a report of such complication in the article.

Response

Response were defined as evidence in the article of reported “response” OR improvement in platelet count, LDH, and either organ function or transfusion burden.

100-Day Survival

A patient achieved a 100-day survival if the overall survival from the date of HSCT_TMA diagnosis of the patient was ≥ 100 days. If the 100-day survival status of a patient was unknown (i.e., censored before 100 days), this patient was considered to have died prior to 100 days.

6.2.2.3. Statistical Analysis Plan, Literature Historical Review

Sample Size Determination

Not planned

Interim Analyses

Not planned

Missing Data

Different imputations were used to impute missing baseline characteristics and risk factors information for all literature-based patients to enable treatment comparisons between narsoplimab-wuug–treated and literature-control patients. These imputation methods aimed to represent the best- and worst-case scenarios that would cover the actual risk-factor status of the literature-based patients.

The risk-factor status of all narsoplimab-wuug–treated patients was known.

The reported demographics and risk factors from the literature studies were not consistent across studies. In order to perform the propensity score analyses, unknown (i.e., not reported) risk factors for the literature patients were imputed by 4 methods:

- All unknown risk factors are imputed as absent.
- All unknown risk factors are imputed as present.
- Unknown risk factors are imputed as present for responders, and absent for nonresponders.
- Unknown risk factors are imputed as absent for responders, and present for nonresponders.

Exploratory Analyses

The Applicant conducted post-hoc exploratory analyses include propensity score analyses, where propensity scores were estimated by a logistic regression for treatment with the following covariates: age and days from HSCT to TMA diagnosis as continuous variables, and GVHD, infection, renal dysfunction, and neurologic dysfunction as categorical variables (Yes/No). Pulmonary dysfunction, GI dysfunction and relapsed/refractory primary disease were not used because of the large number of unknown (i.e., not reported) statuses in the literature database.

- Model 1 included: Age, days from HSCT to TMA diagnosis, GVHD, infection, renal dysfunction, and neurologic dysfunction
- Model 2 included: Age, GVHD, infection, renal dysfunction, and neurologic dysfunction
- Model 3 included: Days from HSCT to TMA diagnosis, GVHD, infection, renal dysfunction, and neurologic dysfunction
- Model 4 included: GVHD, infection, renal dysfunction, and neurologic dysfunction

Weighted logistic regression for response with a single treatment covariate (narsoplimab-wuug or literature) weighted by stabilized inverse probability of treatment weighting (SIPTW) was performed for each model and imputation method. Odds ratios with 95% CI were calculated. A similar approach was taken for 100-day survival.

Sensitivity analyses using matching were performed on Model 1. 1:k matching (matching k literature patients to 1 narsoplimab-wuug patient, where k =1 to 4) using a greedy matching method with a caliper of 0.5 (with respect to the pooled standard deviation of the logit of the

propensity score from the 2 treatment groups) was performed for each imputation method. For each matched set and imputation method, a conditional logistic regression for response with a single treatment covariate (narsoplimab-wuug or literature) was performed. Odds ratios with their 95% CIs were calculated.

Diagnostics were performed to evaluate goodness of fit for various models and imputations and to evaluate balancing of risk factors in the matched patient cohorts.

6.2.2.4. Results of Analyses, Literature Historical Review

Demographics and Risk Factors

Baseline demographics including age, sex, and time from HSCT to TMA diagnosis for the literature review patients compared to the narsoplimab-wuug–treated patients from Study TMA-001 are shown in [Table 17](#). Note that these are the Applicant’s results.

Table 17. Applicant’s Results - Demographics for Literature and Narsoplimab-wuug–Treated HSCT-TMA Patients

Demographics	Narsoplimab-wuug (N=28)	AP Group (N=179)	NPTP Group¹ (N=149)
Age (years)			
n	28	155	134
Mean (SD)	48.0 (13.32)	40.1 (12.90)	40.4 (12.98)
Median	48.0	40.0	41.5
Min, max	22, 68	18, 66	18, 66
Sex, n (%)			
Male	20 (71.4%)	88 (49.2%)	76 (51.0%)
Female	8 (28.6%)	67 (37.4%)	58 (38.9%)
Not reported	0	24 (13.4%)	15 (10.1%)
Time from HSCT to TMA diagnosis (days)			
n	28	150	121
Mean (SD)	121 (108.80)	132.8 (267.12)	133.8 (286.42)
Median	73.5	47.0	48.0
Min, max	21, 436	1, 2500	1, 2500

Source: Page 18 of the literature review report

¹ This group excluded additional treatments, collectively including rituximab, vincristine, pravastatin, recombinant thrombomodulin, etanercept, prednisone, mycophenolate mofetil, cyclosporin, imatinib, doxycycline, and limaprost
Abbreviations: AP, all patients (includes pharmacologically treated and nonpharmacologically treated); HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; NPTP, nonpharmacologically-treated patients; SD, standard deviation

The Applicant stated that patient demographics were broadly comparable between the Study TMA-001 population and the literature reported AP and NPTP datasets. In particular, they noted that Based on the available data, there appears to be a slightly higher proportion of males (71.4%) in the clinical trial dataset compared to the literature (approximately 50%). Their reported time from HSCT to TMA diagnosis was consistent with the natural history of HSCT-TMA observed in clinical practice (trial population median =73.5 days versus 47 and 48 days for the literature groups). The observed differences are not likely to be clinically meaningful.

The Applicant’s summarized literature reports were also reviewed for critical HSCT-TMA risk factors, including infection, acute GVHD, renal, neurologic, pulmonary, and gastrointestinal dysfunction, and relapsed or refractory primary disease. The resulting risk factors are summarized

in (Table 18). It should be noted that there are missing (not reported) data in the literature risk-factor assessment and therefore results should be interpreted with caution although the Applicant stated that they have addressed the issue by using different imputation methods.

Table 18. The Applicant's Summary of Reported Risk Factors From Literature and Narsoplimab-wuug-Treated HSCT-TMA Patients

Risk Factor	Narsoplimab-wuug (N=28)	AP Group (N=179)	NPTP Group (N=149)
Significant infection			
Yes	24 (85.7%)	44 (24.6%)	34 (22.8%)
No	4 (14.3%)	39 (21.8%)	35 (23.5%)
Not reported	0	96 (53.6%)	80 (53.7%)
GVHD			
Yes	19 (67.9%)	106 (59.2%)	88 (59.1%)
No	9 (32.1%)	50 (27.9%)	43 (28.9%)
Not reported	0	23 (12.8%)	18 (12.1%)
Renal dysfunction			
Yes	21 (75%)	65 (36.3%)	58 (38.9%)
No	7 (25%)	17 (9.5%)	12 (8.1%)
Not reported	0	97 (54.2%)	79 (53.0%)
Neurologic dysfunction			
Yes	16 (57.1%)	53 (29.6%)	42 (28.2%)
No	12 (42.9%)	61 (34.1%)	48 (32.2%)
Not reported	0	65 (36.3%)	59 (39.6%)
Pulmonary dysfunction			
Yes	5 (17.9%)	7 (3.9%)	7 (4.7%)
No	23 (82.1%)	17 (9.5%)	15 (10.1%)
Not reported	0	155 (86.6%)	127 (85.2%)
Gastrointestinal dysfunction			
Yes	1 (3.6%)	6 (3.4%)	6 (4.0%)
No	27 (96.4%)	6 (3.4%)	4 (2.7%)
Not reported	0	167 (93.3%)	139 (93.3%)
Relapsed or refractory primary disease			
Yes	6 (21.4%)	19 (10.6%)	17 (11.4%)
No	22 (78.6%)	46 (25.7%)	39 (26.2%)
Not reported	0	114 (63.7%)	93 (62.4%)
Number (%) of patients with			
0 risk factor	0	22 (12.3%)	19 (12.8%)
1 risk factor	0	65 (36.3%)	52 (34.9%)
2 risk factors	6 (21.4%)	53 (29.6%)	46 (30.9%)
3 risk factors	10 (35.7%)	28 (15.6%)	21 (14.1%)
≥3 risk factors	22 (78.6%)	39 (21.8%)	32 (21.5%)
≥4 risk factors	12 (42.9%)	11 (6.1%)	11 (7.4%)

Source: Page 19 of the literature review report

Abbreviations: AP, all patients (includes pharmacologically treated and nonpharmacologically treated); GVHD, graft-versus-host disease; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; NPTP, nonpharmacologically treated patients

As shown in Table 18, the Applicant also reported a variety of risk factors associated with HSCT-TMA were reported in the literature and captured for the clinical study population. These included: significant infections, renal dysfunction, GVHD, pulmonary dysfunction, GI dysfunction, neurological dysfunction, and relapsed or refractory primary disease. It should be

noted that there are missing (not reported) data in the literature risk-factor assessment, which has been addressed using different imputation methods.

Efficacy Results Literature Review

StudyTMA-001 utilized, endpoint is a composite endpoint which was comprised of an improvement in LDH level and platelet count and a clinical improvement (organ function or freedom from transfusion). There are no standard response criteria for HSCT-TMA and the, collectively a clinically meaningful endpoint and a rigorous test for response to therapy. The literature reports a variety of response criteria, which, for the most part, are not as rigorous as the clinical trial endpoint. We have analyzed these criteria according to a definition of stringency as follows:

Laboratory

Criteria or clinical criterion/criteria only = less stringent compared to Study TMA-001; LDH and platelets and clinical criterion/criteria = “equal” stringency to the narsoplimab-wuug clinical trial endpoint. The response criterion/criteria that were not defined in literature publications were designated as incomplete.

[Table 19](#) summarizes the breakdown for the 35 studies, using the definitions of stringency above, that comprise the AP group and the corresponding response rates. While the NPTP group is most comparable for the narsoplimab-wuug clinical trial population, the AP group, which includes patients receiving therapeutic interventions, is included to provide the most conservative analysis. As can be seen from [Table 19](#), the literature-based response rates across stringency levels range from approximately 29% to 37% in the AP group and 18% to 32% in the NPTP group. For main Study TMA-001, the Applicant estimated response is 61% and FDA estimated response is 43%.

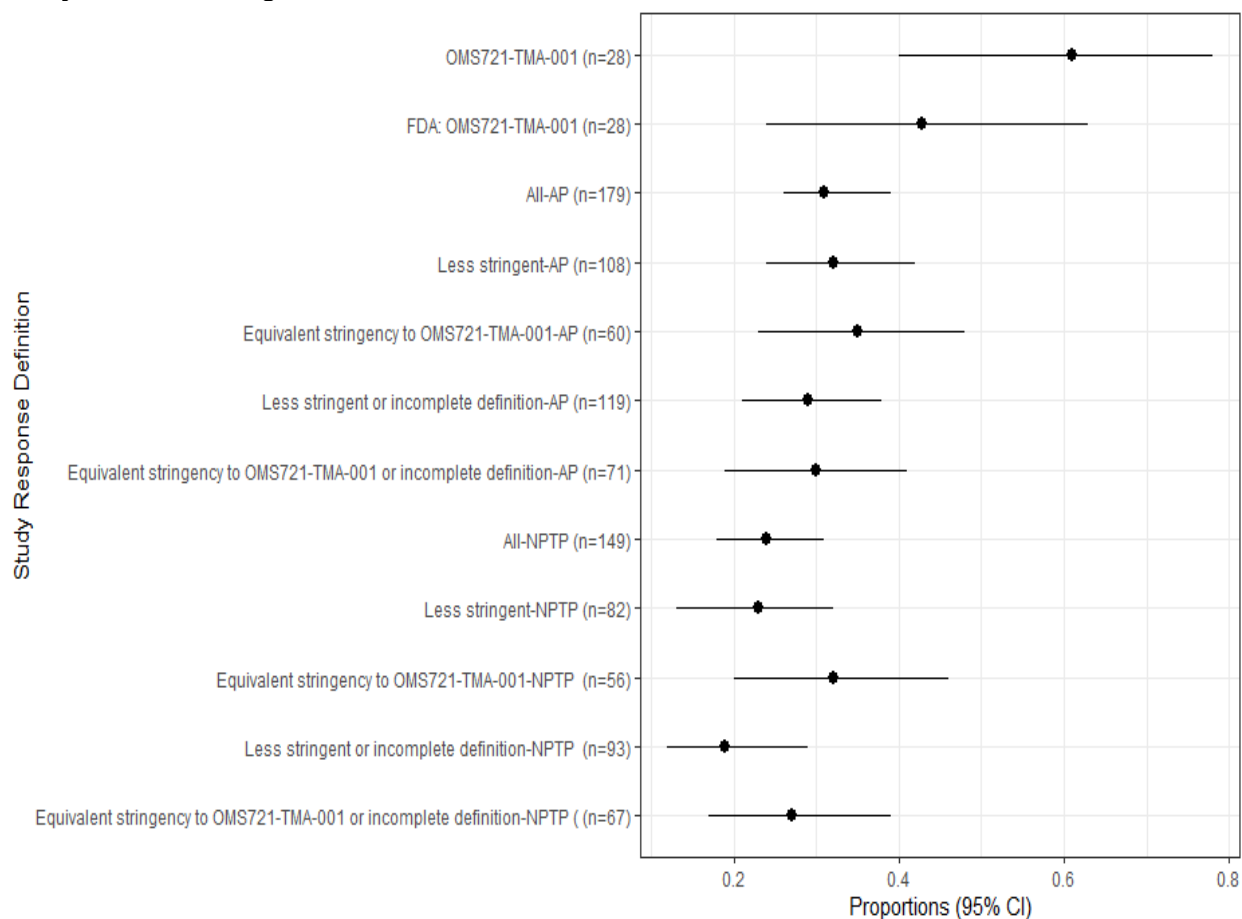
Table 19. Literature Response Rate by Response Definition and Main Study Results, Study TMA-001

Study Response Definition	# of Studies	# of Responders/# of Patients (%)¹
Main study		
Applicant estimated response rate: OMS721-TMA-001		17/28 (61%)
FDA estimated response rate: OMS721-TMA-001		12/28 (42.8%)
All patients		
All	35	56/179 (32.5%)
Less stringent	20	35/108 (36.8%)
Equivalent stringency to OMS721-TMA-001	9	21/60 (36.0%)
Less stringent or incomplete definition	26	35/119 (31.7%)
Equivalent stringency to OMS721-TMA-001 or incomplete definition	15	21/71 (28.7%)
Nonpharmacologically treated patients		
All	25	36/149 (23.3%)
Less stringent	13	18/82 (22.8%)
Equivalent stringency to OMS721-TMA-001	6	18/56 (32.3%)
Less stringent or incomplete definition	19	18/93 (18.4%)
Equivalent stringency to OMS721-TMA-001 or incomplete definition	12	18/67 (25.7%)

Source: FDA reviewer

To further investigate these responses, a forest plot (Figure 9) is shown to provide both point estimates and 95% CI. The forest plot shows that for AP the response rate and 95% CI were 31% (25%, 39%), for NPTP 24% (17%, 31%), and for FDA estimated response rate for main Study TMA-001 43% (24%, 63%).

Figure 9. Forest Plot of Literature Response Rate by Response Definition and Main Study Results, Study TMA-001 Along With 95% CI

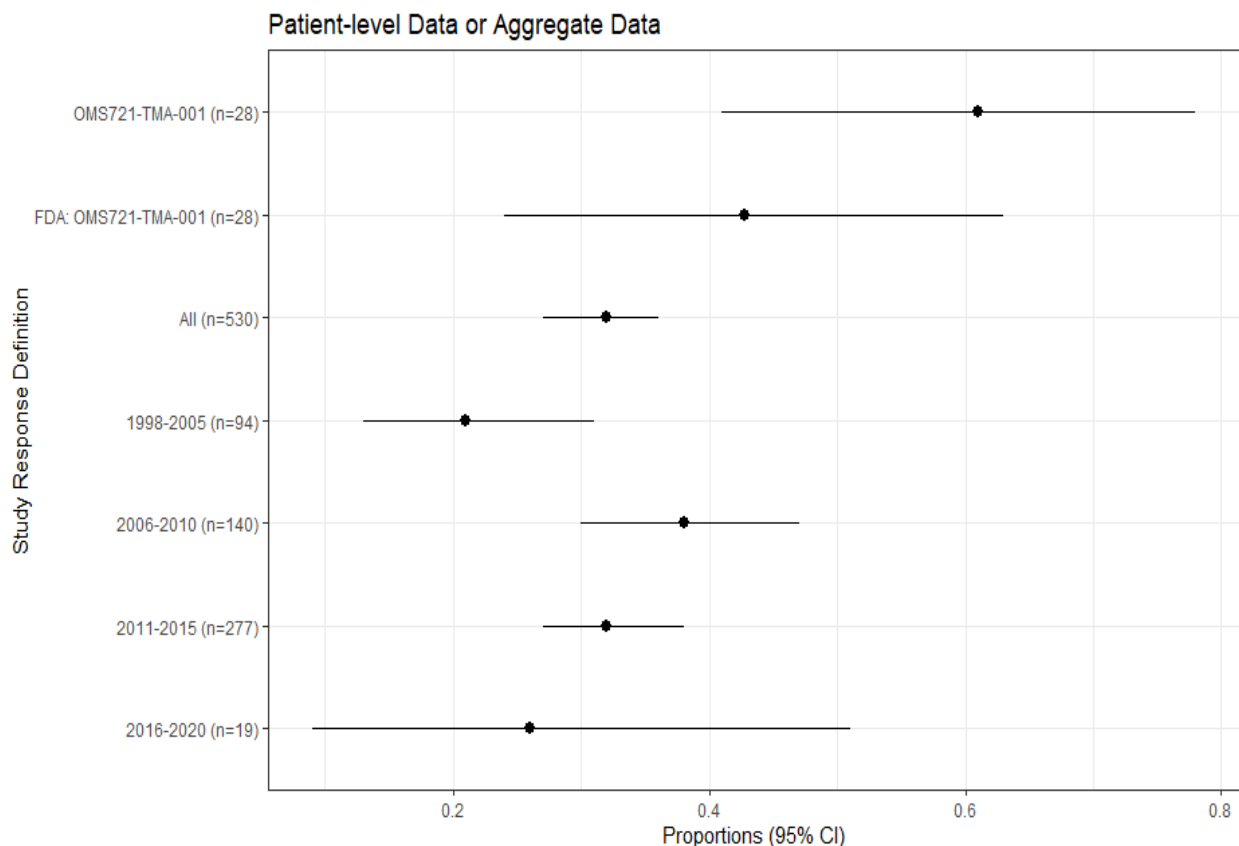


Source: FDA reviewer

Abbreviations: AP, all patients (includes pharmacologically treated and nonpharmacologically treated); CI, confidence interval; NPTP, nonpharmacologically treated patients

[Figure 10](#) shows forest plot of point estimate and 95% CI of response rate by year grouping. As seen in Figure 11, it appears that the response rate was higher from 2005 to 2020 than that before 2005 and the overall response rate is around 30%. For all patient's response rate and 95% CI were 32% (28%, 36%), for study population between 1998 to 2005 21% (13%, 31%), for 2006 to 2010 38% (30%, 47%), for 2011 to 2015 32% (26%, 38%), and for 2016 to 2020 26% (9.1%, 51%).

Figure 10. Forest Plot of Patient Level and Aggregate Data From Literature Review



Source: FDA reviewer. These response rates were estimated by combining both patient level and aggregate data from literature review published in the period 2000 to 2020 and using study population from years 1998 to 2020.

100-Day Survival Rates by Year Grouping

For the literature published in the period 2000 to 2020, analyses of response and 100-day survival rates were conducted for the time periods 2000 to 2009 (10 years), 2010 to 2014 (5 years) and 2015 to 2020 (6 years). In general, the reported response rates and 100-day survival numbers were similar in all the time periods and across the AP and NPTP datasets, with the following exceptions: reported response rates were higher in 2010 to 2014 than in the other 2 periods, and for 2015 to 2020, no 100-day survival rates were available.

Table 20. Literature Response Rate and 100-Day Survival Rate by Time Period

Time Period	Response Summary		100-Day Survival Summary	
	# of Studies	# of Responders/ # of Patients (%)	# of Studies	# Achieved 100-Day Survival/ # of Patients (%)
All patients				
All	35	56/179 (32.5%)	24	55/125 (47.5%)
2000-2009	19	31/118 (26.7%)	17	44/98 (50.7%)
2010-2014	7	13/27 (52.9%)	4	10/24 (41.7%)
2015-2020	9	12/34 (36.5%)	3	1/3 (31.1%)
Nonpharmacologically treated patients				
All	25	36/149 (23.3%)	16	41/107 (37.3%)
2000-2009	14	21/103 (19.3%)	11	32/83 (39.1%)
2010-2014	3	8/22 (36.3%)	3	9/22 (40.9%)
2015-2020	8	7/24 (30.1%)	2	0/2 (NE)

Source: Page 29 of the literature review report
Abbreviations: NE, not estimable

Data Quality and Integrity

Materials reviewed include the protocol, statistical analysis plan, and study report for this study. Data of this submission, provided with SDTM and ADaM formats, are acceptable. The Applicant also provided clear definition file for datasets and, reviewer guide and detailed analysis SAS programs for assisting review. Please refer to Appendix III, section [III.20](#) for discussion on Office of Scientific Investigation inspection.

Statistical reviewer comment

The Applicant submitted sufficient materials to the Agency for the FDA reviewers to confirm the Applicant's trial results and literature search and analyses.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Determination of Response Rate: Applicant's vs. FDA's analysis

Issue

The primary endpoint of Study TMA-001 was the proportion of HSCT-TMA patients who responded to narsoplimab-wuug treatment. There was no control group; therefore, accurate interpretation of the response rate is critical in being able to demonstrate efficacy. Response rate was determined based on improvement in platelets, a reduction in LDH, and clinical improvement. The Applicant concluded that 61% [95% CI: 41%-78%] of patients met the primary endpoint. There are challenges in interpreting the response in the setting of a very complex patient population, disease related issues, endpoint issues and lack of adherence to the protocol. The clinical team reviewed each patient narrative and provided adjudicated responses for the 28 patients. The FDA concluded that the response rate was 43% [95% CI: 24%, 63%].

Background

Explanation Regarding Relevance of Review Issue

The patient population included in Study TMA-001 was complex, consisting of mostly critically ill patients with multiple confounders (i.e., concurrent diseases, concomitant medications), posing a challenge to determine the response rate.

The clinical review team assessed all 28 patient narratives submitted with the application. What became apparent during the review is that while the primary endpoint had mostly objective components (i.e., platelet count, LDH, serum creatinine, transfusion freedom, increase in haptoglobin) the complexity of the patient population, comorbid illnesses, along with trial design features, impacted the interpretability.

Specific issues identified that impacted the interpretation of the response to narsoplimab-wuug can be further categorized by disease-related issues, lack of adherence to protocol defined enrollment and response criteria and difficulty in determining magnitude and durability in endpoint (response). These included:

Disease-Related Issues

- Concurrent diseases: The majority of patients had a diagnosis of GVHD, significant infection, or other concurrent disease process for which they were actively treated for around the time of HSCT-TMA diagnosis and/or narsoplimab-wuug administration.
- Concurrent medications: Patients were receiving concomitant medications that may impact the response to narsoplimab-wuug, such as modification of calcineurin inhibitors or sirolimus, in addition to other therapies or treatments (i.e., plasma therapy, rituximab, and defibrotide).

Lack of Adherence to Protocol Defined Enrollment and Response Criteria

- Not all patients who were classified by the Applicant as responders met all three components (platelet, LDH and improvement in organ function (renal, pulmonary, or gastrointestinal) of the primary endpoint definition. deviating from protocol defined response.
- A significant number of patients did not meet the predefined inclusion/exclusion criteria but were still included in the study. Magnitude of serum creatinine change may be difficult to interpret for patients who did not meet the inclusion criteria of doubling of serum creatinine from pre-HSCT level.

Difficulty in Determining Magnitude of Laboratory Changes and Durability of Response

- The significance of magnitude of change was difficult to assess in patients with LDH just above the ULN.
- Difficulty interpreting improvement in neurologic and/or GI dysfunction as these clinical manifestations could be multifactorial and were treated concurrently
- Durability of response and time to response

Assessment

Disease-Related Issues

Confounding Concurrent Disease and Treatments

GVHD and infections are common complications of HSCT. The basis of the pathophysiology of HSCT-TMA involves endothelial injury and microthrombi formation ([Khosla et al. 2018](#)). First-line treatment of HSCT-TMA is typically to limit and when possible, completely remove the condition which is causing endothelial injury, which includes treatment of infections and GVHD ([Khosla et al. 2018](#)). This may be an effective treatment strategy in particular when HSCT-TMA is mild-moderate ([Rosenthal 2016](#)). The clinical review team evaluated the rates of infections and GVHD in Study TMA-001 in order to assess the possible impact of these disease processes on the primary endpoint.

In total, 19/28 (67.9%) of patients had a diagnosis of GVHD (acute and/or chronic) around the time of HSCT-TMA diagnosis and/or during narsoplimab-wuug treatment. This included 12/17 (70.6%) responders and 7/11 (63.6%) nonresponders with GVHD. Patients were treated with corticosteroids along with other medications used to treat GVHD.

In addition, most patients had significant infections. This included 23/28 (82.1%) of patients with a significant infection. [Table 21](#) shows significant infections as defined by the Applicant that occurred 2 weeks prior to the first dose of narsoplimab-wuug dose or during the treatment period. Of the responders 15/17 (88.2%) had significant infections and 9/11 (81.8%) nonresponders had significant infections. Patients were treated with antibiotics, antifungals, and/or antivirals depending on the type of infection.

While the clinical review team acknowledges that these concurrent diseases may increase the risk of poor outcomes, it can be challenging to determine if the treatment impacted the response in the setting of single-arm trial. Notably, responders and nonresponders had similar rates of GVHD and infections.

Table 21. Patients With Significant Infections as a Risk Factor

Pt	Significant Infection Event Term	Assessment
(b) (6)	Strep bacteremia	Before diagnosis
	HHV6 Infection	Before diagnosis
	CMV reactivation	Before diagnosis
	Pneumonia	Before diagnosis
	CMV reactivation	Before diagnosis
	Pneumocystis	Before diagnosis
	CMV reactivation	Before diagnosis
	Klebsiella pneumonia	During treatment
	Septic shock	During treatment
	Gram-negative rod bacteremia	During treatment
	Aspergillus	During treatment
	Gram negative blood stream infection	Before diagnosis
	<i>Enterococcus faecalis</i> + from bronchoscopy	Before diagnosis
	CMV viremia (reactivation)	During treatment
	Staph sepsis	Before diagnosis
	CMV viremia	Before diagnosis

Pt	Significant Infection Event Term	Assessment
(b) (6)	CMV reactivation	Before diagnosis
	Rotoviral infection	Before treatment
	Giardia infection	Before treatment
	Bilateral pneumonia	During treatment
	Intermittent periods CMV viral load reactivation	Before diagnosis
	EBV viral load reactivation	Before diagnosis
	PJP pneumonitis	Before diagnosis
	Pneumococcal pneumonitis	Before diagnosis
	Thrombophlebitis left arm <i>Staph aureus</i>	Before diagnosis
	Fever of unknown origin	Before treatment
	CMV reactivation	Before diagnosis
	HHV6 infection	Before diagnosis
	Probable pulmonary infection	Before diagnosis
	BK viral hemorrhagic cystitis	Before diagnosis
	Febrile neutropenia	Before diagnosis
	CMV reactivation	Before diagnosis
	EBV reactivation	Before diagnosis
	CMV reactivation	Before diagnosis
	Suspected fungal pneumonia	During treatment
	Multiple episodes of sepsis	Before diagnosis
	CMV reactivation	Before diagnosis
	Sepsis	Before diagnosis
	Acute on chronic maxillary sinusitis	Before diagnosis
	Recurring EBV infection	Before diagnosis
	Neutropenic fever	Before diagnosis
	Respiratory infection	Before diagnosis
	Hickman Line infection	Before diagnosis
	Abdominal cellulitis	Unknown ^a
	CMV infection	Before treatment
	Carbapenem-resistant <i>Enterobacteriaceae</i>	Before diagnosis
	Intermittent CMV infection reactivation	Before diagnosis
	Fever	day
	MRCONS infection	Before diagnosis
	CMV infection	Before diagnosis
	Viral fever	During treatment
	BK virus cystitis	Before diagnosis
	Adenovirus cystitis	Before diagnosis
	Non-neutropenic sepsis	During treatment
	Urinary tract infection	During treatment
	Asymptomatic BK cystitis	Before diagnosis
	CMV positivity	Before diagnosis

Source: Applicant's IR response

^a Onset of event is listed as the same month as HSCT-TMA diagnosis and initiation of narsoplimab-wuug treatment so it is unknown what the timing is with regard to either time point.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; MRCONS, methicillin-resistant coagulase-negative staphylococci; PJP, pneumocystis jirovecii; pt, patient

Concomitant Medications

CNI or Sirolimus

While there are no approved therapies for the treatment of HSCT-TMA, one of the first management steps includes removing the potential offending agent, such as CNIs and/or sirolimus. The Bone Marrow Transplant Clinical Trials Network Toxicity Committee consensus

summary recommended CNI cessation as the first line management ([Ho et al. 2005](#); [Epperla et al. 2020](#)). Not all patients respond to this method of HSCT-TMA management. Replacing CNIs with other immunosuppressive agents has been demonstrated to be more successful than CNI dose reductions ([Elsallabi et al. 2016](#)). Experts have recently disputed the effectiveness of CNI or sirolimus dose reductions and discontinuations, however. Recent cohort studies have suggested that immunosuppression withdrawal does not impact patient outcomes ([Li et al. 2019](#); [Epperla et al. 2020](#)). Therefore, this issue remains controversial.

In an information request (IR) response to the Agency, the Applicant reported CNI change in 7/17 (41.2%) of responders and 7/11 (63.6%) of nonresponders. The clinical reviewer conducted a separate analysis by reviewing the 28 narratives for CNI change or discontinuations in both responders and nonresponders. CNI or sirolimus dose reduction or discontinuation was considered relevant if it occurred either within 2 weeks before starting narsoplimab-wuug or during treatment. In total, 10/17 (58.9%) of responders had CNI or sirolimus changes, compared to 3/11 (27.3%) of nonresponders ([Table 22](#)).

While more responders had CNI and/or sirolimus modifications or discontinuations compared to nonresponders, the significance of this is uncertain given there is no control arm in this study.

Table 22. CNI or Sirolimus Reduction or Discontinuation

Patient ID	CNI or Sirolimus Change Days	Narsoplimab-wuug Dosing Days	CNI or Sirolimus Dose Reduction or Discontinuation Within 2 Weeks of Initiating Narsoplimab-wuug or During Therapy
RESPONDERS			
(b) (6)	Tacrolimus discontinued on day 89	85-105	Y
	Tacrolimus discontinued on day 125	167-187	N
	Tacrolimus discontinued on day 16 and sirolimus on day 22, intermittent exposure during treatment	36-86	N
	Tacrolimus discontinued on day 121	121-170	Y
	Cyclosporin discontinued on day 42	41-90	Y
	Tacrolimus discontinued on day 68	230-279	N
	Cyclosporin discontinued one month prior to HSCT-TMA diagnosis	232-281	N
	Cyclosporin discontinued on day 384	428-497	N
	Conflicting information: Cyclosporin taper day 41 and discontinued day 170.	64-111	Y
	Cyclosporin taper day 226-312, discontinued on day 312	263-312	Y
	Cyclosporin discontinued day 23	33-82	Y
	Cyclosporin reduced day 48 and stopped on day 61	53-103	Y
	Cyclosporin discontinued on day 194	201-250	Y

Patient ID	CNI or Sirolimus Change Days	Narsoplimab-wuug Dosing Days	CNI or Sirolimus Dose Reduction or Discontinuation Within 2 Weeks of Initiating Narsoplimab-wuug or During Therapy
(b) (6)	Cyclosporin stopped day 50 and sirolimus day 55	74-123	N
	Cyclosporin discontinued day 137 and sirolimus discontinued day 142. Sirolimus restarted on day 199-274	145-253	Y
	Cyclosporin stopped day 40	117-167	N
	Cyclosporin reduced day 75 and stopped day 100	82-132	Y
NONRESPONDERS			
(b) (6)	Tacrolimus discontinued day 14, Sirolimus discontinued on day 34	54-68	N
	Tacrolimus discontinued on day 114, Sirolimus discontinued day 101	135-149	N
	Tacrolimus tapered 187-229	444-451	N
	Tacrolimus discontinued day 191	299-327	N
	Cyclosporin dose reduction on day 89	82-96	Y
	Cyclosporin dose reduction day 75, discontinued day 93	76-98	Y
	Cyclosporin dose reduction day 153-185	137-186	Y
	Cyclosporin discontinued day 30	47-54	N
	Cyclosporin continued	47-96	N
	Cyclosporin discontinued day 29	224-245	N
	Cyclosporin discontinued day 95	185-213	N

Source: Clinical reviewer, data extrapolated from patient narratives and ADEX.jmp dataset

* Day 0 = day of HSCT

Abbreviations: CNI, calcineurin inhibitor; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; ID, identification; N, no; Y, yes

Plasma Therapy

As specified in the protocol, patients were allowed to receive plasma exchange while on study. According the Applicant's CSR, a total 7 patients (25%) received plasma therapy while on study. Per protocol four patients received supplemental doses of narsoplimab-wuug at 2 mg/kg IV while receiving narsoplimab-wuug. Of the patient's that received extra doses of narsoplimab-wuug, 2 (50%) were responders while receiving plasma exchange. While plasma exchange may be an effective treatment for TTP, this mode of therapy is thought to be less beneficial in HSCT-TMA. Plasma exchange has variable response rates and an unclear impact on mortality ([Khosla et al. 2018](#)).

Rituximab

According to the Applicant's CSR, 5 patients received rituximab as a concomitant medication. Patients were allowed to receive rituximab therapy during the Study TMA-001. In reviewing the concomitant medication dataset (adcm.jmp), 6 patients were identified who received rituximab within the month (30 days) before receiving narsoplimab-wuug and/or during narsoplimab-wuug treatment. Three out of 6 (50%) of patients were responders ([Table 23](#)).

While no large clinical trials have been conducted with rituximab in patients with HSCT-TMA, there has been some sparse data suggesting a role for rituximab as a therapy option for patients with HSCT-TMA ([Jodele et al. 2015](#)). An equal number of responders and nonresponders received rituximab, although the overall number of patients receiving rituximab is small, and interpretation may be confounded by the fact that 3 patients received plasma therapy as well. Plasma therapy in combination with rituximab may be effective therapy in some patients (insert reference).

Table 23. Patients Treated With Rituximab, Study TMA-001

Pt ID	Rituximab Dosing Days	Narsoplimab-wuug Dosing Days	Responder
(b) (6)	-32, -25, -18, -11	1, 8, 14, 21	Y
	-6, +2	1, 8	N
	-32, -25	1, 5, 8, 15, 22, 29	N
	-25, -18	1, 8, 15, 22, 29, 36, 43, 50	N
	-21	1, 8, 10, 15, 22, 29, 36, 44, 50	Y
	-47, -40, -33, -12, -5	1-3, 5, 7-11, 15-18, 22-25, 28-32, 35-39, 43, 50, 57, 60, 64, 67, 71, 74, 78, 81, 85, 88, 92, 95, 100, 102, 106, 109	Y

Source: Clinical reviewer, adcm.jmp dataset
Day 1 = Day of first narsoplimab-wuug administration
Abbreviations: ID, identification; N, no; pt, patient; Y, yes; N, no

Defibrotide

Two patients received defibrotide as a concomitant medication, both were nonresponders.

Lack of Adherence to Enrollment and Response Criteria

Not all patients considered to be responders by the Applicant met all three components of the primary composite endpoint. The definition of response was described previously ([6.2.1.1](#) and [6.2.1.2](#)):

In total, 3 patients (b) (6) who were considered responders by the Applicant never engrafted platelets and therefore were not able to be evaluated for a platelet response. Of note, one additional patient (b) (6) was reported as not engrafting platelets on the case report form, but after reviewing the narrative it was clear that this patient did have a platelet response, with a platelet increase from 17/ μ L to 103/ μ L. Therefore, this patient was considered a responder by the clinical reviewer.

The Applicant's rationale for including the patients with a nonevaluable platelet count was that the protocol states in section 13.2.5.1, "If a patient is not evaluable for a response criterion due to confounding factors, the nonevaluable response criterion will not be included in the determination of responder." However, we do not agree with this approach as it is unknown if data missingness would have affected the efficacy analysis. Patients with missing data should be classified as non-responders.

Two additional patients, (b) (6) should not be defined as responders. The Applicant's rationale for including the patient (b) (6) as a responder was a robust hemoglobin response (hemoglobin improved from 9.8 g/dL to 11.7 g/dL), in addition to a reduction in LDH and improvement platelet count. Although this patient did have a hemoglobin increase, this was

not a clinical endpoint of the primary composite endpoint and therefore this patient should not be considered a responder.

The rationale for the Applicant including (b) (6) is that patient had an improvement for neurological condition of posterior reversible encephalopathy syndrome (PRES).

Narratives for these five patients are described below and in more detail in Section [III.16](#).

Patient (b) (6)

The patient was diagnosed with HSCT-TMA on day 21 post-HSCT. The patient entered the clinical study on day 35. At the time of study entry, the platelet count was $17 \times 10^9/L$ (normal $130-400 \times 10^9/L$), LDH was 792 U/L (normal 125-220 U/L), creatinine was 0.73 mg/dL (normal 0.72-1.18 mg/dL), haptoglobin <3 g/L (normal 14-268 g/L), and the patient was receiving transfusions. The patient started narsoplimab-wuug on day 38 and received 8 weekly doses. Per the Applicant, the patient met a response (based on TMA markers only) 7 days after starting narsoplimab-wuug. This was based on a LDH reduction to 278 U/L. Platelet response was not evaluated as the patient had not engrafted platelets and remained transfusion dependent. The patient met a clinical improvement response of serum creatinine 37 days after starting narsoplimab-wuug with creatinine reduction to 0.57 mg/dL (baseline creatinine was 0.76 mg/dL). The patient did not meet a response based on transfusions. While not a component of the response definition, the haptoglobin did normalize on treatment. Of note, the patient had a HSCT-TMA relapse 62 days after starting narsoplimab-wuug, although this was complicated by neutropenic sepsis. The patient died shortly after. The full narrative can be found in the Section [16](#).

With a delayed modest improvement in creatinine, it is difficult to say that this is a robust response. In addition, haptoglobin was not part of the primary response criteria. In terms of a protocol defined response, this patient is likely a nonresponder.

Patient (b) (6)

This patient was diagnosed with HSCT-TMA on day 23 post-HSCT. At the time of study entry, on day 31 post-HSCT, the platelet count was $10 \times 10^9/L$ (normal $150-400 \times 10^9/L$), LDH was 712 U/L (normal 125-220 U/L), creatinine was 1.48 mg/dL (normal 0.64-1.04 mg/dL), haptoglobin was <3 (normal 14-268 mg/dL) and the patient was receiving transfusions. The patient started narsoplimab-wuug on day 33 post-HSCT and received 8 once weekly doses. Per the Applicant the patient met a response (based on TMA markers only) 15 days after starting narsoplimab-wuug. This was based on a LDH reduction to 225 U/L. The platelet count was not evaluable as the patient never engrafted platelets and remained transfusion dependent. The patient met a clinical improvement in response based on serum creatinine reduction to 1.2 mg/dL (baseline creatinine was 1.68 mg/dL) although this was not a 40% reduction in serum creatine as specified in the protocol. The patient remained transfusion dependent. While not a component of the primary endpoint the patient's haptoglobin normalized on narsoplimab-wuug therapy. Of note the patient's HSCT-TMA relapsed 43 days after starting narsoplimab-wuug, but this was due to a transient increase in LDH that reduced back to $<1.5 \times ULN$ within one week.

The patient died approximately 200 days after starting narsoplimab-wuug. A more detailed narrative can be found in the Section [16](#).

It is the reviewer's opinion that patient (b) (6) should be called a non-responder. There is an improvement in LDH and an improvement in serum creatinine could be considered a response although the LDH appeared to be down trending (see narrative in Section [16](#)) prior to narsoplimab-wuug treatment. The patient was also receiving blood transfusions and did not have transfusion freedom, although this could be due to poor graft function. In the strict definition of a response criteria per the protocol, the less than 50% reduction in serum creatinine does not meet the response criteria definition for improvement in renal function. Although there was an improvement in LDH, the magnitude of response is not large. The improvement in haptoglobin is notable and once again, in a clinical setting the patient would likely be considered as having a favorable response to therapy, but in terms of strict adherence to the protocol definition, this patient likely a nonresponder or partial responder.

Patient (b) (6)

This patient was diagnosed with HSCT-TMA on day 113 post-HSCT, based on colon biopsy. At the time of study entry, on day 121 post-HSCT, the platelet count was $22 \times 10^9/L$ (normal $130-400 \times 10^9/L$), LDH was 328 U/L (normal 125-220 U/L), creatinine was 1.9 mg/dL (normal 0.55-1.02 mg/dL), haptoglobin was normal at 221 (normal 35-273 mg/dL) and the patient was receiving transfusions. The patient started narsoplimab-wuug on day 121 post-HSCT and received 8 once weekly doses. Per the Applicant, the patient met a response (based on TMA markers only) 11 days after starting narsoplimab-wuug. This was based on a LDH of 394 U/L (further decrease to <250 U/L later in treatment course). The platelet count was not evaluable as the patient never engrafted platelets. The patient met a clinical improvement in response based on serum creatinine reduction to 1.06 mg/dL (baseline creatinine was 1.9 mg/dL). The patient remained transfusion dependent. Of note the patient's HSCT-TMA relapsed 15 days after starting narsoplimab-wuug, but this was due to a transient increase in LDH that reduced back to <1.5x the upper limit of normal within one week. This occurred a few times. The patient died approximately 170 days after starting narsoplimab-wuug. A more detailed narrative can be found in Section [16](#).

It is the reviewer's opinion that patient (b) (6) should not be called a responder. Given the complexity of this patient's condition which is described in the patient narrative in Section [16](#). The reduction in creatinine does appear to be >40% but the transient nature of the response to LDH is difficult to interpret and the patient did not meet all of the defined response criteria. The patient was also receiving blood transfusions (in addition to platelet transfusions) and there was no improvement with narsoplimab-wuug, although this could have been secondary to poor graft function. In the clinical setting, could consider this patient as having a partial response but in terms of the protocol defined response, would consider a nonresponder.

Patient (b) (6)

This patient was diagnosed with HSCT-TMA on day 36 post-HSCT. The patient's enrollment into Study TMA-001 was delayed due to a positive direct antiglobulin test (DAT). At the time of study entry on day 92 the platelet count was $14 \times 10^9/L$ (normal $142-350 \times 10^9/L$), LDH was 550 U/L (normal 240-480 U/L), creatinine was 0.52 mg/dL (normal 0.62-1.06 mg/dL), and the patient was not receiving transfusions. The patient started narsoplimab-wuug on day 117 post-HSCT and received 8 once weekly doses. Per the Applicant, the patient met a response (based on TMA markers only) 228 days after starting narsoplimab-wuug. This was based on a LDH reduction to 315 U/L. The platelet count improved to $196 \times 10^9/L$ (baseline platelet count was $65 \times 10^9/L$). All the clinical components of the response definition was not evaluable. A more detailed narrative can be found in Section [16](#).

It is in the reviewer's opinion that patient (b) (6) should not be defined as a responder. The Applicant's rationale for including this patient as a responder was a robust hemoglobin response (hemoglobin improved from 9.8 g/dL to 11.7 g/dL), in addition to a reduction in LDH and improvement platelet count. In the reviewer's opinion while this patient did have a hemoglobin increase, this was not a clinical endpoint of the primary composite endpoint and therefore this patient should not be considered a responder. In addition, the response occurring at 227 days after starting narsoplimab-wuug is far beyond any expected response.

Patient (b) (6)

The patient was a 32-year-old male with a history of high-risk ALL who underwent a matched related donor transplant. Day 1 post-transplant, he developed mucositis requiring parental nutrition and opioid management. On day 6, he developed bacteremia (blood culture was positive for staphylococcal aureus), he was treated initially with meropenem. The patient achieved neutrophil and platelet engraftment on day 18 and 22, respectively. On day 88, he was diagnosed with oral GVHD. His cyclosporine was discontinued on day 145. On day 159, he had elevated liver function tests, liver biopsy demonstrated severe panlobular hepatitis with hepatocyte necrosis, concerning for aGVHD. The patient was treated with prednisone. He also had CMV reactivation. Around day 178, he was diagnosed with acute skin and liver GVHD, in addition to chronic GVHD of the eye.

On day 194 he was diagnosed with HSCT-TMA, based on thrombocytopenia, elevated LDH, elevated creatinine and anemia. The patient had been restarted on cyclosporin two weeks prior but this was discontinued once HSCT-TMA was diagnosed. At this time, he was also diagnosed with PRES. With blood pressure control the patient recovered. He also had a low-grade fever. He received his first dose of narsoplimab-wuug on day 201 and received 8 total doses. Response occurred 153 days after starting narsoplimab-wuug and was based on improvement in LDH, platelets, neurologic dysfunction and transfusions per the Applicant. Following initiation of narsoplimab-wuug he had recurrent episodes of delirium and confusion, this was thought to be secondary to steroids, and/or self-discontinuation of lorazepam and haloperidol.

It is the reviewer's opinion that it is difficult to determine if the patient's neurologic improvement was related to narsoplimab-wuug. While PRES can be a manifestation of HSCT-TMA, it appears the patient improved with blood pressure control, the timing of the improvement in PRES is unclear in the patient narrative and therefore the impact of narsoplimab-wuug is unclear. Euphoria, delirium and confusion occurred after narsoplimab-wuug was started so it is therefore confounded by a new treatment and was managed with multiple other therapies including; hyperglycemia control, steroid taper, lorazepam and haloperidol. It is the reviewer's opinion that this patient should be considered a non-responder.

In summary, it is in the reviewer's opinion that 5 patients (b) (6) did not meet all three components of the response definition and should not be called responders.

Significant number of patients did not meet the predefined inclusion/exclusion criteria but were still included in the study. Magnitude of serum creatinine change may be difficult to interpret for patients who did not have the inclusion criteria of doubling of serum creatinine from pre-HSCT level.

The Applicant states 11/28 (39%) of patients did not meet inclusion/exclusion criteria but were granted waivers. Waivers were mostly granted for the creatinine criteria not being met (n=6) and for a positive Coombs test (n=3). The Applicant's rationale for waivers included; a diagnosis of HSCT-TMA could be made based on other criteria, renal dysfunction is a late finding in TMA progression and patients with HSCT-TMA may have a positive Coomb's test due to transfusions. A list of all patients who received a waiver and rationale why the investigator chose to continue to enroll those patients in the study is listed in [Table 113](#).

Exclusion Criteria of Positive Coombs Test

A positive Coombs test was an exclusion criterion in Study TMA-001. Despite this exclusion criteria 3 patients were included in Study TMA-001 who had a positive Coombs test. Patient's diagnosed with HSCT-TMA typically have a negative Coombs test in order to differentiate HSCT-TMA from Coombs positive autoimmune hemolytic anemia (AIHA) ([Khosla et al. 2018](#)). AIHA occurs in 4-6% of patients following allogeneic stem cell transplantation ([Barcellini et al. 2019](#)). AIHA can have overlapping features of HSCT-TMA, such as hemolytic anemia, elevated LDH, reduced haptoglobin, increase in transfusion requirements, and/or thrombocytopenia when associated with Evan's syndrome. Therefore, to ensure an accurate diagnosis of HSCT-TMA, patients with a Coombs positive test should not be included in this study. Although, the Applicant reports that the while the local laboratory reported a weakly positive Coombs test, the central laboratory report was negative for all three patients. Therefore, in this reviewer's opinion it is acceptable to include these patients in the analysis.

Inclusion Criteria of Doubling Serum Creatinine

A key inclusion criterion for Study TMA-001 was doubling of serum creatinine from the pre-HSCT level. In total, 6 of the 28 patients did not meet the renal inclusion criteria of doubling of

serum creatinine, yet the Applicant claimed these patients had other laboratory markers or clinical findings to support a diagnosis of HSCT-TMA.

While not all patients with HSCT-TMA have renal dysfunction, the kidney is the most common organ affected ([Khosla et al. 2018](#)) and it is included in the diagnostic criteria by the Blood and Marrow Transplant Clinical Trials Network ([Elsallabi et al. 2016](#)). While serum creatinine is an imperfect marker for renal injury, this was a reasonable choice for inclusion criteria (doubling of serum creatinine from baseline) and was agreed upon by the Agency during the clinical development of Study TMA-001. Further, this provided an objective measurement for assessing clinical improvement. Therefore, ignoring this inclusion criterion is an important protocol violation. One exception is patient (b) (6) who had biopsy proven TMA.

Five of the 6 patients who did not meet renal inclusion criteria were still evaluated for the renal response endpoint. The one patient (b) (6) who was not evaluated for a renal response had a normal creatinine at baseline. Of the 5 patients who were evaluated for renal response, 3 were responders (b) (6) per the Applicant, however by the FDA only (b) (6) were considered responders by the FDA.

Patient (b) (6) was the only patient who was dependent on the renal response as the clinical component to meet the definition of response. While the patient had an elevated serum creatinine of 1.25 mg/dL at the time of HSCT-TMA diagnosis it had down trended to 0.78 mg/dL prior to narsoplimab-wuug administration. While the serum creatinine further decreased to 0.6 mg/dL on narsoplimab-wuug therapy, this change is not clinically meaningful. It is in the clinical reviewer's opinion that patient (b) (6) should not be considered a responder. Additionally, this patient had a nonevaluable platelet count (see discussion on patients not meeting response definition). The clinical benefit of narsoplimab-wuug in this patient is therefore not evident.

In addition, the Applicant reports improvement in renal function occurred in 18/27 (74%) of patients. It is in the clinical reviewer's opinion that renal function should only be evaluated in patients who had doubling of serum creatinine from the pre-HSCT level, to ensure a significant and meaningful magnitude of change. Considering only patients who had a doubling of serum creatinine, the proportion of patients who had a renal response was 15/22 (68.2%).

In conclusion, the number of patient waivers for inclusion criteria reflects the challenges in the diagnosis of HSCT-TMA and the lack of uniform diagnostic criteria as there can be a variety of factors in diagnosis that may lead investigator to conclude a patient has HSCT-TMA. The rationale for the waivers may not be unreasonable as change in renal function can be a late finding and DAT positivity may be impacted by transfusions; however, this aspect of the clinical course of TMA should have been considered at the protocol development stage.

Difficulty in Determining Magnitude of Response

The clinical significance of magnitude of change in LDH was difficult to assess in patients with LDH values just above the upper limit of normal.

Inclusion criteria included laboratory values consistent with microangiopathic hemolysis, including LDH above the upper limit of normal; this is consistent with most diagnostic criteria

for HSCT-TMA ([Elsallabi et al. 2016](#)). Most patients included in Study TMA-001 had a significantly elevated LDH value with a mean LDH of 580.5U/L (range 237-1140U/L), normal range can vary depending upon laboratory but usually range between 140U/L to 280U/L, consistent with hemolysis (although LDH can increase due a variety of factors i.e., tissue damage, liver injury, bone injuries, infections and more). There were 2 patients ((b) (6)) who were responders that met the inclusion criteria of LDH, but the LDH value was just above the upper limit of normal. The LDH values of these patients are described below. As the criteria for LDH response was based on an LDH <1.5x ULN, it is difficult to determine the significance of LDH reduction as the patients described below already had an LDH <1.5x ULN prior to narsoplimab-wuug treatment.

Patient (b) (6)

The patient was diagnosed with HSCT-TMA on day 66, at that time the LDH was 221 U/L (normal range: 100-200 U/L). At the time of study entry on day 76 the LDH was 278 U/L (normal range: 125-220 U/L). Baseline LDH was 237 U/L (normal range: 125-220). LDH at time of first meeting response definition was 227 U/L (normal range: 125-220). Lowest LDH following narsoplimab-wuug treatment was 165 U/L (normal range: 125-220). See patient narrative in Section [16](#).

Clinical reviewer comment

Although the patient had a decrease of LDH per the protocol defined criteria, the magnitude of change is small.

Patient (b) (6)

The patient was diagnosed with HSCT-TMA on day 76, LDH was not reported in the patient narrative. Screening LDH was 290 U/L (normal range: 125-220 U/L). Baseline LDH was 261 U/L (normal range: 125-220 U/L). LDH at time of first meeting response definition was 187 U/L (normal range: 125-220). Lowest LDH following narsoplimab-wuug treatment was 104 U/L (normal range: 125-220). See patient narrative in Section [16](#).

Clinical reviewer comment

While the patient had a LDH just above the ULN at baseline, the clinical reviewer still believes it is likely the patient had a diagnosis of HSCT-TMA. The patient had other features of HSCT-TMA including thrombocytopenia, anemia, increased serum creatinine, and schistocytes. While the interpretation of LDH response is limited with a baseline value just ULN, the patient had a reduction in serum creatinine and improvement in platelet count. To further support response the patient also had improvement in haptoglobin and hemoglobin.

In conclusion, while both patients ((b) (6)) had mildly an elevated LDH, diagnosis of HSCT-TMA and response could be confidently determined based on other criteria. The clinical reviewer agrees both patients are responders.

Neurologic Dysfunction

Improvement in neurological function was defined in the protocol as; (1) improvement in reversible neurological conditions (e.g., cessation of seizures); or 2) stabilization of irreversible neurological conditions (e.g., stability of neurological deficits following stroke without further deterioration or subsequent strokes). The neurological deficits considered for improvement were limited to stroke, seizures, PRES, and weakness. Improvement in neurologic function was evaluable in 6 out of 28 (21.4%) of patients ([Table 24](#)). Of those 6 patients in which neurologic function could be evaluated, 3 were responders, narratives describing neurologic improvement are included below.

In a Type A meeting on January 6, 2020, the Applicant asked the Agency if they agreed with the proposal to assess neurologic improvement. The Agency responded that they did not agree due to the difficulty assessing improvement in the intensive care setting. In addition, the Agency had the following comments: “The evaluation of weakness is difficult in patients with multiple comorbidities and who require intensive care treatment. There may be multiple causes for a patient’s weakness therefore we do not agree with the assessment of weakness to assess neurological improvement. In addition, please note that improvement in confusion, agitation, headache will be difficult to assess given multitude of contributing factors to these signs and symptoms.” Therefore, weakness while included as a neurologic deficit for evaluation, was not agreed upon by the Agency.

Neurologic improvement was difficult to assess in all three patients, this is described in more detail in the narratives below. Neurologic manifestations included PRES, confusion, delirium, and weakness, all of which can be multifactorial (i.e., concomitant medications, deconditioning, and concurrent illnesses) and were treated during with other therapies along with narsoplimab-wuug. For example, one patient ^{(b) (6)}, had a diagnosis of Guillain Barré syndrome (GBS) at the time of HSCT-TMA diagnosis, therefore it is difficult to determine if the weakness experienced by the patient was due to GBS or HSCT-TMA. Overall, the treatment effect on neurologic manifestations of HSCT-TMA is difficult to interpret.

Narratives for Patients With Improvement in Neurologic Dysfunction

^{(b) (6)}

Approximately two weeks prior to the diagnosis of HSCT-TMA the patient developed polyneuropathy with profound weakness restricting the patient to bed. The patient experienced improvement in polyneuropathy clinically and based on electrophysiological evaluation while receiving narsoplimab-wuug. The neurologic response occurred approximately 27 days after starting narsoplimab-wuug.

Neuropathy is not a common manifestation of HSCT-TMA. While temporally it appears that narsoplimab-wuug may have improved the patient’s polyneuropathy, one must also consider that neuropathy can be multifactorial. For example, the patient was on a cyclosporin taper at the time of improvement. In addition, weakness was not agreed upon by the Agency as a neurologic deficit to assess for TMA improvement.

(b) (6)

Approximately one day after the diagnosis of HSCT-TMA the patient developed PRES. Cyclosporin had been discontinued the day prior to the PRES diagnosis. The patient improved with blood pressure control. The patient developed euphoria, delirium, and agitation approximately 4 days after starting narsoplimab-wuug and was managed with steroid taper (previously had euphoria while receiving steroids) and supportive treatment. Approximately 25 days after starting narsoplimab-wuug the patient developed delirium and confusion in the setting of uncontrolled hyperglycemia and self-discontinuation of lorazepam and haloperidol. His neurologic symptoms improved.

It is difficult to determine if the patient's neurologic improvement was related to narsoplimab-wuug. While PRES can be a manifestation of HSCT-TMA, it appears the patient improved with blood pressure control, the timing of the improvement in PRES is unclear in the patient narrative and therefore the impact of narsoplimab-wuug is unclear. Euphoria, delirium and confusion occurred after narsoplimab-wuug was started so it is therefore confounded by a new treatment and was managed with multiple other therapies including hyperglycemia control, steroid taper, lorazepam and haloperidol. It is the reviewer's opinion that this patient should be considered a non-responder.

(b) (6)

The patient experienced intermittent seizures starting 5 days prior to narsoplimab-wuug therapy. The patient was treated with antiepileptics and narsoplimab-wuug.

Seizures can be a manifestation of HSCT-TMA. It is challenging to determine if seizure improvement was due to narsoplimab-wuug or treatment with antiepileptics. Of note, the patient was subsequently found to have post-transplant lymphoproliferative disorder with a cerebellar lesion. This could have also contributed to the seizures.

Table 24. Patients With Neurologic Dysfunction, Study TMA-001

Pt ID	Baseline Neurologic Dysfunction Description	Neurologic Response	Neurologic Improvement Description	Met Primary Endpoint Response Definition
(b) (6)	Encephalopathy, weakness	N	N/A	Y
	Peripheral neuropathy with profound weakness	Y	Improvement in peripheral neuropathy demonstrated both clinically and on electrophysiological evaluation	Y
	PRES (prior to narsoplimab-wuug), delirium and confusion (after narsoplimab-wuug)	Y	Improvement in PRES. Euphoria, delirium, and confusion (onset occurred after administration of narsoplimab-wuug)	Y
	Seizures	Y	seizure improvement	Y
	Weakness, confusion	N	N/A	N
	Encephalopathy	N	N/A	N

Source: Clinical reviewer, patient narratives

Abbreviations: ID, identification; N, no; N/A, not applicable; PRES, posterior reversible encephalopathy syndrome; pt, patient; Y, yes

GI Dysfunction

Improvement in GI function was measured by improvement in the gastrointestinal staging in the MAGIC criteria (6.2.1.2). One patient (b) (6) was evaluated for improvement in GI dysfunction. The patient narrative can be found in Section 16. The patient had a GI biopsy consistent with HSCT-TMA and GVHD. Melena improved approximately 12 days following narsoplimab-wuug administration. While temporally narsoplimab-wuug appears to have improved melena, this is confounded by the concurrent diagnosis of GI-GVHD which was actively being treated with steroids at the same time.

It is in the clinical reviewer's opinion that patient (b) (6) improvement in GI dysfunction (melena) was likely secondary to narsoplimab-wuug. Although the patient was receiving concurrent corticosteroids, it does not appear the dose of had changed and was relatively low (prednisone, 25 mg daily). Therefore, this unlikely impacted the response.

Time to Response and Duration of Response

Time to Response

Response was assessed anytime postbaseline therefore, there was a wide range of response times.

As stated in the Applicant's protocol for Study TMA-001, the primary endpoint which was based on HSCT-TMA laboratory markers could be assessed anytime post baseline. There is a wide range of response times from 7 to 228 days, with a median response of 36 days. There were two patients who met response criteria >100 days after starting narsoplimab-wuug based on HSCT-TMA laboratory markers, patient (b) (6) at 228 days and patient (b) (6) at 153 days. Patient narratives can be found in Section 16. The remainder of patients had a response between days 7-77. It seems unlikely that these two outlier responses can confidently be attributed to narsoplimab-wuug. It is therefore, in the clinical reviewer's opinion that patients (b) (6) and (b) (6) should not be called responders. (Refer to Table 28 for brief narratives for these patients).

In the TMA-001 study protocol, time to response was defined as the time from the first dose of narsoplimab-wuug to the first date of platelet count and LDH response achieved. Of note, although per the protocol laboratory assessments were to be performed weekly, many patients who were hospitalized had more frequent laboratory tests. Time to response, based on these TMA markers was 36 days (range: 7-228 days). As this is not a complete definition of the primary endpoint the Applicant was asked to submit a time to response analysis based on all three components of the primary endpoint.

In the IR response from the Applicant, the Applicant presented time to response based on all three components of the primary endpoint. Time to response was calculated as the number of days between the date of the first dose of narsoplimab-wuug to the first date that the TMA marker improvement and clinical benefit was achieved. Based on the Applicant's analysis, the median time to response was 57 days (range: 13 to 228 days). This consideration will be important for providers caring for patients with HSCT-TMA. It remains difficult to determine

when providers should expect to see a response to narsoplimab-wuug given the wide range of response times.

Duration of Response

Duration of response was defined as the time between the first date a response is achieved and the first date the platelet count decreases by more than 50% from the maximum and LDH increases to >150% of the upper limit of normal. The median duration of response was 561 days (range: 5 to 823+ days). In total 6 patients experienced a relapse based on the duration of response definition. As this definition of response is not a complete definition of the primary endpoint the Applicant was asked to submit duration of response analysis based on all three components of the primary endpoint.

In the IR response from the Applicant, the Applicant presented duration of response based on all components of the primary endpoint. The Applicant defined relapse as having a platelet count below a level equal to at least a 50% decrease from the maximum platelet count, an LDH level greater than 1.5 times the upper limit of normal, and a creatinine increase $\geq 20\%$ from the minimum creatinine if the minimum creatinine is < ULN or an increase $\geq 40\%$ from the minimum creatinine if the minimum creatinine is $\geq$ ULN. No patient experienced worsening organ function and transfusion worsening could not be defined for patients who achieved freedom of transfusion given its definition. Based on the revised analysis the Applicant stated the median duration of response could not be calculated. The range of duration of response was 13 to 794 days. Based on the revised analysis, 3 patients relapsed.

Summary

Taking into consideration the issues presented above and after review of each of the patient narratives, the clinical team identified five additional patients (Subject ID (b) (6)) as not achieving response as defined in the protocol. The reasons for excluding these patients as responders is that these 5 subjects did not meet at least 3 components of the response criteria. In a clinical setting, some of these patients could be described as having a partial response but in terms of protocol defined response are considered nonresponders. Based upon this analysis, the proportion of patients in Study TMA-001 who responded to narsoplimab-wuug would be 12/28; 42.9% [CI: 25%, 63] of patients. A detailed summary of the patient's narratives can be found in Section 16; in addition, Table 25 provides a brief synopsis of the reviewers' concerns.

Table 25. List of Nonresponders as Determined by the Agency

Pt	Applicant's Efficacy Results	Reviewer Comments	Reasons For Non-Responders By Agency
(b) (6)	NE platelet response + LDH response + Renal response - Transfusion response	- The patient never engrafted platelets, response was based only on LDH and renal response. The patient was evaluated for but did not meet transfusion response. Of note, while not a component of the primary endpoint haptoglobin was undetectable and normalized with narsoplimab-wuug. - At the time of HSCT-TMA diagnosis which occurred 10 days before the first dose of narsoplimab-wuug, the patient was recently diagnosed with liver GVHD, PRES, and fever. Cyclosporin stopped approximately 10 days before starting narsoplimab-wuug. - Patient had a positive test for E. coli 0157 (while asymptomatic at the time of the test, the patient had diarrhea 2 weeks prior) - The patient died approximately 200 days after starting narsoplimab-wuug due to neutropenic sepsis.	- Unable to determine platelet count - Did not meet at least 3 response criteria as platelet response could not be determined.
(b) (6)	NE platelet response + LDH response + Renal response - Transfusion response	- The patient never engrafted platelets, response was based only on LDH and renal response. The patient was evaluated for but did not meet transfusion response. While not a component of the primary endpoint haptoglobin was initially low and normalized with narsoplimab-wuug. - The patient did not meet renal inclusion criteria (although had proteinuria). Baseline creatinine was 0.76 mg/dL, which was down trending prior to narsoplimab-wuug administration. - ADAMTS13 not documented - The patient had DAH, pneumonia, typhlitis, and GVHD around the time of HSCT-TMA diagnosis. HSCT-TMA diagnosis occurred approximately 14 days before the first dose of narsoplimab-wuug. - Patient died about 70 days after starting narsoplimab-wuug due to septic shock	- Unable to determine renal response - Did not meet at least 3 response criteria as platelet response could not be determined.

Pt	Applicant's Efficacy Results	Reviewer Comments	Reasons For Non-Responders By Agency
(b) (6)	NE platelet response + LDH response + Renal response - Transfusion response	- The patient never engrafted platelets, response was based only on LDH and renal response. The patient was evaluated for but did not meet transfusion response. - No ADAMTS13 (but GI biopsy confirmed HSCT-TMA) - Received plasma exchange while receiving narsoplimab-wuug - The patient had fungal infection, bacteremia and steroid refractory GVHD around the time of HSCT-TMA diagnosis. HSCT-TMA diagnosis occurred approximately 4 days before the first dose of narsoplimab-wuug. Tacrolimus was stopped the same day as initiating narsoplimab-wuug.	- Did not meet at least 3 response criteria as platelet response could not be determined. - Transient LDH response
(b) (6)	+ Platelet response + LDH response	- Did not meet renal inclusion criteria (normal creatinine) - Response only based on only LDH and platelets, clinical improvement was not included - Patient was diagnosed with MAHA for approximately 80 days prior to his first dose of narsoplimab-wuug. Delay in entering the study was due to a persistently positive DAT - Response occurred 228 days after starting therapy	Did not meet three response criteria. Only met platelet and LDH response criteria.

Pt	Applicant's Efficacy Results	Reviewer Comments	Reasons For Non-Responders By Agency
(b) (6)	+ Platelet response + LDH response - Renal response + Neuro response + Transfusion response	• Did meet exclusion criteria- weakly positive Coombs at local laboratory, although repeated at central laboratory and was negative, and + shiga toxin • Response occurred 153 days after starting therapy • Neurologic response was not clearly due to narsoplimab-wuug • GVHD and CMV reactivation at time of HSCT-TMA diagnosis. HSCT-TMA diagnosis occurred approximately 7 days before the first dose of narsoplimab-wuug. • Received platelets and PRBC transfusions during treatment with narsoplimab. Unable to determine if 4-week interval of not requiring transfusions was due to narsoplimab as too many confounders.	• Clinical response could not clearly be attributed to narsoplimab. Only met two response criteria. • Received platelets and PRBC transfusions during treatment with narsoplimab. Unable to determine if 4 week interval of not requiring transfusions was due to narsoplimab as too many confounders.

Source: Clinical reviewer

Abbreviations: CMV, cytomegalovirus; DAH, diffuse alveolar hemorrhage; DAT, direct antiglobulin test; GI, gastrointestinal; GVHD, graft-versus-host disease; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; NE, not estimable; PRES, posterior reversible encephalopathy syndrome; pt, patient

Conclusion

In summary, the results of Study TMA-001 based on the FDA analysis compared to the Applicant's analysis are shown in the table [below](#). As shown, the FDA's estimated response rate is lower than the Applicant's. The lower bound of the 95% CI is 24.5% which has implications on conclusions of efficacy when comparing the response rate to the literature-based estimate of response in non-treated patients. See discussion below in section [6.3.2](#).

Table 26. Summary of Response for Patients With HSCT-TMA

Parameter	FDA Analysis FAS	Applicant Analysis FAS
Responders	12/28 (43%)	17/28 (60.4%)
95% confidence interval	[24.5%, 62.8%]	[41%, 78%]

Source: FDA Analysis

Abbreviations: FAS, full analysis set; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy

6.3.2. External Literature-Based Validation of Non-Treated Response Rate.

Issue

The Applicant provided an external literature review to justify the response rate in untreated patients.

Background

The Applicant submitted an external literature review during the review cycle of the application. The submission of this additional data warranted and required additional time for analysis and thus a major amendment was issued to the Applicant on May 19, 2021.

The study design was a retrospective patient level data from published publications between 2000-2020 identified using PubMed electronic database search. The criteria for publication selection were adult patients and any component of the primary response endpoint used in Study TMA-001 trial and report of response and at least 1 risk factor present in the Study TMA-001 trial patients. The literature search identified 459 manuscripts of which 35 met the predefined criteria and 179 patients identified for the final analysis of which 149 are nonpharmacologically treated patients.

Assessment

A summary of response and 100-day survival are provided in [Table 27](#). Please note that in Study OMS721-TMA-001, 100-day survival is defined as survival 100 days after diagnosis of HSCT-TMA. The definition of 100-day survival was not always provided for the literature-based review.

Table 27. Literature Based Historical Control TMA Response Rate

Parameter	Applicant Analysis of Study TMA-001	Literature-Based Historical Control Nonpharmacologically Treated		FDA Analysis of Study TMA- 001
	All Patients			
Response rate (95% CI)	17/28 (60.7%) (41% to 78%)	58/179 (32%) (26% to 40%)	36/149 (23.3%) (15.1% to 34.2%)	12/28 (24%, 63%)
100-day survival (all time periods)	19 (68%) (48% to 84%)	55/125 (47.5%)	41/107 (37.3%)	NA

Source: FDA Analysis

Abbreviation: CI, confidence interval; NA, not applicable

Assessment of survival (100-day survival) cannot be adequately assessed or compared due to lack of uniform definition. In the transplantation setting, 100 day survival often refers to survival 100 days after Day 0 of the hematopoietic stem cell transplantation.

Conclusion

In Study TMA-001, the Applicant used a 15% efficacy threshold and this was based on expert opinion only provided by the Applicant. There are significant limitations to literature-based review to support and verify this estimate. The Division sought expertise from Real World Evidence (RWE) internal FDA expert regarding quality of data. The limitations include unknown validity and accuracy of data, potential measurement errors associated with endpoints (response rates) and definition of 100-day survival across different publications, propensity score analysis performed on limited confounding variables, timing of treatment visits not standardized across different publications, study conducted using convenience samples and likely selection bias affects generalizability of the results. Therefore, the literature based review cannot be considered sufficient to Estimate response rate in an untreated group.

6.3.3. Subject Matter Expert Analysis

Issue

The Applicant submitted a position paper by subject matter experts stating that the responses observed in Study OMS721-001 represent a true response to treatment with narsoplimab and that all 17 patients who Applicant identified are true responders.

The Division consulted with two subject matter experts to provide expert opinion.

Background

The Division sought input regarding the use of narsoplimab-wuug in patients with HSCT-TMA and requested input to address the following questions:

- Is there evidence of effectiveness for narsoplimab-wuug in the HSCT-TMA population taking into account the rarity of the disease, no FDA available therapies, trial limitations (single-arm trial), confounders in the interpretation of treatment effect of the efficacy endpoint (concomitant medications and illnesses), and discrepancies and inconsistencies in the application of the response definition for the subjects?
- Is the response demonstrated in Study TMA-001 a significant change from what would be expected based upon the natural history and accepted standard of care treatment of this disease?

The Division provided the 28 narrative summaries, the clinical study report and background document to the SGEs. The SGEs provided summary response documents and the Division also met via teleconference with the SGEs to discuss responses.

Assessment

Response to the First Question

SGE number one reviewed all 28 cases and stated that 15/28 (%) patients appear to have a response to treatment and that all patients enrolled in the study were consistent with patients who had diagnosis of TMA.

SGE number two reviewed all 28 cases and stated that 16/28 (%) patients appeared to have a response to treatment and that all patients enrolled in the study were consistent with patients who had a diagnosis of TMA. Both SGE's did note that response was not always durable and that response consisted mostly of modest improvements in laboratory parameters of LDH or haptoglobin. Both consultants did comment that they would likely the this drug in the treatment of HSCT-TMA after failure of standard of conventional therapy (immunosuppressants modifications, off-label use of C5 inhibitors):.

Response to the Second Question

SGE 2 did comment that he felt that the survival observed in the study was a departure from what would be expected for this severely affected population. SGE 1 also commented that the response observed was an improvement from the known literature of response rates for patients with HSCT-TMA with the caveat that there has been difficulties in uniform consensus on diagnosis and response criteria. SGE 2 did note that the enrolled population appeared consistent with a severe population and that survival observed was better than what one would expect from similar population.

The table [below](#) provides a summary of response from the Applicant analysis, FDA analysis, literature review and the SGE review.

Table 28. Summary of Response for Patients With HSCT-TMA

Parameter	Applicant Analysis FAS	FDA Analysis FAS	Literature Review		SGE Analysis	
			All Patients	Nonpharmacologically Treated	SGE 1	SGE 2
Response rate n/N, (%)	17/28 (61%)	12/28 (43%)	56/179 (32.5%)	36/149 (23.3%)	14/28 (50%)	15/28 (54%)
95% confidence interval	(40.6,78.5)	(24.5,62.8)	(24.5, 41.7)	(15.1, 34.2)	(30.7,69.4)	(33.9,72.5)

Source: FDA Analysis

Abbreviations: FAS, full analysis set; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; SGE, special government employee

Conclusion

Overall, the SGE's assessment of the individual narratives concluded that there was a response rate of 50% to 54%. Both SGEs concluded that the patients enrolled in the study are representative of a patient population with HSCT-TMA some who had severe HSCT-TMA. SGE 2 believed that the survival observed in the study was better than what one would expect from a similar population.

Both SGEs noted that the limitation of the study is the lack of a control arm but based on clinical experience, some patients had responses although not always robust responses. They also noted that most of the responses were primarily based on LDH and haptoglobin. Both SGEs stated they would likely use this medication in the clinical setting for patients with HSCT-TMA.

The SGE's used clinical judgment to assess response rate but did not necessarily adhere to the protocol definition of response rate. The opinions provided by the SGE's did not alter the conclusions of the clinical reviewers' assessment of response rate.

6.3.4. Pediatric Indication

Issue

The Applicant proposed to include a pediatric indication in the USPI but, there were no formal pediatric studies.

Background

The Applicant proposed to include a pediatric indication including ages 2 years of age and older. There are no approved therapies for HSCT-TMA in pediatric patients. The Applicant states that MASP-2 levels increase by age 2 and remain stable throughout childhood and are similar to adult levels. As stated in the Applicant's clinical overview the rationale for the proposal of a pediatric indication was based on dosing reasons of biological plausibility and consistency of the disease mechanism, role and levels of MASP-2 and lectin pathway activation across broad age groups, and the satisfactory therapeutic window enabled by weight-based dosing.

Assessment

No pediatric patients were treated in narsoplimab-wuug clinical trials. There was one 14-year-old adolescent patient treated on compassionate use that appeared to respond (based on clinical judgment) to narsoplimab-wuug. In the 90-day safety update it was reported four additional patients were treated with narsoplimab-wuug. Given the very limited experience of pediatric patients with narsoplimab-wuug the clinical review team does not agree with including a pediatric indication. It is not clear if pediatric patients will respond the same to narsoplimab-wuug as adults, in addition pediatric patients may have different comorbidities that may impact response. In addition, pediatric patients are more often transplanted for nonmalignant conditions compared to adults, and it's not clear how the indication for transplant may impact response to narsoplimab-wuug. Lastly, there is not sufficient safety data in the pediatric population.

Conclusion

The clinical review team believes that the sponsor must perform a pediatric assessment in order to support a pediatric indication and that full extrapolation from adults is unlikely to be acceptable.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Preclinical safety of OMS721 was evaluated in a standard battery of nonclinical studies including safety pharmacology studies, repeat-dose toxicity studies in mice and monkeys for durations up to 4 and 26 weeks, respectively, reproductive toxicity studies in mice and rabbits, a juvenile toxicity study in mice, and a local tolerance study in rabbits. There were no nonclinical

safety issues of concern that substantially impacted clinical development as assessed by these studies.

Note that functional potency of OMS721, measured as inhibition of C4 and C3 activation in serum, is lower in nonclinical species than in humans; however, exposures evaluated in the pivotal toxicology studies achieved near- to complete inhibition of lectin-mediated complement activation, enabling a reasonable toxicological assessment of inhibiting the intended pharmacological target, MASP-2, by OMS721.

Cardiovascular and respiratory safety pharmacology assessments in monkeys and a CNS safety pharmacology assessment in mice showed no OMS721-related effects. In repeat-dose toxicology studies in mice and monkeys, minimal to mild subcutaneous injection site reactions were observed in both species. Sporadic increases were observed in AST and ALT in mice and monkeys in 28-day studies but were not present in the 26-week studies. Intravenous administration was also assessed, resulting in one instance of mild edema and minimal adventitial necrosis at the injection site, and one female that experienced pronounced decreases in total protein and albumin during treatment which became more severe during the recovery period. The adverse response of this female is of limited relevance to clinical risk, as the proposed clinical route of administration is subcutaneous, not intravenous. The no observed adverse effect level (NOAEL) identified in the 26-week monkey study was 300 mg/kg/week by the SC route (38-fold the maximum recommended human dose (MRHD)), while the NOAEL for the IV route was not established due to irreversible changes in protein and albumin levels at 150 mg/kg, the only IV dose studied (43-fold the MRHD).

Table 29. Comparative Mean Systemic Exposure in Repeat-Dose Studies Following Subcutaneous or Intravenous Administration of OMS721

Study	NOAEL (mg/kg/week)	Nonclinical Exposure (µg.hr/mL)	Exposure Margins ¹ (Multiples)	Exposure Margins ² (Multiples, Adjusted for Species Potency Difference)
28-day mice	IV: 10	2565	1x	0.3x
	SC: 50	4420	2x	0.5x
28-day monkey	IV: 10	15350	7x	0.7x
	SC: 150	41650	18x	2x
26-week monkey	IV: Not established	99450	43x	4x
	SC: 300	86900	38x	4x

Source: FDA Analysis

¹ Human AUC_(0-168h) was determined in hematopoietic stem cell transplant-associated thrombotic microangiopathy patients using population pharmacokinetic modeling of males and females combined (AUC_(0-168h) 2310.816 µg.h/mL).

² OMS721 potency in mouse is 3.8-fold less, monkey is 9.7-fold less, and rabbit is 2.7-fold less than human

Abbreviations: IV, intravenous(ly); NOAEL, no observed adverse effect level, SC, subcutaneous

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns were reviewed based on known information for other approved complement inhibitor therapies and literature review of patients with MASP-2 deficiency.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Narsoplimab-wuug is not approved or marketed in the United States or worldwide.

7.4. FDA Approach to the Safety Review

The Applicant's safety database consisted of 6 completed or ongoing studies and a compassionate use program. The safety population consisted of all patients or subjects who received any amount of study drug.

For this review, the clinical review team considered the primary safety population to consist of the 28 patients with HSCT-TMA from Study OMS721-TMA-001 (TMA-001). The supportive safety population consisted of 256 patients from studies OMS721-NHV-001, OMS721-NHV-002, TMA-001 (excluding the 28 patients with HSCT-TMA included in the primary safety population), OMS-721-GNP-001, OMS721-IGA-001, OMS721-HUS-002, and the compassionate use program. Study OMS721-IGA-001 is ongoing and blinded and is minimally discussed in the safety review.

The data cutoff date for the safety assessments submitted in the initial BLA was December 20, 2019. The 90-Day safety update provided additional safety data collected from the 2 ongoing clinical trials from December 21, 2019 to August 31, 2020 (Studies OMS721 HUS-002 and OMS721-IGA-001) and safety data from compassionate use patients from December 21, 2019 to October 31, 2020.

Review of safety was based upon:

- CSR for studies
- Protocol for studies
- Data sets for the populations described above
- Summary of clinical safety
- 90-day safety update
- Patient narratives
- Case report forms

Case report forms and narratives were provided and reviewed for adverse events (AEs) of interest, serious adverse events (SAEs), and deaths that occurred in the primary and supportive safety populations. Treatment-emergent adverse events (TEAEs) of special interest included infections.

No major issues were identified with respect to recording, coding, and categorizing AEs. The analysis dataset for adverse events (ADAE.xpt) data file was reviewed for accuracy of translation of the verbatim to preferred term by manual review. Based on this review a modified table ([Table 30](#)) was produced where additions of preferred terms were added based on the verbatim

term. With additions of preferred terms, the adverse event file was copied with the new preferred term. Adverse events were analyzed by MedDRA [version 22.0] preferred term. Similar preferred terms were grouped by standardized groupings of related preferred terms through FDA Medical Dictionary for Regulatory Activities queries (FMQs). Additional analyses were provided by the Clinical Data Scientist support team. The clinical review team did not identify any major data quality or integrity issues that precluded performing a safety review.

Table 30. Additions of Preferred Terms to ADAE Data File

AETERM (Verbatim Term)	AEDECOD (Preferred Term)	Added Preferred Term 1	Added Preferred Term 2
Gi disturbance. feeling of fullness and loss of appetite	Abdominal distention	Decreased appetite	
Fever and chills	Pyrexia	Chills	
Viral fever	Pyrexia	Viral infection	
Worsening of general conditions (due to AML disease progression)	General physical health deterioration	Disease progression	
Granuloma orchitis	Orchitis	Granuloma	
Pneumonia (bacterial, EBV positive)	Pneumonia bacterial	Epstein-Barr virus test positive	
Enterococcus faecalis positive blood culture	<i>Enterococcus faecalis</i> test positive	Enterococcal bacteremia	
Metabolic acidosis (secondary to renal dysfunction diarrhea and volume resuscitation)	Metabolic acidosis	Renal impairment	Diarrhea
Thrombocytopenic epistaxis	Epistaxis	Thrombocytopenia	
Uvula pain (from snoring)	Oropharyngeal pain	Snoring	
Cutaneous lesion (2×2 cm) overlying ecchymosis	Skin lesion	Ecchymosis	
Hypertension crisis due to exacerbation of chronic kidney disease	Hypertensive crisis	Chronic kidney disease	

Source: Clinical reviewer

Abbreviations: ADAE, analysis dataset for adverse events; AML, acute myeloid leukemia; EBV, Epstein-Barr virus; GI, gastrointestinal

7.5. Adequacy of Clinical Safety Database

The clinical safety database is limited in patients with HSCT-TMA who were exposed but adequate given the rarity of HSCT-TMA and the availability of data from non-HSCT-TMA patients exposed to study drug to provide supportive safety data. In Study TMA-001, 28 patients with HSCT-TMA received at least one dose of narsoplimab-wuug. In total, 24 (85.7%) patients received weight-based dosing at 4 mg/kg IV, after protocol amendment 11.1, 4 (14.3%) patients received fixed doses of 370 mg IV. The mean duration of exposure was 6.7 weeks. A summary of exposure is shown in [Table 31](#).

Duration of exposure in the supportive safety population can be found in [Table 123](#).

Table 31. Duration of Exposure, Primary HSCT-TMA Safety Population, Study TMA-001

Parameter	Narsoplimab-wuug 4 mg/kg N=24	Narsoplimab-wuug 370 mg N=4	Narsoplimab-wuug Total N=28
Duration of treatment (weeks)			
Mean (SD)	6.6 (3.3)	7.3 (1.5)	6.7 (3.1)
Median (min, max)	8 (2, 16.4)	8 (5, 8.1)	8 (2, 16.4)
Patients treated, by duration, n (%)			
Any duration (at least 1 dosage)	24 (100%)	4 (100%)	28 (100%)
≥1 to <4 weeks	7 (29.2%)	0 (0%)	7 (25%)
≥4 weeks to <8 weeks	4 (16.7%)	1 (25%)	5 (17.9%)
≥8 weeks	13 (54.2%)	3 (75%)	16 (57.1%)

Source: Clinical data analyst [adex.xpt; Software: Python]

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, Study TMA-001

It is important to note that because the safety database is composed of only uncontrolled data, causality assessment of adverse reactions is very challenging. Therefore, all adverse events are assumed to be drug related adverse reactions for the purposes of this review. In Study TMA-001, infections, hemorrhage, diarrhea, neutropenia, pyrexia and vomiting were the most common adverse reactions. Infections were also the most common serious adverse reaction. In total, four (14%) of patients died during the AE evaluation period, including two (7%) due to adverse reactions of sepsis. One patient discontinued narsoplimab-wuug due to underlying disease progression which is likely unrelated to narsoplimab-wuug. The described safety profile is not unexpected in a complex, immunosuppressed, and ill patient population with multiple comorbidities, cytopenias, and who are receiving multiple concomitant medications.

A 90-day safety update was provided additional safety data on two ongoing clinical trials; HUS-002 and IGA-001, in addition to safety data from compassionate use patients with HSCT-TMA. Only SAEs, deaths, and discontinuations were reported. There were no events that changed the safety profile of narsoplimab-wuug.

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Study TMA-001

Grading of AEs was based on the National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0. An overview of TEAEs that occurred in patients with HSCT-TMA during the AE evaluation period in Study TMA-001 is presented in [Table 32](#). The AE evaluation period was defined from the time of informed consent to 37 days after the last narsoplimab-wuug administration. All but one patient experienced at least one TEAE. Most patients experienced a TEAE that was moderate or severe. In addition, the majority of patients had a SAE. In total, 4 patients had SAEs with fatal outcomes. There were low rates of AEs leading to discontinuation

or interruption of narsoplimab-wuug. See an overview of adverse events in the supportive safety population in [Table 124](#).

Table 32. Overview of Treatment-Emergent Adverse Events During the AE Evaluation Period, Primary HSCT-TMA Safety Population, Study TMA-001

Event	Narsoplimab- wuug 4 mg/kg N=24 n (%)	Narsoplimab- wuug 370 mg N=4 n (%)	Narsoplimab- wuug Total N=28 n (%)
Any treatment-emergent AE ¹	24 (100%)	3 (75%)	27 (96.4%)
Moderate or severe AEs (Grade 3-5) ²	22 (91.7%)	2 (50%)	24 (85.7%)
SAEs	15 (62.5%)	2 (50%)	17 (60.7%)
SAEs with fatal outcome	3 (12.5%)	1 (25%)	4 (14.3%)
AEs leading to discontinuation of study drug	1 (4.2%)	0 (0%)	1 (3.6%)
AEs leading to dosage modification of study drug	2 (8.3%)	0 (0%)	2 (7.1%)
AEs leading to interruption of study drug	2 (8.3%)	0 (0%)	2 (7.1%)
AEs leading to reduction of study drug	0 (0%)	0 (0%)	0 (0%)
AEs leading to dosage delay of study drug	0 (0%)	0 (0%)	0 (0%)

Source: Clinical Data analyst [adae.xpt; Software: Python]

¹ Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

² Grading scale used was National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Abbreviations: AE, adverse event; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Study TMA-001

In total, 16 (57.1%) of 28 patients died during Study TMA-001. [Table 33](#) provides an overview of the deaths. An additional 2 patients died after withdrawing consent; the cause of death was unknown. Of the 11 (39.3%) patients who experienced a treatment-emergent death, the most common TEAE leading to death were infections: neutropenic sepsis, septic shock, gastrointestinal candidiasis, Escherichia sepsis, pneumonia, and pseudomonal sepsis. There were 4 (14.3%) patient deaths that occurred during the AE evaluation period as presented in [Table 33](#), narratives are presented below.

Reviewer comment

Infections were most the most common cause of death and discussed more in Section [7.7.1](#) (key review issues).

See Section [17](#) for additional details regarding [Deaths](#) in the safety population.

Table 33. Deaths in Primary HSCT-TMA Safety Population, Study TMA-001

Deaths	Narsoplimab- wuug 4 mg/kg N=24 n (%)	Narsoplimab- wuug 370 mg N=4 n (%)	Narsoplimab- wuug Total N=28 n (%)
Total deaths	14 (58.3%)	2 (50%)	16 (57.1%)
Death during AE evaluation period ¹	3 (12.5%)	1 (25%)	4 (14.3%)
Death after AE evaluation period ¹	11 (45.8%)	1 (25%)	12 (42.9%)
Primary cause of death			

	Narsoplimab- wuug 4 mg/kg N=24 n (%)	Narsoplimab- wuug 370 mg N=4 n (%)	Narsoplimab- wuug Total N=28 n (%)
Deaths			
Treatment-emergent ² adverse event	10 (41.7%)	1 (25%)	11 (39.3%)
Other	4 (16.7%)	1 (25%)	5 (17.9%)
Treatment-emergent ² deaths during AE evaluation period ¹	3 (12.5%)	1 (25%)	4 (14.3%)
Acute myeloid leukemia	1 (4.2%)	0 (0%)	1 (3.6%)
Graft versus host disease in GI tract	1 (4.2%)	0 (0%)	1 (3.6%)
Neutropenic sepsis	1 (4.2%)	0 (0%)	1 (3.6%)
Thrombotic microangiopathy	1 (4.2%)	0 (0%)	1 (3.6%)
Septic shock	0 (0%)	1 (25%)	1 (3.6%)
Treatment-emergent ² deaths following the AE evaluation period ¹	7 (29.2%)	0 (0%)	7 (25%)
Acute myeloid leukemia	1 (4.2%)	0 (0%)	1 (3.6%)
Gastrointestinal candidiasis	1 (4.2%)	0 (0%)	1 (3.6%)
Escherichia sepsis	1 (4.2%)	0 (0%)	1 (3.6%)
Neutropenic sepsis	1 (4.2%)	0 (0%)	1 (3.6%)
Disease progression	1 (4.2%)	0 (0%)	1 (3.6%)
Pneumonia	2 (8.3%)	0 (0%)	2 (8.3%)
Pseudomonal sepsis	1 (4.2%)	0 (0%)	1 (3.6%)
Nontreatment-emergent ² deaths	4 (16.7%)	1 (25%)	5 (17.9%)
Cardiopulmonary arrest	1 (4.2%)	0 (0%)	1 (3.6%)
HSCT related cause	0 (0%)	1 (25%)	1 (3.6%)
Unknown	3 (10.7%)	0 (0%)	3 (10.7%)

Source: Clinical reviewer [adae.xpt; Software: Python]

¹ AE evaluation period defined as from the informed consent date to the last dose date +37 days

² Treatment-emergent defined as those occurred or worsened in intensity after the start of study treatment

Abbreviations: AE, adverse event; GI, gastrointestinal; HSCT; hematopoietic stem cell transplant N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.3. Serious Adverse Events, Study TMA-001

The most common (>5%) SAEs reported by preferred terms in Study TMA-001 for HSCT-TMA patients included graft-versus-host-disease (GVHD) of the gastrointestinal tract, acute kidney injury, confusional state, acute respiratory failure, neutropenic sepsis, pulmonary edema, vomiting, and septic shock ([Table 34](#)). The most common (>10%) SAEs reported by FDA MedDRA Queries included infections in particular sepsis, GVHD, acute kidney injury, neutropenia, and confusional state ([Table 35](#)).

Table 34. Treatment-Emergent Serious Adverse Events, Primary HSCT-TMA Safety Population, Study TMA-001

	Narsoplimab- wuug 4.0 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total IV N=28 n (%)
Preferred Term			
Any SAE	15 (62.5)	2 (50.0)	17 (60.7)
Graft versus host disease in gastrointestinal tract	4 (16.7)	0	4 (14.3)
Acute kidney injury	3 (12.5)	0	3 (10.7)
Confusional state	2 (8.3)	1 (25.0)	3 (10.7)
Acute respiratory failure	2 (8.3)	0	2 (7.1)
Neutropenic sepsis	2 (8.3)	0	2 (7.1)

	Narsoplimab- wuug 4.0 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total IV N=28 n (%)
Preferred Term			
Pulmonary edema	2 (8.3)	0	2 (7.1)
Vomiting	2 (8.3)	0	2 (7.1)
Septic shock	1 (4.2)	1 (25.0)	2 (7.1)
Acute myeloid leukemia	1 (4.2)	0	1 (3.6)
Acute myocardial infarction	1 (4.2)	0	1 (3.6)
Bacteremia	1 (4.2)	0	1 (3.6)
Colitis	1 (4.2)	0	1 (3.6)
Dehydration	1 (4.2)	0	1 (3.6)
Diarrhea	1 (4.2)	0	1 (3.6)
Diffuse large B-cell lymphoma	1 (4.2)	0	1 (3.6)
End stage renal disease	1 (4.2)	0	1 (3.6)
Epstein-Barr virus associated lymphoma	1 (4.2)	0	1 (3.6)
Escherichia sepsis	1 (4.2)	0	1 (3.6)
Fungal infection	1 (4.2)	0	1 (3.6)
Gastroenteritis	1 (4.2)	0	1 (3.6)
General physical health deterioration	1 (4.2)	0	1 (3.6)
Graft versus host disease	1 (4.2)	0	1 (3.6)
Hemolytic uremic syndrome	1 (4.2)	0	1 (3.6)
Hemorrhage intracranial	1 (4.2)	0	1 (3.6)
Infection	1 (4.2)	0	1 (3.6)
Lethargy	1 (4.2)	0	1 (3.6)
Muscular weakness	1 (4.2)	0	1 (3.6)
Nausea	1 (4.2)	0	1 (3.6)
Neutropenia	1 (4.2)	0	1 (3.6)
Orthostatic hypotension	1 (4.2)	0	1 (3.6)
Pneumonia viral	1 (4.2)	0	1 (3.6)
Pulmonary alveolar hemorrhage	1 (4.2)	0	1 (3.6)
Pyrexia	1 (4.2)	0	1 (3.6)
Respiratory tract infection viral	1 (4.2)	0	1 (3.6)
Thrombotic microangiopathy	1 (4.2)	0	1 (3.6)
Urosepsis	1 (4.2)	0	1 (3.6)
Delirium	0	1 (25.0)	1 (3.6)
Pneumonia	0	1 (25.0)	1 (3.6)

Source: Clinical data analyst [adae.xpt; Software: Python]

Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

Table 35. Treatment-Emergent Serious Adverse Events*, Primary HSCT-TMA Safety Population, Study TMA-001

Preferred Term or Query	Narsoplimab- wuug 4.0 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total IV N=28 n (%)
Infections*	9 (37.5)	1 (25.0)	10 (35.7)
Sepsis*	4 (16.7)	1 (25.0)	5 (17.9)
Infection, bacterial*	2 (8.3)	0	2 (7.1)
Infection, viral*	2 (8.3)	0	2 (7.1)
Pneumonia*	1 (4.2)	1 (25.0)	2 (7.1)
Bacteremia	1 (4.2)	0	1 (3.6)
Infection, fungal	1 (4.2)	0	1 (3.6)
Respiratory tract infection	1 (4.2)	0	1 (3.6)
Urinary tract infection	1 (4.2)	0	1 (3.6)
Immune system disorders			
Graft versus host disease*	5 (20.8)	0	5 (17.9)
Renal and urinary disorders			
Acute kidney injury*	3 (12.5)	0	3 (10.7)
Blood and lymphatic system disorders			
Neutropenia*	3 (12.5)	0	3 (10.7)
Psychiatric disorders			
Confusional state*	2 (8.3)	1 (25.0)	3 (10.7)
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	2 (8.3)	0	2 (7.1)
Pulmonary edema	2 (8.3)	0	2 (7.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignancy*	2 (8.3)	0	2 (7.1)
Gastrointestinal disorders			
Vomiting	2 (8.3)	0	2 (7.1)
Diarrhea	1 (4.2)	0	1 (3.6)
Nausea	1 (4.2)	0	1 (3.6)
Musculoskeletal and connective tissue disorders			
Weakness	1 (4.2)	0	1 (3.6)
Vascular disorders			
Hemorrhage*	2 (8.3)	0	2 (7.1)
Shock	1 (4.2)	1 (25.0)	2 (7.1)
Hypotension	1 (4.2)	0	1 (3.6)
Metabolism and nutrition disorders			
Dehydration	1 (4.2)	0	1 (3.6)
General disorders and administration site conditions			
Fatigue	1 (4.2)	0	1 (3.6)
Pyrexia	1 (4.2)	0	1 (3.6)

Preferred Term or Query	Narsoplimab- wuug 4.0 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total IV N=28 n (%)
Cardiac disorders			
Myocardial infarction	1 (4.2)	0	1 (3.6)

Source: Clinical reviewer and Clinical data analyst [adae.xpt; Software: Python]

*Treatment-emergent serious adverse events defined as those occurred or worsened in intensity after the start of study treatment

The following terms were combined:

* Acute kidney injury: acute kidney injury, hemolytic uremic syndrome

* Confusional state: confusional state, delirium

* Graft versus host disease: graft versus host disease, graft versus host disease in gastrointestinal tract

* Hemorrhage: hemorrhage intracranial, pulmonary alveolar hemorrhage

* Infections: neutropenic sepsis, septic shock, bacteremia, Escherichia sepsis, fungal infection, gastroenteritis, infection, pneumonia viral, respiratory tract infection viral, urosepsis and pneumonia

* Infections, bacterial: bacteremia, Escherichia sepsis

* Infections viral: pneumonia viral, respiratory tract viral

* Malignancy: acute myeloid leukemia, diffuse large b-cell lymphoma

* Neutropenia: neutropenic sepsis, neutropenia

* Pneumonia: pneumonia viral, pneumonia

* Sepsis: neutropenic sepsis, septic shock, Escherichia sepsis, urosepsis

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with adverse event

Clinical reviewer comment

SAEs occurred in approximately 61% of patients with HSCT-TMA treated with narsoplimab-wuug. This is not unexpected given patients were acutely ill at the time of HSCT-TMA diagnosis and with multiple comorbidities. Infections were most the most common treatment-emergent SAE and discussed more in Section 7.7.1 (key review issues). While GVHD was the next most common TEAE, this was unlikely related to narsoplimab-wuug, as this commonly occurs in the post-transplant setting. The clinical review team did not consider GVHD or malignancy to be an adverse reaction. However, given the lack of an adequate control, cannot fully determine attribution.

7.6.1.4. Dropouts and / or Discontinuations Due to Adverse Events, Study TMA-001

One patient had an AE leading to discontinuation of study drug ([Table 36](#)). Patient (b) (6) received two doses of narsoplimab-wuug and then discontinued due to progressive general deterioration from failed HSCT, although the ADAE dataset reports the drug was discontinued due to worsening acute myeloid leukemia (AML). The patient died shortly after discontinuing narsoplimab-wuug. This TEAE was unlikely related to narsoplimab-wuug. See narrative in Section [17 Deaths](#).

Table 36. Adverse Events Leading to Dose Interruption, Primary HSCT-TMA Safety Population, Study TMA-001

	Narsoplimab-wuug 4 mg/kg IV N=24 n (%)	Narsoplimab-wuug 370 mg IV N=4 n (%)	Narsoplimab-wuug Total N=28 n (%)
Adverse Event¹			
Patients with at least 1 AE leading to discontinuation	1 (4.2%)	0 (0%)	1 (3.6%)
Acute myeloid leukemia progression	1 (4.2%)	0 (0%)	1 (3.6%)

Source: Clinical Data Analyst [adae.xpt; Software: Python]

¹ Coded as MedDRA preferred terms

Abbreviations: AE, adverse event; IV, intravenous(ly); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

In the supportive safety database, there were 6 discontinuations due to TEAEs. [Table 127](#) lists the TEAEs leading to narsoplimab-wuug discontinuation. The Applicant highlighted three patients' discontinuations due to TEAEs as adverse events of special interest (AESI). The patient narratives describing TEAEs that led to premature narsoplimab-wuug discontinuation are described in the [Section 17](#), this included a TEAE of supraventricular tachycardia (SVT) in a healthy volunteer, a TEAE of granulomatous orchitis in a patient with aHUS, and a TEAE of liver insufficiency in a patient with aHUS.

Clinical reviewer comment

There were low rates of drug discontinuations in the HSCT-TMA population despite consisting of an acutely ill population with multiple comorbidities. One patient in Study TMA-001 discontinued narsoplimab-wuug, this was likely related to the patient's underlying disease diagnosis of AML. In the supportive safety database one healthy volunteer discontinued narsoplimab-wuug due to an event of SVT. One other patient in the safety database developed SVT, this was a patient with HSCT-TMA, the patient did not discontinue therapy due to this event. It does not appear that SVT is an adverse reaction given low rates in the safety population. The TEAE of granulomatous orchitis and liver insufficiency are discussed in key review issues for safety.

7.6.1.5. Dosage Interruptions Due to Adverse Events, Study TMA-001

Two patients (7.1%) with HSCT-TMA had a TEAE leading to drug interruption of narsoplimab-wuug ([Table 37](#)). Narratives are described below.

Patient (b) (6) is a 67-year-old female who received an allogeneic HSCT for AML. Following the diagnosis of HSCT-TMA the patient was enrolled on study and received narsoplimab-wuug 4 mg/kg IV once a week. On study day 41 (b) (6) 7 days from the last dose of narsoplimab-wuug, the patient developed nausea, malaise, diarrhea, chills, and fever. She was hospitalized and found to be hypertensive and tachycardic. Blood culture was positive for *E. coli*. She was treated with antibiotics. During the event, narsoplimab-wuug was held for sepsis from (b) (6). Treatment resumed on (b) (6). Three days later on day 55 (b) (6) the patient developed grade 3 pyrexia and was hospitalized. Infectious work up was significant for a positive urine culture for *Enterococcus faecium*, weakly positive Epstein-Barr virus (EBV) PCR, and moderate bilateral pleural effusions. The patient was treated with

antibiotics. Narsoplimab-wuug was held during the event of pyrexia from (b) (6). On (b) (6) the patient received the eighth and final dose of narsoplimab-wuug.

Patient (b) (6) is a 48-year-old male who received an allogeneic HSCT for high grade myelodysplastic syndrome. The patient started narsoplimab-wuug 4 mg/kg IV once a week on (b) (6) for HSCT-TMA. After receiving 5 doses of narsoplimab-wuug the study drug was interrupted (b) (6) for the events of pulmonary alveolar hemorrhage and myocardial infarction. On (b) (6) the patient had an ejection fraction of 50% and mild global left ventricular hypokinesia. On (b) (6) the patient developed hemoptysis and bronchoscopy was suggestive of diffuse alveolar hemorrhage (DAH). The patient was transferred to the intensive care unit (ICU) and found to have an elevated troponin T to 1194 ng/L (normal <30 ng/L) and concern for type II myocardial infarction. The investigator believed the type II myocardial infarction was possibly due to post-dialysis hypotension. Both events resolved. The patient's TMA markers remained abnormal, and the patient subsequently withdrew from the study and died.

Table 37. Adverse Events Leading to Drug Interruptions, Primary HSCT-TMA Safety Population, Study TMA-001

	Narsoplimab-wuug 4 mg/kg IV N=24 n (%)	Narsoplimab-wuug 370 mg IV N=4 n (%)	Narsoplimab-wuug Total N=28 n (%)
Adverse Event¹			
Patients with at least 1 AE leading to discontinuation	2 (8.3%)	0 (0%)	2 (7.1%)
Acute myocardial infarction	1 (4.2%)	0 (0%)	1 (3.6%)
Escherichia sepsis	1 (4.2%)	0 (0%)	1 (3.6%)
Pulmonary alveolar hemorrhage	1 (4.2%)	0 (0%)	1 (3.6%)
Pyrexia	1 (4.2%)	0 (0%)	1 (3.6%)

Source: Clinical reviewer [adae.xpt; Software: Python]

¹ Coded as MedDRA preferred terms

Abbreviations: AE, adverse event; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

Clinical reviewer comment

There were low rates of drug interruption of narsoplimab-wuug. The relationship of the TEAEs leading to drug interruptions is difficult to determine given the complexity of the patients in a single-arm trial.

7.6.1.6. Treatment-Emergent Adverse Events, Study TMA-001

The most common TEAEs ($\geq 30\%$) in patients with HSCT-TMA in Study TMA-001 were infections, viral infections, hemorrhage, diarrhea, vomiting, neutropenia, pyrexia, fatigue, and GVHD. [Table 38](#) provides TEAEs occurring in $>10\%$ of patients by MedDRA System Organ Class (SOC). Infections were the most common TEAE, occurring in 21/28 (75%) of patients. Further analysis of infections can be found in Section [17 \(AESI Infections\)](#). Hemorrhage was the second most common TEAE, this was a combined term. Further analysis of hemorrhage can be found in key review issues relevant to safety. TEAEs by system organ class are included in [Table 128](#).

Table 38. Treatment-Emergent Adverse Events,¹ Reported in >10% of Patients, Primary HSCT-TMA Safety Population, Study TMA-001

Preferred Term or Query	Narsoplimab- wuug 4.0 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total IV N=28 n (%)
Infections	19 (79.2)	2 (50.0)	21 (75.0)
Infection, viral*	9 (37.5)	1 (25.0)	10 (35.7)
Sepsis*	6 (25.0)	1 (25.0)	7 (25.0)
Pneumonia*	4 (16.7)	1 (25.0)	5 (17.9)
Infection, bacterial*	4 (16.7)	0	4 (14.3)
Bacteremia*	3 (12.5)	0	3 (10.7)
Lower respiratory tract infection	3 (12.5)	0	3 (10.7)
Upper respiratory tract infection	3 (12.5)	0	3 (10.7)
Infection, fungal*	3 (12.5)	0	3 (10.7)
Vascular disorders			
Hemorrhage*	10 (41.7)	2 (50.0)	12 (42.9)
Hypotension*	5 (20.8)	0	5 (17.9)
Systemic hypertension	3 (12.5)	0	3 (10.7)
Epistaxis	2 (8.3)	1 (25.0)	3 (10.7)
Gastrointestinal disorders			
Diarrhea	10 (41.7)	0	10 (35.7)
Vomiting	9 (37.5)	0	9 (32.1)
Nausea	7 (29.2)	0	7 (25.0)
Abdominal pain*	4 (16.7)	1 (25.0)	5 (17.9)
Blood and lymphatic system disorders			
Neutropenia*	9 (37.5)	1 (25.0)	10 (35.7)
Anemia*	5 (20.8)	0	5 (17.9)
General disorders and administration site conditions			
Pyrexia	8 (33.3)	2 (50.0)	10 (35.7)
Fatigue*	8 (33.3)	0	8 (28.6)
Peripheral edema*	4 (16.7)	0	4 (14.3)
Immune system disorders			
Graft versus host disease*	8 (33.3)	0	8 (28.6)
Metabolism and nutrition disorders			
Hypokalemia*	7 (29.2)	0	7 (25.0)
Acidosis*	3 (12.5)	0	3 (10.7)
Weight loss, cachexia	3 (12.5)	0	3 (10.7)
Hyperglycemia	2 (8.3)	1 (25.0)	3 (10.7)
Hypocalcemia	2 (8.3)	1 (25.0)	3 (10.7)
Musculoskeletal and connective tissue disorders			
Back pain	5 (20.8)	0	5 (17.9)
Respiratory, thoracic and mediastinal disorders			
Cough*	4 (16.7)	0	4 (14.3)
Pulmonary edema	3 (12.5)	0	3 (10.7)
Nervous system disorders			
Dizziness*	4 (16.7)	0	4 (14.3)
Headache	3 (12.5)	0	3 (10.7)
Hepatobiliary disorders			
Hepatic injury*	4 (16.7)	0	4 (14.3)
Hyperbilirubinemia, alkaline phosphatase abnormal*	3 (12.5)	0	3 (10.7)

	Narsoplimab- wuug 4.0 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total IV N=28 n (%)
Preferred Term or Query			
Skin and subcutaneous tissue disorders			
Rash*	4 (16.7)	0	4 (14.3)
Pruritus	3 (12.5)	0	3 (10.7)
Psychiatric disorders			
Confusional state*	3 (12.5)	1 (25.0)	4 (14.3)
Cardiac disorders			
Arrhythmia*	3 (12.5)	0	3 (10.7)
Congestive heart failure*	3 (12.5)	0	3 (10.7)
Tachycardia*	3 (12.5)	0	3 (10.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignancy	3 (12.5)	0	3 (10.7)
Renal and urinary disorders			
Acute kidney injury	3 (12.5)	0	3 (10.7)

Source: Clinical Reviewer and Clinical Data Analyst [adae.xpt; Software: Python]

¹ Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

The following terms were combined:

* Acute kidney injury: Acute kidney injury, Hemolytic uremic syndrome

* Abdominal pain: Abdominal pain, Abdominal pain lower, Abdominal pain upper

* Acidosis: metabolic acidosis, acidosis

* Anemia: anemia, hemoglobin decreased

* Arrhythmia: Atrial fibrillation, Atrial flutter, Sinus tachycardia, Supraventricular tachycardia, Tachycardia

* Bacteremia: Staphylococcal bacteremia, Bacteremia, Enterococcal bacteremia

* Congestive heart failure: Pulmonary edema, Acute pulmonary edema, Cardiac failure

* Cough: cough, productive cough

* Confusional state: confusional state, delirium

* Dizziness: Dizziness, presyncope

* Fatigue: fatigue, asthenia, lethargy, malaise

* Graft versus host disease: acute graft versus host disease in skin, graft versus host disease, graft versus host disease in eye, graft versus host disease in gastrointestinal tract, graft versus host disease in liver

* Hemorrhage: Epistaxis, Ecchymosis, Gastrointestinal hemorrhage, Catheter site hemorrhage, Conjunctival hemorrhage,

Contusion, Cystitis hemorrhagic, Hemorrhage intracranial, Petechiae, Pulmonary alveolar hemorrhage, Respiratory tract hemorrhage

* Hypokalemia: hypokalemia, blood potassium decreased

* Hepatic injury: Alanine aminotransferase increased, Aspartate aminotransferase increased, Graft versus host disease in liver,

Hepatic function abnormal: Blood alkaline phosphatase increased

* Hyperbilirubinemia, alkaline phosphatase abnormal: Blood alkaline phosphatase increased, Blood alkaline phosphatase abnormal, Blood bilirubin increased, Hyperbilirubinemia

* Hypotension: Orthostatic hypotension, Hypotension, Procedural hypotension

* Infection, bacterial: Pneumonia klebsiella, Staphylococcal bacteremia, Bacteremia, Enterococcal bacteremia, Escherichia sepsis

* Infection, fungal: Fungal infection, Oral candidiasis, Pneumonia fungal

* Infection, viral: cytomegalovirus infection, cytomegalovirus viremia, Epstein-Barr virus infection, Epstein-Barr virus test positive, influenza, pneumonia viral, respiratory tract infection viral, viral infection, human herpesvirus 6 infection, hepatitis E virus test positive, adenovirus test positive

* Malignancy: Acute myeloid leukemia, Diffuse large b-cell lymphoma,

* Neutropenia: neutropenia, neutropenic sepsis, neutrophil count decreased

* Peripheral edema: edema peripheral, peripheral swelling

* Pneumonia: Pneumonia klebsiella, Pneumonia, Lung infection, Pneumonia fungal, Pneumonia viral

* Rash: Rash, Rash generalized, Septic rash, Skin exfoliation

* Sepsis: neutropenic sepsis, septic shock, Escherichia sepsis, sepsis, septic rash, urosepsis

* Tachycardia: Sinus tachycardia, Supraventricular tachycardia, Tachycardia

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with adverse event

Clinical reviewer comment

Most patients (96%) in Study TMA-001 with HSCT-TMA experienced one or more TEAEs. Severe Treatment-Emergent Adverse Events, Study TMA-001

The most common (>5%) Severe TEAEs infections in particular sepsis, GVHD, and neutropenia ([Table 39](#)).

Table 39. Severe Treatment-Emergent Adverse Events,* Reported in >5% of the Primary HSCT-TMA Safety Population, Study TMA-001

Preferred Term or Query	OMS721-TMA-001(HSCT-TMA) 4.0 mg/kg IV N=24 n (%)	OMS721-TMA-001(HSCT-TMA) 370 mg IV N=4 n (%)	OMS721-TMA-001(HSCT-TMA) Total IV N=28 n (%)
Infections	12 (50.0)	1 (25.0)	13 (46.4)
Sepsis*	5 (20.8)	1 (25.0)	6 (21.4)
Pneumonia*	3 (12.5)	1 (25.0)	4 (14.3)
Infection, bacterial*	3 (12.5)	0	3 (10.7)
Bacteremia*	2 (8.3)	0	2 (7.1)
Lower respiratory tract infection	2 (8.3)	0	2 (7.1)
Infection, viral*	1 (4.2)	0	2 (7.1)
Blood and lymphatic system disorders			
Neutropenia*	9 (37.5)	1 (25.0)	10 (35.7)
Anemia*	3 (12.5)	0	3 (10.7)
Leukopenia*	2 (8.3)	0	2 (7.1)
Immune system disorders			
Graft versus host disease*	5 (20.8)	0	5 (17.9)
Metabolism and nutrition disorders			
Hypokalemia	3 (12.5)	0	3 (10.7)
Hyperkalemia	2 (8.3)	0	2 (7.1)
Vascular disorders			
Hypotension*	3 (12.5)	0	3 (10.7)
Systemic hypertension	3 (12.5)	0	3 (10.7)
Hemorrhage*	2 (8.3)	0	2 (7.1)
Shock, noncardiogenic	1 (4.2)	1 (25.0)	2 (7.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignancy*	3 (12.5)	0	3 (10.7)
Leukemia	2 (8.3)	0	2 (7.1)
Renal and urinary disorders			
Acute kidney injury*	2 (8.3)	0	2 (7.1)
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	2 (8.3)	0	2 (7.1)
Pulmonary edema	2 (8.3)	0	2 (7.1)
Cardiac disorders			
Arrhythmia*	2 (8.3)	0	2 (7.1)
Congestive heart failure*	2 (8.3)	0	2 (7.1)
Gastrointestinal disorders			
Diarrhea	2 (8.3)	0	2 (7.1)
Vomiting	2 (8.3)	0	2 (7.1)

	OMS721-TMA-001(HSCT-TMA) 4.0 mg/kg IV N=24 n (%)	OMS721-TMA-001(HSCT-TMA) 370 mg IV N=4 n (%)	OMS721-TMA-001(HSCT-TMA) Total IV N=28 n (%)
Preferred Term or Query			
Hepatobiliary disorders			
Hyperbilirubinemia, alkaline phosphatase	2 (8.3)	0	2 (7.1)
Psychiatric disorders			
Confusional state*	1 (4.2)	1 (25.0)	2 (7.1)

Source: Clinical Reviewer and Clinical Data Analyst [adae.xpt; Software: Python]

*Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly)

The following terms were combined:

* Acute kidney injury: acute kidney injury, hemolytic uremic syndrome

* Anemia: anemia, hemoglobin decreased

* Arrhythmia: atrial fibrillation, supraventricular tachycardia

* Bacteremia: bacteremia, Staphylococcal bacteremia

* Confusional state: Confusional state, delirium

* Congestive heart failure: pulmonary edema, acute pulmonary edema, cardiac failure

* Graft versus Host Disease: graft versus host disease, graft versus host disease in gastrointestinal tract

* Hemorrhage: hemorrhage intracranial, Pulmonary alveolar hemorrhage

* Hypotension: hypotension, orthostatic hypotension

* Infection, bacterial: bacteremia, Escherichia sepsis, pneumonia klebsiella, Staphylococcal bacteremia

* Infection, viral: pneumonia viral, hepatitis E virus test positive

* Leukopenia: white blood cell count decreased, leukopenia

* Malignancy: acute myeloid leukemia, diffuse large b-cell lymphoma

* Neutropenia: neutropenia, neutropenic sepsis, neutrophil count decreased

* Pneumonia: pneumonia, lung infection, pneumonia klebsiella, pneumonia viral

* Sepsis: neutropenic sepsis, septic shock, Escherichia sepsis, sepsis

7.6.1.7. Adverse Events of Special Interest, Study TMA-001

Infections

The Applicant identified infections as an adverse event of special interest. In patients with HSCT-TMA, 21 out of 28 (75%) of patients had a TEAE of infection (Tables 40 and 41). The most common types of infections included viral infections, sepsis, pneumonia and bacterial infections. Viral infections occurred in 36% of patients, the most common type of viral infection was cytomegalovirus. Serious TEAE infections occurred in 10 out of 28 (36%) of patients in the HSCT TMA population (Table 3 and Table 42). The most common serious TEAEs included sepsis, bacterial infections, viral infections and pneumonia. Safety analysis for infections are described below. Safety analysis for infections in the entire TMA population is described in Tables 129 and 130.

Table 40. Infections, Adverse Events of Special Interest, Primary HSCT-TMA Safety Population, Study TMA-001

	Narsoplimab-wuug 4 mg/kg IV N=24 n (%)	Narsoplimab-wuug 370 mg IV N=4 n (%)	Narsoplimab-wuug Total N=28 n (%)
Preferred Term or Query			
Infection, all	19 (79.2)	2 (50.0)	21 (75.0)
Infection, viral*	9 (37.5)	1 (25.0)	10 (35.7)
Sepsis*	6 (25.0)	1 (25.0)	7 (25.0)
Pneumonia*	4 (16.7)	1 (25.0)	5 (17.9)
Infection, bacterial*	4 (16.7)	0	4 (14.3)

	Narsoplimab-wuug 4 mg/kg IV N=24 n (%)	Narsoplimab-wuug 370 mg IV N=4 n (%)	Narsoplimab-wuug Total N=28 n (%)
Preferred Term or Query			
Bacteremia*	3 (12.5)	0	3 (10.7)
Lower respiratory tract infection	3 (12.5)	0	3 (10.7)
Upper respiratory tract infection	3 (12.5)	0	3 (10.7)
Infection, fungal*	3 (12.5)	0	3 (10.7)
Urinary tract infection *	2 (8.3)	0	2 (7.1)
Influenza	1 (4.2)	0	1 (3.6)

Source: Clinical reviewer

The following terms were combined:

* Bacteremia: Staphylococcal bacteremia, Bacteremia, Enterococcal bacteremia

* Infection, bacterial: Pneumonia klebsiella, Staphylococcal bacteremia, Bacteremia, Enterococcal bacteremia, Escherichia sepsis

* Infection, fungal: Fungal infection, Oral candidiasis, Pneumonia fungal

* Infection, viral: cytomegalovirus infection, cytomegalovirus viremia, Epstein-Barr virus infection, Epstein-Barr virus test positive, influenza, pneumonia viral, respiratory tract infection viral, viral infection, human herpesvirus 6 infection, hepatitis E virus test positive, adenovirus test positive

* Pneumonia: Pneumonia klebsiella, Pneumonia, Lung infection, Pneumonia fungal, Pneumonia viral

* Sepsis: neutropenic sepsis, septic shock, Escherichia sepsis, sepsis, septic rash, urosepsis

* Urinary tract infection: urinary tract infection, urosepsis

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly);

MedDRA, Medical Dictionary for Regulatory Activities

Table 41. Adverse Events of Special Interest, Infections, Primary HSCT-TMA Safety Population, Study TMA-001

	Narsoplimab- wuug 4 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total N=28 n (%)
Preferred Term			
Cytomegalovirus infection or viremia	4 (16.7)	1 (25.0)	5 (17.9)
Lower respiratory tract infection	3 (12.5)	0	3 (10.7)
Upper respiratory tract infection	3 (12.5)	0	3 (10.7)
Epstein-Barr virus infection or test positive	2 (8.3)	0	2 (7.1)
Neutropenic sepsis	2 (8.3)	0	2 (7.1)
Pneumonia	1 (4.2)	1 (25.0)	2 (7.1)
Pneumonia Klebsiella	2 (8.3)	0	2 (7.1)
Septic shock	1 (4.2)	1 (25.0)	2 (7.1)
Staphylococcal bacteremia	2 (8.3)	0	2 (7.1)
Adenovirus test positive	1 (4.2)	0	1 (3.6)
Aspergillus infection	1 (4.2)	0	1 (3.6)
Bacteremia	1 (4.2)	0	1 (3.6)
Ear infection	1 (4.2)	0	1 (3.6)
Enterococcal bacteremia	1 (4.2)	0	1 (3.6)
Escherichia sepsis	1 (4.2)	0	1 (3.6)
Folliculitis	0	1 (25.0)	1 (3.6)
Fungal infection	1 (4.2)	0	1 (3.6)
Gastroenteritis	1 (4.2)	0	1 (3.6)
Hepatitis E virus test positive	1 (4.2)	0	1 (3.6)
Human herpesvirus 6 infection	1 (4.2)	0	1 (3.6)
Infection	1 (4.2)	0	1 (3.6)
Influenza	1 (4.2)	0	1 (3.6)
Lung infection	1 (4.2)	0	1 (3.6)
Oral candidiasis	1 (4.2)	0	1 (3.6)
Pneumonia fungal	1 (4.2)	0	1 (3.6)
Pneumonia viral	1 (4.2)	0	1 (3.6)
Respiratory tract infection viral	1 (4.2)	0	1 (3.6)

	Narsoplimab- wuug 4 mg/kg IV N=24 n (%)	Narsoplimab- wuug 370 mg IV N=4 n (%)	Narsoplimab- wuug Total N=28 n (%)
Preferred Term			
Sepsis	1 (4.2)	0	1 (3.6)
Septic rash	1 (4.2)	0	1 (3.6)
Skin infection	1 (4.2)	0	1 (3.6)
Urinary tract infection	1 (4.2)	0	1 (3.6)
Urosepsis	1 (4.2)	0	1 (3.6)
Vascular device infection	1 (4.2)	0	1 (3.6)
Viral infection	1 (4.2)	0	1 (3.6)

Source: Clinical Reviewer [adae.xpt]

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly)

Table 42. Adverse Events of Special Interest, Serious Infections, Primary HSCT-TMA Safety Population, Study TMA-001

	Narsoplimab-wuug 4 mg/kg IV N=24 n (%)	Narsoplimab-wuug 370 mg IV N=4 n (%)	Narsoplimab-wuug Total N=28 n (%)
Preferred Term			
Neutropenic sepsis	2 (8.3)	0	2 (7.1)
Septic shock	1 (4.2)	1 (25.0)	2 (7.1)
Bacteremia	1 (4.2)	0	1 (3.6)
Escherichia sepsis	1 (4.2)	0	1 (3.6)
Fungal infection	1 (4.2)	0	1 (3.6)
Gastroenteritis	1 (4.2)	0	1 (3.6)
Infection	1 (4.2)	0	1 (3.6)
Pneumonia viral	1 (4.2)	0	1 (3.6)
Respiratory tract infection viral	1 (4.2)	0	1 (3.6)
Urosepsis	1 (4.2)	0	1 (3.6)
Pneumonia	0	1 (25.0)	1 (3.6)

Source: Clinical Reviewer [adae.xpt]

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly)

7.6.1.8. Laboratory Findings, Study TMA-001

Chemistry and Hematology

There were no notable changes from baseline or trends in clinical chemistry or hematology laboratories to suggest a safety signal. TEAEs of clinically significant chemistry and hematology laboratories are listed in [Table 43](#).

Table 43. Adverse Event of Laboratory Chemistry and Hematology, Safety Population, Study TMA-001

Preferred Term	Narsoplimab-wuug All Grades N=28 n (%)	Narsoplimab-wuug Grade $\geq$3 N=28 n (%)
Electrolytes		
Hypokalemia	7 (25.0)	3 (10.7)
Hyperglycemia	3 (10.7)	0
Hypocalcemia	3 (10.7)	0
Hyperkalemia	2 (7.1)	2 (7.1)
Hypernatremia	2 (7.1)	1 (3.6)
Hypomagnesemia	2 (7.1)	0
Hyponatremia	2 (7.1)	0
Hypercalcemia	1 (3.6)	1 (3.6)
Hypoglycemia	1 (3.6)	1 (3.6)
Hepatic		
Blood alkaline phosphatase increased or abnormal	3 (10.7)	1 (3.6)
Alanine aminotransferase increased	2 (7.1)	0
Aspartate aminotransferase increased	2 (7.1)	0
Hyperbilirubinemia or blood bilirubin increased	2 (7.1)	1 (3.6)
Gamma-glutamyltransferase increased	1 (3.6)	0
Renal		
Blood creatinine increased	1 (3.6)	0 (0)
Hematologic		
Neutropenia or neutrophil count decreased	8 (28.6)	8 (28.6)
Anemia	5 (17.9)	3 (10.7)
Leukopenia	2 (7.1)	2 (7.1)
Thrombocytopenia	2 (7.1)	1 (3.6)

Source: Clinical reviewer [adae.xpt]

Immunogenicity

Per the Applicant's CSR: 11 of 58 patients (19%) who were tested for antidrug antibody (ADA) were confirmed positive at one or more time points after narsoplimab-wuug administration (HSCT-TMA: 3/28, 10.7% and in aHUS or TTP: 8/30, 26.7%). Five patients reported hypersensitivity reactions, but all were attributable to other agents. One patient reported drug hypersensitivity to Tazocin (Patient (b) (6) ADA negative). Two patients reported allergic transfusion reactions (Patients (b) (6) both ADA positive). Two patients reported hypersensitivity reactions, both related to plasma therapy (Patients (b) (6); ADA positive and ADA negative, respectively). No apparent correlation of antibody development to altered clinical response or adverse events was observed.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Infections Were the Most Common TEAE Reported in Patients With HSCT-TMA

Issue

Infections were the most common TEAE reported in patients with HSCT-TMA. The Applicant has proposed to include infections in the Warnings and Precaution section of the USPI.

Background

Infections were identified as an adverse event of special interest by the Applicant. Narsoplimab-wuug is a human mAB that binds to and inhibits MASP-2. MASP-2 is an effector enzyme in the lectin complement pathway, which plays an important role in innate immunity ([Fujita et al. 2004](#)). Therefore, there could be a risk of increased infections in patients who receive narsoplimab-wuug based on its mechanism of action. While there are no approved drugs that specifically inhibit the lectin pathway, other drugs that inhibit different pathways of the complement (i.e., eculizumab and ravulizumab) are associated with an increased risk of infections, especially encapsulated organisms. In the literature, there are several reports of inherited MASP-2 deficiencies, a very rare primary immunodeficiency disorder. MASP-2 deficiency was first reported in 2003, which described a patient suffering from recurrent pneumococcal infections, as well as autoimmune and inflammatory conditions ([Stengaard-Pedersen et al. 2003](#)). MASP-2 deficiency is considered a primary immunodeficiency, associated with pyogenic infections, inflammatory lung disease, and autoimmunity ([Garcia-Laorden et al. 2020](#)). Since the first description, there have been several (although rare) individual case reports describing patients with MASP-2 deficiency. The clinical manifestations appear heterogeneous ranging from recurrent pneumonia, cystic fibrosis, skin abscesses, colorectal cancer, pulmonary tuberculosis, and hepatocellular carcinoma ([Garcia-Laorden et al. 2020](#)). Recently, there were two reported cases of herpes simplex virus encephalitis reported in patients with MASP-2 deficiency ([Bibert et al. 2019](#)). MASP-2 deficiency has also been associated with an increased risk of fever and neutropenia in pediatric patients receiving chemotherapy ([Brodzki et al. 2020](#)). The p.D120G mutation, in a homozygous state is the primary cause of MASP-2 deficiency ([Sokolowska et al. 2015](#)). Yet, there has also been a significant number healthy individuals identified with MASP-2 deficiency with no overt symptoms, including patients with the p.D120G mutation ([Thiel et al. 2007](#); [Garcia-Laorden et al. 2020](#)). For example, homozygosity for pD120G may occur in 7-15 out of every 10,000 individuals of European origin ([Garcia-Laorden et al. 2020](#)). It has been proposed that MASP-2 deficiency is a disease modifier rather than causing the disease ([Thiel et al. 2007](#); [Garcia-Laorden et al. 2020](#)). In addition, the lectin pathway is largely redundant in human defenses and MASP-2 deficiency classification as a primary immunodeficiency disorder has been questioned recently ([Garcia-Laorden et al. 2020](#)). Therefore, the clinical impact, including risk of infections of MASP-2 deficiency remains unclear.

Assessment

Infections were the most common TEAE, occurring in 21/28 (75%) of patients in Study TMA-001. The most common type of infection was viral, occurring in 10/28 (35.7%) of patients and the most frequently reported type of viral infection reported was CMV. Sepsis, pneumonia, bacterial infections, bacteremia, lower respiratory tract infections, upper respiratory tract infections and fungal infections occurred in >10% of patients in HSCT-TMA ([Table 129](#)). No patients experienced an encapsulated organism infection of *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib), or *Streptococcus pneumoniae* during the AE evaluation period. Of note, one patient had pneumococcal pneumonia, but this occurred in the post AE evaluation period. Serious infections occurred in 10/28 (35.7%) of patients. Neutropenic sepsis and septic shock occurred in two patients with HSCT-TMA. The following was reported in one patient; bacteremia, *Escherichia* sepsis, fungal infection, gastroenteritis, infection, viral pneumonia, viral respiratory tract infection, urosepsis, and pneumonia. In total, 7% of HSCT-TMA patients died due to infections.

Infections were also assessed in the integrated summary of safety (ISS) population which confirmed the safety findings from the primary safety population.

There was no comparator arm in Study TMA-001 so it is difficult to determine if infection rates are increased with narsoplimab-wuug compared to a control population. The Applicant provided data in response to an IR from two hospital centers that were sites in the trial ([Table 44](#) and [Table 45](#)). The infection rates at the site for patients undergoing HSCT appear to be similar to what was reported in Study TMA-001, although interpretation is very difficult given this data were reported from only two centers and further data were not provided besides infection incidence post-allogeneic transplant (i.e., demographics, baseline characteristics, conditioning regimen, human leukocyte antigen mismatch, source of cells, immunosuppressants, comorbidities and severity of infections). In addition, these infection rates were not limited to patients with HSCT-TMA.

Table 44. Mayo Clinic Infection Incidence in Post-allogeneic HSCT Patients Through 100 Days Following Transplant

Year	Incidence of Infection
2017	66%
2018	71%
2019	80%

Source: Applicant's IR response

Abbreviation: HSCT, hematopoietic stem cell transplant

Table 45. ASST Papa Giovanni XXIII Hospital Infection in Post-allogeneic HSCT Patients

Year	Number of Allogeneic Transplants	Total Number of Patients with Infections N (%)	Total Number of Patients with Viral Infections N (%)	Total Number of Patients with Bacterial Infections N (%)	Total Number of Patients with Fungal Infections N (%)
2016	71	43 (61%)	37 (52%)	10 (14%)	0 (0%)
2017	66	45 (68%)	37 (56%)	19 (29%)	3 (5%)
2018	71	59 (83%)	58 (82%)	24 (34%)	4 (6%)
2019	56	45 (80%)	37 (66%)	29 (52%)	2 (4%)
2020	57	30 (53%)	19 (33%)	19 (33%)	1 (2%)

Source: Applicant's IR response

Abbreviations: ASST, Azienda Socio Sanitaria Territoriale; HSCT, hematopoietic stem cell transplant

Patients who undergo a HSCT are at increased risk for developing infections. This remains a common cause of morbidity and mortality in the post-transplant setting, due to a variety of factors including, but not limited to, the following: immunosuppressant therapies, multiple comorbidities, immune system dysfunction, neutropenia, and presence of central line. Therefore, patients treated with narsoplimab-wuug for HSCT-TMA are already at risk for serious infections. Based on the mechanism of action of narsoplimab-wuug, as a lectin complement inhibitor that inhibits MASP-2, it is possible that narsoplimab-wuug further increases the risk of infections as the lectin pathway is a component of the innate immune response and patients with inherited MASP-2 deficiency may be at increased risk of infections.

Conclusion

In conclusion, after review of the literature including reports of inherited MASP-2 deficiency, in addition to a significant number of patients experiencing serious or fatal infections in Study TMA-001, and the lack of comparative safety, an increased risk of serious infection with narsoplimab-wuug cannot be ruled out. Therefore, if the product were to be approved, serious infections should be included in the Warnings and Precautions section of the USPI. Serious infections should also be further monitored through a postmarketing requirement.

7.7.2. Based on the Mechanism of Action of Narsoplimab-wuug of Inhibition of MASP-2, Narsoplimab-wuug May Increase Risk of Tuberculosis Infections

Issue

In clinical trials, one patient with aHUS developed a TEAE of granulomatous orchitis. Based on the mechanism of action of narsoplimab-wuug of inhibition of MASP-2, narsoplimab-wuug may increase risk of tuberculosis infections.

Background

One patient with aHUS developed granulomatous orchitis (biopsy proven) following three doses of narsoplimab-wuug. All cultures, including mycobacterium, were negative. The event resolved approximately 2 months after discontinuation of narsoplimab-wuug. Of note, this patient had a

previous mycobacterium infection several years prior to receiving narsoplimab-wuug. The full narrative can be found in Section [17](#).

Assessment

A review of the ADAE dataset did not reveal any additional TEAEs of orchitis, granuloma, or tuberculosis.

The Applicant and the clinical reviewer conducted a literature review to further understand whether inhibition of MASP-2 could increase the risk of tuberculosis. Of the 440 patients tested, two patients had pulmonary tuberculosis with MASP-2 deficiency, as did one healthy volunteer out of 276 healthy controls ([Sokolowska et al. 2015](#)). All three subjects had low MASP-2 concentrations and complex activities. A polymorphism of the MASP-2 gene was associated with nonsmoker's susceptibility to tuberculosis ([Chen et al. 2015](#)). Therefore, it is possible that narsoplimab-wuug, by blocking MASP-2, may have contributed to the development of granulomatous orchitis.

Given the TEAE of granulomatous orchitis in a patient treated with narsoplimab-wuug and literature suggesting that MASP-2 deficiency may increase risk of tuberculosis infection, there may be an increased risk of tuberculosis following treatment with narsoplimab-wuug. Therefore, the USPI should include in the Warnings and Precautions that a patient in clinical trials developed granulomatous orchitis and recommend that patients be assessed for risk factors of tuberculosis when considering the risk/benefit profile of narsoplimab-wuug.

Conclusion

In conclusion, one patient in clinical trials developed granulomatous orchitis. While no patients were reported to have a positive mycobacterium culture in Study MTA-001, the literature suggests that MASP-2 deficiency may increase susceptibility to tuberculosis. Therefore, one cannot rule out the possibility of contributing to the TEAE of granulomatous orchitis. Providers will be informed on this adverse reaction in the Warnings and Precautions of the USPI which will recommend assessing patients for risk factors. As only a small number of patients with HSCT-TMA have been treated with narsoplimab-wuug, we would also recommend that this risk be further assessed in a postmarketing requirement if the product were to be approved.

7.7.3. Additional Analysis Conducted to Try to Determine Whether Narsoplimab-wuug Caused Drug Induced Liver Injury

Issue

In clinical trials, one patient developed grade 4 liver insufficiency.⁵ A clinical reviewer conducted an additional analysis to try to determine whether narsoplimab-wuug caused drug-induced liver injury.

Background

Patient (b) (6) was a 28-year-old female with a history of aHUS and end-stage renal disease requiring hemodialysis, who initiated narsoplimab-wuug per Study HUS-002. While receiving the narsoplimab-wuug the patient developed a TEAE of grade 4 hepatic failure. The hepatic failure occurred after eating a meal consisting of fish and while experiencing fever, hypotension, and hypoxia. In the safety narrative it was noted the patient received hydralazine from an unknown source, which was characterized as “overdosing on hydralazine.” The patient did not continue hydralazine during her hospitalization. Viral studies were negative and the patient did not have a history of consuming alcohol, acetaminophen, herbal supplements, or other over-the-counter medications. Narsoplimab-wuug was discontinued. The patient recovered from the liver insufficiency. A more detailed narrative can be found in Section 17.

The Agency sent an IR asking for additional information regarding the described TEAE. The investigator for the site was not the treating physician so limited details were provided. The interpretation that the event could have been related to hydralazine was based on the patient receiving hydralazine from an unknown source for hypertension and the liver insufficiency resolved in the hospital when the patient was not receiving hydralazine. The investigator also considered ischemic hepatitis to be a possible cause of the liver insufficiency. The differential for the etiology of ischemic hepatitis was the patient’s concurrent infection, hypoxia, and/or hypotension.

Assessment

The clinical reviewer reviewed the narrative to assess for causality. Temporally, narsoplimab-wuug could have contributed to the event of liver insufficiency as the patient was actively receiving narsoplimab-wuug when the event of grade 4 hepatic failure occurred and the TEAE

⁵ Grade 4+, Severe: Raised serum aminotransferase or alkaline phosphatase levels and serum bilirubin ≥ 2.5 mg/dL and at least one of the following:

Prolonged jaundice and symptoms beyond 3 months, or

Signs of hepatic decompensation (INR ≥ 1.5 , ascites, encephalopathy), or

Other organ failure believed to be related to drug induced liver injury

resolved with discontinuation of narsoplimab-wuug. At the same time, the patient did receive an unknown quantity of hydralazine. In the hydralazine USPI, hepatitis is listed as a rare adverse reaction. Hydralazine is described as a less concern for drug induced liver injury in the drug induced liver injury rank dataset. While rare, several case reports of hepatotoxicity associated with hydralazine described in the literature ([Stumpf 1991](#); [Harati et al. 2016](#); [Sharma et al. 2018](#)). The patient also had hypotension at the time of presentation of liver insufficiency, hepatic ischemia could have also contributed to the TEAE.

In clinical trials with narsoplimab-wuug, there were no other events of grade 4 hepatic failure or lesser extent of liver failure. The ISS ADAE dataset was reviewed for evidence of hepatobiliary injury. In patients with TMA (HSCT-TMA, aHUS, or TTP) 9 out of 64 (14.1%) patients experienced a TEAE of hepatobiliary injury ([Table 46](#)). The most common TEAE was blood alkaline phosphatase abnormal or increased, followed by alanine aminotransferase increased. All TEAEs were grade 1 or 2, except for a grade 3 serious TEAE of liver cirrhosis, grade 3 nonserious TEAE of hyperbilirubinemia, and a nonserious grade 3 TEAE of blood alkaline phosphatase increased. The safety narrative for patient (b) (6) was reviewed for the serious TEAE of liver cirrhosis. It is unlikely that the TEAE was related to narsoplimab-wuug as this patient had a history of chronic parenchymal liver disease and hyperammonemia. Two patients with IgA nephropathy experienced TEAEs of grade 2 transaminases increased; however, the study remains blinded to treatment assignment. No healthy volunteers had a TEAE related to hepatobiliary injury.

Table 46. Adverse Events of Hepatobiliary Injury, Safety Population, Trial ISS

	TMA-001 HSCT-TMA N=28 n (%)	TMA-001 aHUS and TTP N=30 n (%)	HUS-002 aHUS N=6 n (%)	Total N=64 n (%)
Preferred Term				
All TEAEs of hepatobiliary Injury	5 (17.9%)	3 (10%)	1 (16.7%)	9 (14.1%)
Blood alkaline phosphatase abnormal or increased	3 (10.7%)	1 (3.3%)	0	4 (6.3%)
Alanine aminotransferase increased	2 (7.1%)	1 (3.3%)	0	3 (4.7%)
Aspartate aminotransferase increased	2 (7.1%)	0	0	2 (3.1%)
Hyperbilirubinemia	2 (7.1%)	0	0	2 (3.1%)
Gamma-glutamyltransferase increased	1 (3.6%)	0	0	1 (1.6%)
Hepatic cirrhosis	0	1 (3.3%)	0	1 (1.6%)
Hepatic enzyme increased	0	1 (3.3%)	0	1 (1.6%)
Hepatic failure	0	0	1 (16.7%)	1 (1.6%)
Hepatic function abnormal	1 (3.6%)	0	0	1 (1.6%)

Source: Clinical reviewer, adae.xpt

Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

The following preferred terms were combined

Hyperbilirubinemia: blood bilirubin increased, hyperbilirubinemia

Abbreviations: AE, adverse event; aHUS, atypical hemolytic uremic syndrome; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse events; TTP, thrombotic thrombocytopenic purpura

In a single-arm clinical trial it is difficult to determine if there is an association between hepatobiliary injury and narsoplimab-wuug given lack of comparative safety data. It is also particularly difficult given the complex nature of the patient population that may have additional

risk factors for hepatobiliary injury such as pre-existing hepatic injury, infections, ischemia, medications, veno-occlusive disease, and GVHD.

Conclusion

In clinical trials with narsoplimab-wuug there was one grade 4 TEAE of hepatic failure. This case was likely multifactorial as hydralazine and/or ischemic hepatitis could have contributed to the TEAE. It is difficult to determine causality as the event resolved with narsoplimab-wuug and hydralazine discontinuation, as well as treatment for the patient's hypotension. In addition, after careful review of hepatobiliary injury TEAEs across clinical trials there does not appear to be a safety signal. Therefore, the clinical reviewer does not recommend that hepatotoxicity be included in the Warnings and Precautions section of the USPI should the product be approved; however, the clinical reviewer does recommend that hepatobiliary injury be further assessed in future post-marketing assessments.

7.7.4. Second Most Common TEAE (FMQ) Was Hemorrhage

Issue

The second most common TEAE (FMQ) was hemorrhage.

Background

Given that hemorrhage was the second most common TEAE observed in Study TMA-001, the Agency asked the Applicant if they had data regarding the frequency of hemorrhage/bleeding events in the post-transplant setting as a comparison. The Applicant did not have access to this data. The Agency reviewed the hemorrhage TEAEs in the single arm trial of Study TMA-001 and the ISS dataset.

Assessment

During the FMQ analysis the second most common TEAE in Study TMA-001 was hemorrhage. Hemorrhage occurred in 12/28 (42.9%) of patients with HSCT-TMA ([Table 47](#)). Most TEAEs were grade 1 or 2. Serious TEAEs of hemorrhage occurred in 2/28 (7.1%) of patients with HSCT-TMA, this included intracranial hemorrhage and pulmonary alveolar hemorrhage.

In the ISS safety population, 8 out of 36 (22.2%) patients with either aHUS or TTP experienced a TEAE of hemorrhage (FMQ). Four out of 29 (13.8%) patients with IgA nephropathy (from study GNP-001) had a TEAE of hemorrhage, 3 of those patients were receiving narsoplimab-wuug and 1 was receiving placebo. In total, 3 healthy volunteers had TEAEs of hemorrhage, two patients were receiving narsoplimab-wuug had had a contusion and one was receiving placebo and had a vessel site puncture site hematoma.

In the ISS safety population, there were two patients with serious TEAEs of hemorrhage. This included one patient with aHUS treated on HUS-002 with a fatal event of cerebral hematoma, this patient had a recent history of subdural hemorrhage and thrombocytopenia prior to the event,

and thrombocytopenia was ongoing at the time of the cerebral hemorrhage. The other patient also had aHUS and was treated on TMA-001 and had a grade 4 TEAE of postprocedural hemorrhage following a kidney biopsy.

In reviewing the literature, hemorrhage does not seem to be described as a component of the phenotype of patients with inherited MASP-2 deficiency.

Table 47. Preferred Terms, Treatment-Emergent Adverse Events, FMQ (narrow) of Hemorrhage, Primary HSCT-TMA Safety Population, Study TMA-001

Preferred Terms	All Grades	Grade ≥3
Hemorrhage (narrow)	12 (42.9)	2 (7.1)
Epistaxis	3 (10.7)	0
Ecchymosis	2 (7.1)	0
Gastrointestinal hemorrhage	2 (7.1)	0
Catheter site hemorrhage	1 (3.6)	0
Conjunctival hemorrhage	1 (3.6)	0
Contusion	1 (3.6)	0
Cystitis hemorrhagic	1 (3.6)	0
Hemorrhage intracranial	1 (3.6)	1 (3.6)
Petechiae	1 (3.6)	0
Pulmonary alveolar hemorrhage	1 (3.6)	1 (3.6)
Respiratory tract hemorrhage	1 (3.6)	0

Source: Clinical reviewer; ADAE.xpt

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy

Conclusion

Hemorrhage is known to occur in patients in the post-transplant setting due to a variety of factors, most notably for thrombocytopenia, coagulopathy, procedures and liver dysfunction and HSCT-TMA. Causality is difficult to assess, given that Study TMA-001 was a single arm trial and all patients had thrombocytopenia. In addition, there may be deficiencies in the coagulation cascade and fibrinogen levels in this seriously ill population. In reviewing the ISS safety database there does not appear to be an increased risk of hemorrhage due to narsoplimab-wuug, but this database is small and patients with other forms of TMA had thrombocytopenia. Hemorrhage will be included in the Adverse Reactions section of the USPI given the high frequency of bleeding events.

7.7.5. Autoimmunity Has Rarely Been Associated With MASP-2 Deficiency; Given That Narsoplimab-wuug Inhibits MASP-2, There Is a Theoretical Risk of Autoimmunity

Issue

Autoimmunity has rarely been associated with MASP-2 deficiency. Given that narsoplimab-wuug inhibits MASP-2, there is a theoretical risk of autoimmunity.

Background

Complement has an important role in autoimmune disease, mostly associated with components of the classical complement pathway. It is not clear if there is an association between deficiencies in components of the lectin pathway and autoimmune disease development. MASP-2 deficiency has been described as a primary immunodeficiency disorder characterized by infections, inflammatory lung disease and autoimmunity ([Bousfiha et al. 2018](#); [Garcia-Laorden et al. 2020](#)). In the novel case of MASP-2 deficiency the patient had autoimmune manifestations but was also noted to have low levels of C1q, C3, and C4 ([Garcia-Laorden et al. 2020](#)). A case report describing a patient with Crohn's disease and MASP-2 deficiency was reported ([Hejazi and Hasosah 2019](#)).

Assessment

The entire ISS dataset was assessed for autoimmune diseases. There were no apparent autoimmune diseases that occurred during time period reviewed for the study. [Table 48](#) describes preferred terms captured under immune system disorders (captured all TEAEs in the AE and post AE evaluation period). Most TEAEs were related to GVHD, which is not unexpected in a post-transplant patient population. Hypersensitivity reactions occurred in three patients and all were reported as unrelated to narsoplimab-wuug. Two patients had an allergic reaction to plasma therapy and one had an allergic reaction to Tazocin.

Table 48. Preferred Terms, Treatment-Emergent Adverse Events, Immune System Disorders, Safety Population, ISS

Preferred Terms	TMA-001 (HSCT Only) N=28 n (%)	TMA-001 (aHUS and TTP Only) N=30 n (%)	HUS-002 N=6 n (%)	GNP-001 (Treatment Only) N=21 n(%)
Immune system disorders (SOC)	13(46%)	2(<1%)	1(<1%)	1(<1%)
Graft vs. host disease	11(39%)	0(0%)	0(0%)	0(0%)
Seasonal allergy	1(<1%)	0(0%)	0(0%)	1(<1%)
Immunodeficiency	1(<1%)	0(0%)	0(0%)	0(0%)
Hypogammaglobinemia	1(<1%)	0(0%)	0(0%)	0(0%)
hypersensitivity	1(<1%)	2(<1%)	0(0%)	0(0%)
Chronic allograft nephropathy	0(0%)	0(0%)	1(<1%)	0(0%)
Renal transplant failure	0(0%)	0(0%)	1(<1%)	0(0%)

Source: clinical reviewer

The following preferred terms were combined:

Graft versus host disease: graft versus host disease in skin, graft versus host disease in liver, graft versus host disease in GI tract, graft versus host disease in eye, graft versus host disease, chronic graft versus host disease in liver, chronic graft versus host disease, acute graft versus host disease

Hypersensitivity: hypersensitivity, drug hypersensitivity

Abbreviations: aHUS, atypical hemolytic anemia; HSCT, hematopoietic stem cell transplant; ISS, integrated safety of summary; SOC, system organ class

Conclusion

While autoimmunity has been described in the setting of MASP-2 deficiency, the association with narsoplimab-wuug is not clear. Autoimmunity due to MASP-2 deficiency has rarely been described in the literature and low levels of MASP-2 occur in healthy individuals as well without autoimmunity. In addition, there were no apparent TEAEs of autoimmune disease development

in clinical trials with narsoplimab-wuug. The current proposed dosing is relatively short and will not be a daily or chronic use medication. However, would recommend long-term follow-up of patients treated with narsoplimab-wuug to monitor for late occurring autoimmunity in context of a postmarketing commitment.

8. Therapeutic Individualization

8.1. Intrinsic Factors

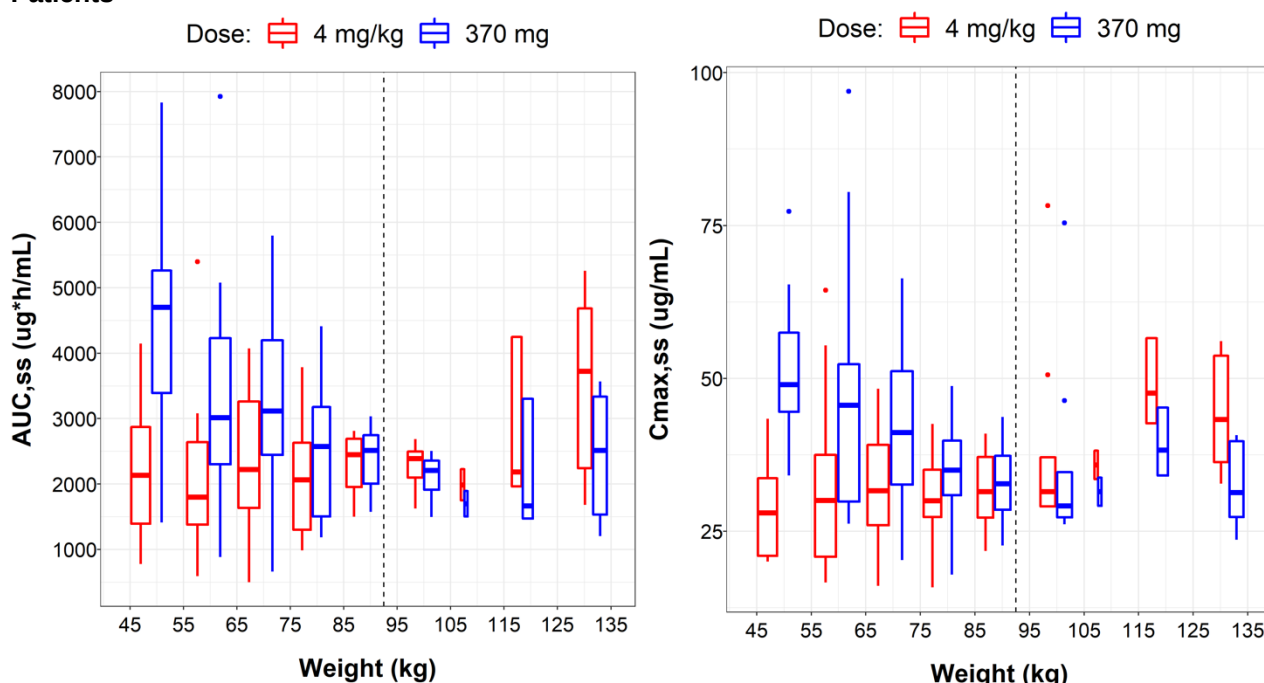
A population PK model was used to assess the effect of covariates on narsoplimab-wuug exposure. The covariates that affect narsoplimab-wuug exposure included patients, body weight, serum albumin, and presence of ADAs. Compared to healthy subjects, patients had a 20% lower maximum elimination rate ($V_{\max}$). Albumin, particularly at high levels, can result in lower narsoplimab-wuug clearance and greater exposure. Presence of ADA increased $V_{\max}$ by 143%, decreased AUC_{ss} by 22%, and decreased $C_{\min,ss}$ by 52% (Section [14.3.2](#)). The effect of weight is discussed in the section [below](#) and in the Pharmacometrics review (Section [14.3](#)).

The covariates that did not affect narsoplimab-wuug exposure included age, race, and sex.

Body Weight

The Applicant's population PK model showed that body weight was a significant covariate for narsoplimab-wuug clearance and, therefore, proposed, dosing of 4 mg/kg narsoplimab-wuug, up to a maximum of 370 mg, administered by intravenous infusion once weekly. The Office of Clinical Pharmacology assessment concluded that the proposed dosing of 4 mg/kg of narsoplimab-wuug capped to 370 mg is appropriate, as it provides comparable steady-state exposure (area under the concentration-time curve over the dosing interval: AUC_{ss} , maximum concentration: $C_{\max}$, and trough concentration: $C_{\min}$) across all body weight ranges ([Figure 27](#), Section [14.3.2](#)).

Figure 11. Predicted Narsoplimab-wuug AUC_{ss} , $C_{max,ss}$, and $C_{min,ss}$ for 4 mg/kg and 370 mg in Patients



Source: FDA Reviewer

The reviewer's PK simulations demonstrated that capping narsoplimab-wuug dosing to 370 mg, particularly in heavier subjects, provides consistent and comparable narsoplimab-wuug exposure (mainly $C_{max,ss}$ and AUC_{ss}) to subjects with body weight below 92.5 kg and receiving 4 mg/kg of narsoplimab-wuug. Conversely, the administration of 4 mg/kg narsoplimab-wuug dose in subjects with body weight above 100 kg or administration of a fixed dose of 370 mg in subjects with body weight below 70 kg is expected to result in relatively higher exposure compared to the studied and current proposed dosing.

8.2. Extrinsic Factors

Plasma Therapy/Plasma Exchange

The objective of plasma therapy (PLT), specifically plasma exchange (PE), in HSCT-TMA patients is to remove thrombogenic and antifibrinolytic molecules and to replenish anticoagulants and profibrinolytics with new plasma. The process removes large molecules such as proteins and monoclonal antibodies from the systemic circulation. (b) (4)

^{(b) (4)} that an additional dose of 2 mg/kg narsoplimab-wuug be administered up to 3 times weekly. However, the Applicant did not provide a justification for the selected supplemental narsoplimab-wuug dose of 2 mg/kg. The effect of PLT on narsoplimab-wuug clearance (CL) and its overall exposure was not investigated in a dedicated clinical study, and the Applicant did not attempt to use a population PK modeling approach to assess the effect of PLT on narsoplimab-wuug exposure or justify the need for the selected supplemental dose of narsoplimab-wuug post-PE.

Five patients received PE during narsoplimab-wuug treatment, and were used to evaluate the effect of PE on narsoplimab-wuug PK. The median duration of PE in these 5 patients was 1.8 h (range: 1.4 h to 2.9 h). Following an information request (see Section 14.3.5), the Applicant's post hoc analysis estimated that PLT increased narsoplimab-wuug CL by 37.1% based upon their population PK modeling and concluded that due to the modest effect size and short duration of PLT, no clinically meaningful effects of PLT on narsoplimab-wuug exposure could be identified

(b) (4). The Office of Clinical Pharmacology's review of the population PK analysis found that PE increased narsoplimab-wuug CL by an average of 47%. However, the estimated effect on narsoplimab-wuug CL could not be precisely estimated, with a 95%CI of the mean effect ranging from 24% to 124%. The difficulty in reliably estimating the effect of PE on CL using the population PK model is most likely related to the lack of informative PK data. There was no PK sampling performed concurrently immediately pre- and post-PE amongst the 5 patients who received PE during narsoplimab-wuug treatment.

The reviewer's PK simulations showed that PE does not seem to have a relevant effect on narsoplimab-wuug PK (see Section 14.3 Pharmacometrics review for more details). However, the population PK modelling was not considered reliable for predicting the effect of plasma therapy on drug exposure. Therefore, the need as well as the strength and frequency of supplemental dosing post-PE could not be reliably evaluated.

The Applicant and the Clinical Pharmacology review team have shown that PE increases narsoplimab-wuug clearance; therefore, supplementation of narsoplimab-wuug at 2 mg/kg following each PE appears to be reasonable. The supplemental dose of 2 mg/kg is supported by safety established in the clinical trials. However, it is unclear if the supplemental dose and dosing regimen is optimal. To identify a precise dose and dosing regimen for narsoplimab-wuug supplementation following PE, the Office of Clinical Pharmacology review team recommends that Applicant conduct a dedicated clinical study to methodically assess the effect of PE on narsoplimab-wuug clearance and to identify a dose and dosing regimen that can replace narsoplimab-wuug that is removed through PE.

8.3. Plans for Pediatric Drug Development

The initial application for approval of narsoplimab-wuug is limited to adults. Pediatric patients were not included in the Phase 2 Study TMA-001. Considering multiple interactions between the complement system and the immune system and the role of complement in some forms of bone remodeling, a juvenile toxicity study in mice was conducted to support future pediatric development. Mice were administered narsoplimab IV twice a week at doses of 0, 50, 150, or 300 mg/kg for 8 injections during the preweaning period (postnatal day 4-28) followed by subcutaneous (SC) once a week for 9 injections during the postweaning period (postnatal day 35-91).

Substantial (>70%) and similar inhibition of the complement lectin pathway was observed at all dose levels and was sustained beyond 28 days after the last dose, verifying that all dose levels tested were pharmacodynamically active.

No treatment-related effects were observed on physical development parameters (vaginal opening and preputial separation), behavioral performance, or bone dimensions. Treatment-related findings included non-adverse increases in neutrophil counts, eosinophilic infiltration in the bone marrow, injection site, and inguinal skin, and moderately elevated IgE plasma levels. These changes showed reversibility and did not affect antibody response to antigen in a T-cell dependent antibody response assessment. The exposure multiple at the NOAEL is 2X MRHD based on estimated AUC_(0-168h).

Table 49. Juvenile Toxicity Safety Margins

Study	Nonclinical Data	NOAEL (mg/kg/dose)	Nonclinical Exposure (µg·hr/mL)	Safety Margins ¹ (Multiples)
Juvenile mouse	- Nonadverse increases in neutrophil counts at all doses corresponded with nonadverse microscopic findings of eosinophilic infiltration in the bone marrow, injection site and inguinal skin. Full resolution at the end of recovery. - ADA response onset occurred after the last dose and it did not interfere with toxicokinetic assessments	300	18,300	2.1

Source: Study Report # 9000601

¹ Exposure multiples were based on population pharmacokinetics analysis where a 4 mg QW clinical dose resulted in systemic exposures of AUC_{0-τ} = 2310.8 µg·hr/mL.

Abbreviations: ADA, antidrug antibody; NOAEL, no observed adverse effect level; QW, once a week

The Applicant received Orphan Drug Designation for hematopoietic stem cell transplant associated thrombotic microangiopathy on October 22, 2018 and thus is exempt from Pediatric Research Equity Act (PREA) requirements.

During the course of the review cycle for this application, the Applicant submitted a proposed pediatric study request to the Division for review. At the time of this review, the proposed pediatric study request was undergoing review.

8.4. Pregnancy and Lactation

Animal Data

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section [13](#).

Table 50. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	Subcutaneous dosing of pregnant female mice had no effect on embryofetal development up to 150 mg/kg at ~3-times the extrapolated AUC_{0-168h} at the MRHD.

Labeling Section	Nonclinical Data
	- Intravenous dosing of pregnant mice led to lower number of live fetuses, decreases in fetal body weights up to 4.8%, and an increase of approximately 2-fold in postimplantation loss and the number of litters with cleft palate malformation occurred in mice at ~22-times the exposure at the MRHD. Potential adverse maternal effects were seen as reduced gestational weight gain. - Subcutaneous dosing of pregnant rabbits had no effect on embryofetal development up to 150 mg/kg or ~8 times the AUC at the MRHD. - Intravenous dosing of pregnant rabbits (150 mg/kg) increased postimplantation loss and reduced fetal body weights up to 8.5% below controls at 91-times the exposure at the MRHD. - In a pre- and post-natal development study in mice dosed IV at 300 mg/kg or SC at 150 mg/kg, transiently reduced maternal body weight gain was observed during gestation. There was no narsoplimab-related adverse effect on growth, sexual maturation, or neurobehavioral or reproductive function in the offspring. - Narsoplimab was present in serum of offspring suggesting maternal transfer in milk during lactation; however, milk levels of narsoplimab were not measured directly.
8.2 Lactation	There are no direct data on the presence of narsoplimab in animal milk
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	- Animal carcinogenicity studies of YARTEMLEA have not been conducted - Narsoplimab has no direct effects on fertility.

(b) (4)

Source: FDA Reviewer

Abbreviations: IV, intravenous(ly); MRHD, maximum recommended human dose; SC, subcutaneous

Details of above information and exposure multiples shown are based on systemic exposures compared between animals and humans. Further details are available in Section [13.1](#).

9. Product Quality

This application will not be approved during this assessment cycle due to clinical only deficiencies. From a product quality perspective, the Office of Product Quality, CDER, does not note any product quality deficiencies that would preclude approval of submission tracking number (STN) BLA 761152 for YARTEMLEA manufactured by Omeros Corp. Because the application will not be approved in this cycle, the noncomplete response issues related to product quality listed below will be communicated to the Applicant in the FDA complete response letter. If manufacturing changes are made before the Applicant submits their responses to the complete response deficiencies, additional assessment may be needed during the next assessment cycle.

Non-complete response issues:

- Provide low endotoxin recovery hold time study summary report and data from two additional lots of narsoplimab-wuug drug product.
- Submit the container closure integrity test (CCIT) method validation study summary report and data. The CCIT method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (*i.e.*, less than or equal to 20 µm) and note that a more sensitive and consistent method for dye detection (*e.g.*, spectrophotometry) is recommended. Perform annual sterility test in lieu of CCIT in the stability program until the CCIT method validation is complete.

Refer to the review memos by the Office of Product Quality, available in Panorama.

9.1. Device or Combination Product Considerations

There are no device or combination product considerations for this application.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The Applicant provided a statement that the study was conducted in accordance with the protocol and ethical principles stated in the Declaration of Helsinki, good clinical practice, and all other applicable national, state, and local laws, rules and regulations. The protocol and amendments were submitted to Independent Ethics Committees and/or Institutional Review Boards for review and written approval.

The Applicant adequately disclosed financial interests/arrangements with clinical investigators for Study TMA-001 protocol. No investigators self-disclosed financial interests. Please see Section [23](#) of the integrated review for financial disclosure discussion.

11. Advisory Committee Summary

An Advisory Committee meeting was not convened to discuss this application.

The Division consulted with two subject matter experts to provide expert opinion. Please see discussion of the subject matter expert interaction with the Agency under Section [6.3.3](#).

III. Appendices

12. Summary of Regulatory History

The following provides a regulatory overview for biologics license application (BLA) 761152, product name OMS721 (also referred to as narsoplimab-wuug). OMS721 is a monoclonal antibody that binds to and blocks mannan-binding lectin-associated serine protease 2, the effector enzyme of the lectin pathway of complement, inhibiting the inflammatory and prothrombotic responses to endothelial injury. The proposed indication is hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). OMS721 is stored as a single dose yellow/brown solution in a vial to be administered as an intravenous injection. Currently, no Food and Drug Administration (FDA)-approved products are indicated for the treatment of HSCT-TMA.

On January 23, 2014, the Agency received the submission for an investigational new drug (IND) application under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IND 120524. Prior to the submission a Type B pre-IND meeting was conducted with Omeros Corporation on January 23, 2014, for OMS721 under PIND 120524. The Applicant obtained Agency advice on the development plans for the investigation of OMS721 for inhibition of complement mediated thrombotic microangiopathy (TMA) under Section 351(a) of the Public Health Service Act. On April 2, 2014, Omeros Corporation was advised that the 30-day, safety review of the application had concluded and that the study may proceed with their proposed clinical investigation for the treatment of chemotherapy induced neutropenia with nonhold comments. On September 8, 2014, an institutional review board waiver was granted under 21 CFR Part 56 for the use of OMS721 for the conduct of Study TMA-001 in Germany.

A type B, end-of-phase 2 meeting was held in person on April 24, 2018, to discuss a Phase 3 program design and the clinical studies to support submission of a BLA for OMS721 in the treatment of HSCT-TMA. The Division stated that the Applicant should provide an explanation for the following:

- Why OMS721 demonstrated little efficacy in patients with thrombotic thrombocytopenia purpura (TTP) or aHUS.
- Why the biweekly or three times a week dosing of OMS721 was given to the compassionate-use patient compared to the weekly dosing used in Study TMA-001.
- Why the volume of distribution of OMS721 (0.071 L/kg) is similar to that of blood volume (~0.08 L/kg). The Division requested the Applicant address if changes in volume status (such as hypervolemia due to therapy interventions) may have an impact on the pharmacokinetic/pharmacodynamic (PK/PD) and/or efficacy of OMS721 in patients with HSCT-TMA.

On April 26, 2018, breakthrough therapy designation was granted for OMS721 for the treatment of patients with HSCT-TMA. Breakthrough therapy designation was followed by a July 31,

2018, Type B – breakthrough therapy meeting. Discussions from this meeting included the following:

- The Division stated that multiple hurdles would need to be overcome using a chart-based historical control and recommended that the Applicant use TMA response rate as primary endpoint in a single-arm trial with duration of response as a secondary endpoint. The Applicant noted the challenges with a TMA response rate endpoint due to confounding effects of transplantation and other concomitant medical conditions.
- The Applicant discussed their plan for conducting a historical control using chart review. The Agency expressed several concerns, to include: ensuring matching populations, contemporaneous review of charts and study patients, data integrity, time involved, endpoint definition, and various aspects of the propensity score analysis.
- The Agency stated that they could not agree with the Applicant's proposal to use a chart based historical control until further review and internal discussion. The Division recommended that the Applicant submit a detailed proposal of the chart based historical control for the Agency to review and provide feedback.

On January 29, 2019, a Type B meeting was held. Discussion at this meeting included the following:

- The Division stated that the decision on whether to accept a proposed surrogate endpoint is based on the scientific support for that endpoint and that confirmatory trials are usually ongoing at the time of an application submission.
- The Division recommended that the Applicant assemble the data to define a responder endpoint definition for both surrogate and clinical benefit endpoints.
- The Division recommended that the Applicant include the scientific rationale for endpoints selected. Additionally, the Applicant should prespecify the endpoints to reduce or minimize potential bias and include discussions of why some response outcomes are excluded from responder endpoint definition.

On March 2, 2019, a Type A meeting was held to discuss response-based clinical endpoints for a registrational trial. Discussion point(s) for this meeting included:

- The Agency expressed concerns that the magnitude of change in platelet count based on their current proposal may not be meaningful.
- The Agency recommended that the Applicant prespecify an endpoint definition for platelets based on proportion of patients who achieve a prespecified threshold.
- The Agency also recommended that the Applicant review data with their drug to determine appropriate threshold for a proposal.

On March 12, 2019, preliminary comments were issued for a type B, chemistry, manufacturing, and controls (CMC) meeting. The Meeting request was then withdrawn by the Applicant on March 15, 2019, citing acknowledgment and understanding of The Division's preliminary comments.

BLA 761152
Narsoplimab-wuug

On July 18, 2019, a type B pre-BLA CMC meeting was held to discuss the CMC process validation strategy for submission in the narsoplimab-wuug.

On September 4, 2019, a request for rolling submission and review of portions of planned BLA for OMS721 was granted.

A pre-BLA clinical meeting was scheduled for November 21, 2019, to discuss and reach agreement on the analyses and overall package for the administrative, nonclinical, and clinical information to be included in the BLA for OMS721. Preliminary comments for this meeting were issued on November 8, 2019. The Applicant withdrew the meeting request on November 20, 2019, due to internal scheduling conflicts.

A Type A guidance meeting was held on January 6, 2020, to discuss the preliminary comments related to the pre-BLA meeting briefing package and to review preliminary efficacy results and dose justification.

On January 31, 2020, the name Yartemlea was conditionally approved for narsoplimab-wuug, with further review being requested under the officially submitted BLA.

A type B, pre-BLA CMC meeting was held on February 19, 2020, to discuss the CMC information to be included in the BLA for narsoplimab-wuug.

A complete BLA was received on November 17, 2020, under section 351(a) of the Public Health Service Act for narsoplimab-wuug solution for injection. BLA 761152 was assigned to the application. No filling issues were identified, and the application was filed on January 16, 2021. The review classification for BLA 761152 was priority, therefore the established user fee goal date was July 17, 2021. The Applicant submitted a major amendment on April 23, 2021, requiring an extended timeline to assess the new information. The updated user fee goal date was extended to October 17, 2021.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

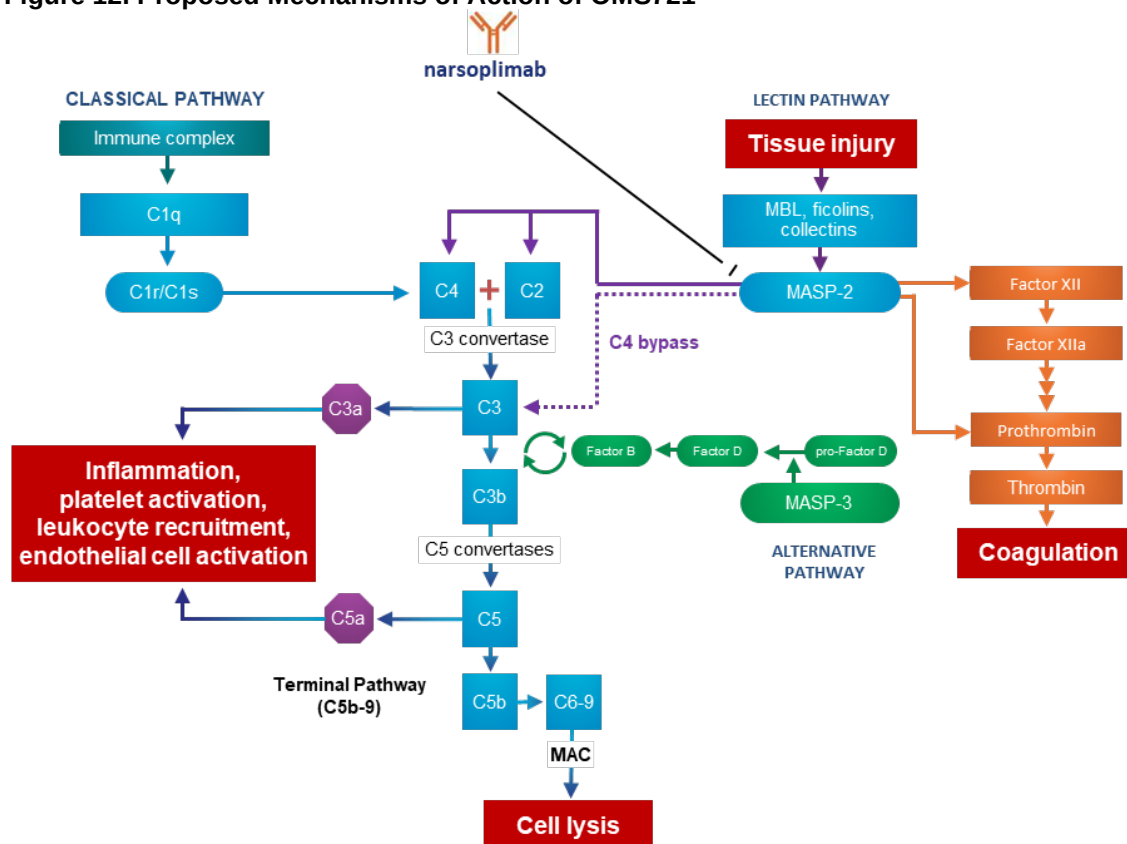
13.1.1. Pharmacology

Primary Pharmacology

- 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, see [Figure 12](#).

- MASP-2 also reportedly contributes to cleavage of prothrombin to thrombin independent of downstream complement activation ([Krarup et al. 2007](#)); see orange arrows/boxes, [Figure 12](#). Narsoplimab was not tested against this reported MASP-2 activity.
- In vitro binding studies using plasmon resonance and enzyme-linked immunosorbent assay (ELISA) showed high affinity binding of OMS721 with human MASP-2 (62-73pM). Intact bivalent OMS721 demonstrated 100-fold greater binding affinity compared to a monovalent Fab indicating that functional bivalency is an important contributor to high-affinity binding, see [Table 51](#).
- OMS721 exhibited a selectivity ratio of >8,000-fold for MASP-2 relative to other serine proteases of the complement system (C1r, C1s, MASP-1, and MASP-3).
- In vitro functional assays demonstrated that OMS721 inhibited human lectin pathway-dependent C3, C4 (IC₅₀ 2.5nM), and membrane attack complex (MAC) (IC₅₀ 1nM) activation without affecting the classical and alternative pathway-dependent MAC activation at concentrations up to 100nM.

Figure 12. Proposed Mechanisms of Action of OMS721



Source: Excerpted from the Applicant's submission

Table 51. Bivalent OMS721 mAb Displays Higher Affinity Than OMS721-Related Fab

	Surface Plasmon Resonance ^{a,b}			ELISA ^{c,d}
	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)	K_D (nM)
Fab	$2.55 \pm 0.81 \times 10^6$	$2.57 \pm 0.36 \times 10^{-2}$	10.3 ± 2.8	14.9
OMS721	$3.46 \pm 1.1 \times 10^6$	$2.47 \pm 0.55 \times 10^{-4}$	0.073 ± 0.007	0.062 ± 0.023

Source: See below

^a Fab mean $\pm$ standard error, n=4 [Source: study TR13-020]

^b OMS721 mean $\pm$ standard error, n=3 [Source: study TR13-043]

^c Fab mean of 2 experiments [Source: study TR13-043]

^d OMS721 mean $\pm$ standard deviation, n=12 [Source: study TR13-043]

Abbreviations: ELISA, enzyme-linked immunosorbent assay; Fab, antigen-binding fragment; k_a , association rate constant; k_d , dissociation rate constant; K_D , dissociation equilibrium constant; MASP-2, mannan-binding lectin-associated serine protease 2

- OMS721 displayed functional activity in mouse, rabbit, and cynomolgus monkey, with potencies 3.8, 2.7 and 10-fold less than human. No functional activity was observed in rats. Functional potency was determined from ELISA and flow cytometric measurement of C4 and C3 activation in serum from each species tested against mannan immobilized on a substrate.
- An ex-vivo and an in vivo pharmacodynamic study showed that narsoplimab reduced platelet/endothelial adherence, and delayed the initiation of thrombus formation and time to complete vessel occlusion providing evidence of its mode of action in conditions with a microvascular thrombotic component, see Section 5.1. Inhibition of the lectin pathway by narsoplimab is evident from the reduction in C5b-9 deposition on endothelial cells; however, other complement and coagulation pathways remain active which ultimately led to similar levels of microvascular occlusion in the murine TMA study regardless of treatment with narsoplimab.
- The minimum pharmacodynamically active dose of OMS721 in mice and monkeys was 5 mg/kg and 0.5 mg/kg, intravenously (IV), respectively. There was a consistent correlation in both species between OMS721 serum concentrations and percent inhibition of lectin pathway activity. Based on PK-PD response modelling, an in vivo EC₅₀ value for lectin pathway inhibition in cynomolgus monkey was estimated to be approximately 7 µg/mL.

Secondary Pharmacology

- A mouse tail bleeding assay was conducted to evaluate whether MASP-2 inhibition affects hemostasis. A recombinant mouse monoclonal antibody, AbD04211, which binds to mouse MASP-2 and blocks the lectin pathway of complement in mice, was used in this study. MASP-2 blockade did not significantly affect the bleeding time in mice assessed after a standard cut applied to the tail. This result suggests that any contribution of MASP-2 to cleavage of prothrombin, as reported in the literature, is marginal and insufficient to alter the hemostatic or thrombotic responses by this mechanism.

Safety Pharmacology

- Cardiovascular and respiratory safety pharmacology assessment in monkeys and CNS safety assessments in mice were incorporated into 28-day repeat dose toxicology studies.

- OMS712 showed no effect on cardiovascular and respiratory parameters in cynomolgus monkeys or on neurobehavioral parameters in mice.

13.1.2. Toxicology

Study Number/ Title: 1235-013: A 28-Day Subcutaneous and Intravenous Toxicity Study in Mice With a 56-Day Recovery Period

10, 50, 150 mg/kg/week subcutaneous (SC), 10 mg/kg/week IV

Exposure margins

0.8, 2 and 4-times (SC) and 1-times (IV) the clinical dose of 4 mg/kg/week IV, based on AUC

Key study findings

- Injection site reactions consisting of minimal to mild subacute/chronic inflammation were observed in all groups, including control, but were of greater severity in the dosed groups.
- The no observed adverse effect level (NOAEL) with IV route is 10 mg/kg given once weekly for 4 weeks.
- The NOAEL with SC route is conservatively 50 mg/kg given once weekly for 4 weeks, based on potential adverse hepatic effects:
 - Increases in AST (2-fold) and ALT (2.6-fold) in SC treated females (at 150 mg/kg) relative to controls at the end of treatment period (largely a result of changes observed in female animal no. 4509)
 - Liver histopathology (necrosis) in animals receiving 150 mg/kg SC (although liver necrosis was also observed in 2 control females).

Table 52. Methods, 28-Day Mice Study (1235-013)

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	10, 50, 150 mg/kg (SC); 10 mg/kg (IV) Once/week for 4 weeks
Route of administration:	SC and IV
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, pH 5.0±0.2
Species/strain:	CD-1 mice
Number/sex/group:	10/sex/group (main); 10/sex/group (recovery)
Age:	5 weeks old
Satellite groups/unique design:	TK group (39/sex in control and 58/sex in TK group)
Deviation from study protocol affecting interpretation of results:	None

Source: Study 1235-013

Abbreviations: GLP, good laboratory practice; IV, intravenous(ly); SC, subcutaneous; TK, toxicokinetic

Table 53. Observations and Results, 28-Day Mice Study (1235-013)

Parameters	Major Findings
Mortality	One (incidental)
Clinical signs	Scabbed areas and red discoloration of the skin was observed at the subcutaneous injection sites on the dorsal surface.
Body weights	No effects on body weights but food consumption was decreased in animals receiving OMS721 via IV route with some recovery during the 8-week recovery period.
Ophthalmoscopy	No effect
Functional observational battery	No effect
Hematology	No effect
Clinical chemistry	At termination and recovery collections, some females in all OMS721 treatment groups had mild to moderate elevations in AST (up to +9.6-fold in one HD female animal 4509) and occasionally ALT (up to +15.0-fold in one HD female animal 4509), relative to control means. Similar changes were also noted in occasional males receiving 10 mg/kg/IV at the recovery collection (AST up to +2.8-fold; ALT up to +3.6-fold). Increases in ALT and AST in animal 4509 correlated with microscopic changes in the liver (minimal hepatocellular necrosis). The increase in liver enzyme seemed to be dose-related at least in the females.
Urinalysis	No effect
Gross pathology	No effect
Organ weights	No effect
Histopathology	<u>Injection site</u> Minimal to mild subacute/chronic inflammation at injection sites were observed in all groups including control but increased incidence and severity were noted in OMS721 treated groups. By the end of recovery period, injection site findings were similar in incidence and severity across all groups including controls.
	<u>Liver</u> Minimal liver necrosis was observed in 2 control females and with a higher incidence of 3 HD males and 2 HD females. No liver findings were observed in recovery groups.
Toxicokinetics	TK was evaluated on Days 1 and 22 with blood samples collected at predose, 0.083, 0.5, 2, 6, 24, 72, and 168 hours after dosing. Exposures to OMS721 (C_{max} and $AUC_{0-168 \text{ hour}}$) increased with increasing SC dose (less than dose proportional, especially at mid to high dose increase). At 10 mg/kg, systemic exposure was greater following IV bolus as compared to SC administration. Systemic exposure (C_{max} and $AUC_{0-168 \text{ hour}}$) exhibited accumulation following repeated SC and IV administration (mean accumulation ratios ranged from 1.26 to 2.03). A single control animal (male 6031) had a quantifiable OMS721 concentration of 682 ng/mL on Day 22 (72 hour), which did not affect interpretation of the results. Terminal half-lives after SC and IV administration ranged from 216 to 321 hours.

Parameters	Major Findings

Table 54. Toxicokinetics, 28-Day Mice Study

Dose (mg/kg)	C _{max} (µg/mL)		C _{max} (µg/mL)		AUC _(0-168hr) µg·h/mL		AUC _(0-168hr) µg·h/mL	
	Day 1		Day 22		Day 1		Day 22	
	M	F	M	F	M	F	M	F
10 SC	10	7	17.1	21	1290	709	2440	1410
50 SC	24.6	31.7	44	30.7	2950	4060	4820	4020
150 SC	50.9	30.5	108	121	5150	3840	10500	7740
10 IV	18.7	25	31.5	26.5	1490	1890	2790	2340

Immunogenicity	Blood (serum) was collected on Day 1 (168 hours following the first dose), Day 8 (168 hours following the second dose), Day 22 (predose), and on Days 49 (648 hours), and 84 (1488 hours after fourth dose). Of the 532 samples collected, 140 were screened for the presence of antidrug antibodies (ADA). 63 samples screened positive, of which 26 samples were confirmed to be positive for ADA (including 3 samples from the control group).
Pharmacodynamic activity	Samples were collected from designated animals on Days 1 (0, 2, and 24 hours post-dose), 22 (2 and 24 hours post-dose), 49 (648 hours) and 84 (1488 hours after the fourth dose). The percent MASP-2 inhibition was generally low (if detectable) in control animals, and in 10 mg/kg SC animals, on Day 1. By Day 22 most of the samples from animals treated with 150 mg/kg SC and 10 mg/kg IV exhibited MASP-2 inhibition on the order of ≥90%. The MASP-2 inhibition was considerably decreased in the recovery samples, but the effect was not entirely absent.

Source: Study 1235-013

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HD, high dose; IV, intravenous(ly); MASP-2, mannan-binding lectin-associated serine protease 2; SC, subcutaneous; TK, toxicokinetic

Study Number/ Title: 1235-012: A 28-Day Subcutaneous and Intravenous Toxicity Study in Cynomolgus Monkeys with a 56-Day Recovery Period

10, 50, 150 SC mg/kg/week SC, 10 mg/kg/week IV

Exposure margins

4, 12 and 18-times (SC) and 7-times (IV) the clinical dose of 4 mg/kg/week IV, based on AUC

Key study findings

- Test article-related findings were seen at the injection sites at all SC doses in females in a nondose-dependent manner. One female showed mild edema and minimal adventitial necrosis of the vessel at the IV injection site.
- Minimal increases in ALT and AST levels at 150 mg/kg SC without microscopic correlates in the liver.
- The NOAEL in monkeys is 10 mg/kg given IV and 150 mg/kg given SC once weekly for 4 weeks.

- One high dose (150 mg/kg) female died within 4 hours of ketamine sedation on Day 27 due to lung inflammation, likely a secondary effect to ketamine sedation (also, no lung inflammation was observed in the subsequent 26-week study at doses up to 300 mg/kg).

Table 55. Methods, 28-Day Monkey Study (1235-012)

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	10, 50, 150 mg/kg (SC); 10 mg/kg (IV) Once/week for 4 weeks
Route of administration:	SC and IV
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, pH 5.0±0.2
Species/strain:	Cynomolgus monkey
Number/sex/group:	3/sex/group (main); 2/sex/group (recovery)
Age:	2-4 years old
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Source: Study 1235-012

Abbreviations: GLP, good laboratory practice; IV, intravenous(ly); SC, subcutaneous

Table 56. Observations and Results, 28-Day Monkey Study (1235-012)

Parameters	Major Findings
Mortality	One high dose female given 150 mg/kg SC died on Day 27 of lung inflammation (possibly secondary to ketamine administration prior to terminal physical exam).
Clinical signs	Black discoloration of the injection site was observed in a single male monkey in the IV (10 mg/kg) treatment group. Sporadic instances of skin redness around the injection sites were observed, mainly in animals treated with OMS721.
Body weights	No effect
Ophthalmoscopy	No effect
ECG	No effect
Respiration rate	No effect
Hematology	No effect
Clinical chemistry	Minimal (<2-fold) increases in ALT and AST levels (relative to pretest values) were observed in some animals given 150 mg/kg SC; however, the ALT and AST values were not notably different than concurrent controls.
Urinalysis	No effect
Gross pathology	No effect
Organ weights	No effect
Histopathology Adequate battery: Yes Peer reviewed: Yes	Test article-related findings were seen at the injection sites at the end of treatment at all SC doses in females in a nondose-dependent manner. Mild edema and minimal adventitial necrosis of the vessel at the site of the first IV bolus injection was observed in one female. At recovery, there was no clear dosage-dependence or test article related pattern to the injection site findings.

Parameters	Major Findings
Toxicokinetics	TK was evaluated on Days 1 and 22 with samples collected at pre dose, 0.083, 0.5, 2, 6, 24, 72, and 168 hours after dosing, and on Days 35, 49, 63, and 84. Exposures to OMS721 (C_{max} and $AUC_{0-168 \text{ hour}}$) were similar in males and females on Days 1 and 22. The increases in exposures to SC OMS721 (C_{max} and $AUC_{0-168hr}$) were slightly less than dose proportional to increases in dose. Systemic exposure (C_{max} and $AUC_{0-168hr}$) exhibited minimal accumulation following repeated SC (mean accumulation ratios ranged from 1.54 to 1.96) At 10 mg/kg, systemic exposure was greater following IV slow bolus as compared to SC administration. Mean bioavailability was ~42.6 and 54.4% on days 1 and 22, respectively. Mean $t_{1/2}$ calculated for recovery animals following SC and for all animals following IV bolus of OMS721 ranged from 120 to 202 hours. All control group sample results were below the lower limit of quantification (LLOQ, <391 ng/mL).

Table 57. Toxicokinetics, 28-Day Monkey Study

Dose (mg/kg)	C_{max} (µg/mL) Day 1		C_{max} (µg/mL) Day 22		$AUC_{(0-168hr)}$ µg·h/mL Day 1		$AUC_{(0-168hr)}$ µg·h/mL Day 22	
	M	F	M	F	M	F	M	F
10 SC	32.7	22.8	57.9	48.2	5130	3380	9120	7650
50 SC	92.3	96	161	197	14000	13900	24900	30200
150 SC	192	180	291	325	27300	24700	42500	40800
10 IV	131	108	120	210	10200	9740	12300	18400

Immunogenicity	Blood (serum) was collected on Day 8 (336 hours following the first dose), Day 22 (168 hours post-dose), and on Days 35, 49, 63, and 84. Antidrug antibodies were observed sporadically in only a few animals (5 of 40 OMS721 treated monkeys) across dose groups. In the IV dose group (10 mg/kg/week), ADAs were detected in 3 of 10 monkeys, but when present corresponded with decreased serum OMS721 concentration. In the SC groups, there was no clear effect of ADA status on serum OMS721 concentration.
Pharmacodynamic activity	Samples were collected from designated animals on Days 1 and 22 (at pretest, 0.5 and 24 hours post-dose) and on Days 49 and 77 during the recovery period. Percent inhibition of serum lectin pathway activity (surrogate for MASP-2 activity) was correlated to OMS721 serum concentrations. Maximal inhibition was evident in samples taken from animals given 150 mg/kg SC and 10 mg/kg IV.

Source: Study 1235-012

Abbreviations: ADA, antidrug antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; IV, intravenous(ly); SC, subcutaneous; TK, toxicokinetic

Study Number/ Title: 8299929/A Repeat-Dose Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Administered OMS721 by Subcutaneous and/or Intravenous Injection Once Weekly for 26 Weeks with a 10-Week Recovery

50, 150 and 300 mg/kg/week SC, 150 mg/kg/week IV

Exposure margins

18, 26 and 38-times (SC) and 43-times (IV) the clinical dose of 4 mg/kg/week IV, based on AUC

Key study findings

- One female in 150 mg/kg/week IV group showed pronounced decreases in total protein and albumin at the end of the treatment period which became more severe during the recovery period. This animal presented clinical pathology changes consistent with inflammation (mildly increased white blood cell and absolute neutrophil counts) at the end of the recovery period.
- The NOAEL was considered to be 300 mg/kg/week SC due to the reversibility of serum protein changes and injection site inflammatory changes at this dose.

Table 58. Methods, 26-Week Monkey Study (8299929)

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	50, 150, 300 mg/kg (SC); 150 mg/kg (IV) Once/week for 26 weeks
Route of administration:	SC and IV
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, and 0.01% Tween 80 in sterile water for injection, USP
Species/strain:	Cynomolgus monkey
Number/sex/group:	3/sex/group (main); 2/sex/group (recovery)
Age:	27 to 41 months old
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Source: Study 8299929

Abbreviations: GLP, good laboratory practice; IV, intravenous(ly); SC, subcutaneous

Table 59. Observations and Results, 26-Week Monkey Study (8299929)

Parameters	Major Findings
Mortality	None
Clinical signs	No effect
Body weights	No effect
Ophthalmoscopy	No effect
ECG	No effect
Respiration rate	No effect
Hematology	No effect

Parameters	Major Findings
Clinical chemistry	A nondose dependent minimal decrease was observed in total protein (-2.7 to -9.5% compared with control) and albumin (-4.4 to -11% compared with control) on Days 91 and 183 of the dosing phase in females at >50 mg/kg IV or SC. 1 female (I03200) in 150 mg/kg IV group showed the most pronounced decreases in total protein (-7 to -9% compared to predose) and albumin (-16 to -28%) on Days 91 and 183 of the dosing phase which became more severe during the recovery phase (-28% total protein and -53% albumin). This female also showed increased WBC and absolute neutrophil counts (3-fold of predose values) at the end of the recovery phase. However, microscopic evidence of inflammation was not observed in the tissues. All other animals showed reversibility in serum protein changes at the end of the recovery phase.
Urinalysis	No effect
Gross pathology	No effect
Organ weights	No effect
Histopathology Adequate battery: Yes Peer reviewed: Yes	OMS721-related minimal to slight mononuclear cell infiltrates were observed at SC injection sites of most animals at all doses. Injection sites reaction showed no dose-response relationship to incidence or severity and showed reversibility at the end of recovery period. No OMS721-related microscopic findings were seen in animals given 150 mg/kg IV.
Toxicokinetics	TK was evaluated on Days 1, 85 and 176 with samples collected at pre dose, 0.083, 0.5, 2, 6, 24, 72, and 168 hours post-dose. Additionally, samples were collected from all dose groups 10 minutes predose and 72 hours post-dose on Days 29, 57, 120 and 148 and during the recovery phase on Days 28, 56 and 71. No remarkable sex differences in OMD721 exposures were observed. OMS721 exposure increased less than dose proportionally with SC route. Accumulation with SC route ranged from 1.2 to 4.85. Accumulation was minimal with IV route (0.9-1.8). Mean half-life values ranged from 191-367 hours with SC and 208-300 hours with IV route on Day 176. Mean bioavailability was ~40, 90 and 60% on days 1, 85 and 176, respectively.

Parameters	Major Findings							
Table 60. Toxicokinetics, 26-Week Monkey Study								
Dose (mg/kg)	C _{max} (µg/mL)		C _{max} (µg/mL)		AUC _(0-168hr) µg·h/mL		AUC _(0-168hr) µg·h/mL	
	Day 1		Day 176		Day 1		Day 176	
	M	F	M	F	M	F	M	F
50 SC	98.6	89.8	294	297	14100	13300	39700	41600
150 SC	201	167	446	446	26800	23400	62800	58500
300 SC	399	404	730	488	56100	51600	105000	68800
150 IV	2280	2360	3260	2920	62200	58700	109000	89900
Immunogenicity	Blood samples were collected on Days 10 and 17 of the predose phase; predose on Days 29, 57, 85, 120, 148 and 176 of the dosing phase; on Days 28, 56, and Day 71 of the recovery phase. Antidrug antibodies were observed in only 2 of 40 OMS721 treated monkeys. There was no effect of ADA status on serum OMS721 concentration.							
Pharmacodynamic activity	Blood samples were collected on Days 10 and 17 of the predose phase; 24 hours post-dose on Day 1; and predose and 72 hours post-dose on Days 29, 57, 85, 120, 148 and 176 of the dosing phase; on Days 28, 56, and Day 71 of the recovery phase. Percent inhibition of serum lectin pathway activity (surrogate for MASP-2 activity) correlated to OMS721 serum concentrations at all doses. There was no effect of ADA status on OMS721 PD activity.							

Source: Study 8299929

Abbreviations: ADA, antidrug antibody; ECG, electrocardiogram; IV, intravenous(ly); MASP, mannan-binding lectin-associated serine protease; PD, pharmacodynamic; SC, subcutaneous; WBC, white blood cell

Individual Reviews of Studies Submitted to the NDA

Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study Number/Title: 20050868 / NARSOPLIMAB: A Fertility and General Reproduction Toxicity Study by Subcutaneous and Intravenous Injection in Mice

GLP compliance: Yes

Key study findings:

- Body weight gain was 71% lower compared to controls during the overall premating period in 300 mg/kg (IV) females.
- Significant increase in percent abnormal, detached head and no-head sperm parameters occurred in 300 mg/kg (SC/IV) males at 5.4-times the exposure at the MRHD with no direct effects on fertility. MASP-2 is not known to be expressed in testicular tissue ([Atlas](#)).

- Reproductive NOAEL of OMS721 was 300 mg/kg SC for male and female mice at ~7- and ~12-times, respectively, the exposure at the MRHD, based on the lack of a functional effect on fertility.
- Inhibition of the lectin pathway occurred at all doses through the end of the study.

Table 61. Methods, Fertility and Early Embryonic Development (FEED) Study in Mice

Parameter	Method Details
Dose and frequency of dosing:	SC: 0, 50, 150 or 300 mg/kg/dose; IV: 0 or 300 mg/kg/dose Males: weekly 28 days before cohabitation through Study Day (SD) 57 and euthanized on SD 57 through 60 Females: weekly 15 days before cohabitation through cohabitation and after mating confirmation on gestation day (GD) 0 through 13
Route of administration:	SC or IV
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, and 0.01% (v/v) Tween® 80 in sterile water for injection, USP, pH 5.0
Species/strain:	Mouse / Crl:CD1(ICR)
Number/sex/group:	25/sex/group
Satellite groups:	TK: 8/sex control, 40/sex/drug groups; PD and ADA assessments
Study design:	Standard FEED study design based on ICH S5(R3) included PD and ADA assessments
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Study Report # 20050868

Abbreviations: ADA, antidrug antibody; ICH, International Council for Harmonisation; IV, intravenous(ly); PD, pharmacodynamic; SC, subcutaneous; TK, toxicokinetic

Table 62. Observations and Results, Fertility and Early Embryonic Development (FEED) Study in Mice

Parameters	Major Findings
Mortality	No narsoplimab-related mortality occurred in the study.
Clinical signs	Piloerection was observed in single occasions in 3/25 females receiving 300 mg/kg IV on SD 15; one of those female mice also presented ptosis (dropping eyelid) on SD 1.
Body weights	<u>Males:</u> Mean body weight gains for Days 1 through 57 compared to control males were +13, +13, +23, and -6% in the LD, MD, and HD (SC) and in the HD (IV), respectively. <u>Females:</u> <u>Days 1 to 15, pre mating period:</u> Mean body weight gains during the overall pre mating period interval of SD 1 through 15 compared to control females were -29, +43, +57, and -71% in the LD, MD, and HD (SC) and in the HD (IV), respectively. <u>GD 0 through GD 13:</u> Mean maternal body weight gains during GD 0 through 13 compared to controls were +2, -4, -1, and +4% in the LD, MD, and HD (SC) and in the HD (IV), respectively.
Sperm evaluations (motility, density, and morphology)	The mean numbers of normal sperm were reduced or significantly reduced ($\downarrow$ 1.9%, $\downarrow$ 4.6%) and the mean percentages of abnormal sperm ($\uparrow$ 47%, $\uparrow$ 77%) and mean numbers of sperm with detached heads ($\uparrow$ 57%, $\uparrow$ 84%) and no heads ($\uparrow$ 47%, $\uparrow$ 76%) were increased or significantly increased ($p \leq 0.05$ or $p \leq 0.01$) compared to controls. Except for the mean number of sperm with no heads at 300 mg/kg SC, these values were also outside the range of historical control data for the Testing Facility.

Table 63. Narsoplimab-Related Effects on Sperm Evaluation Parameters in Mice (Excerpted From Submission)

Morphology Parameters	0 mg/kg (SC/IV)	50 mg/kg (SC)	150 mg/kg (SC)	300 mg/kg (SC)	300 mg/kg (IV)	Historical Control Range
Normal	181.7	187.2	181.3	178.3	173.3*	178.7-200.2
Percent Abnormal	7.5	6.4	9.3	11.0	13.3**	4.0-10.6
Detached Head	9.0	9.6	12.0	14.1	16.6*	3.9-6.6
No Head	5.3	3.0	6.5	7.8	9.3*	4.2-9.0
Broken Flagellum	0.4	0.2	0.2	0.2	0.7	0.0-0.6

* - Significant at $p \leq 0.05$; ** - Significant at $p \leq 0.01$

Bold - Data shown in bold indicates test article-related effect.

Overall, the increase in mean number of sperm with detached head was minimal at the LD SC and dose-related at the MD and HD and therefore, it is considered narsoplimab-related.

Estrous cycling, mating and fertility	No narsoplimab-related effects on estrous cycling in females at any dose level. There were no narsoplimab-related effects on days of cohabitation before mating was confirmed, mating index, or fertility index.
Pregnancy parameters (ovarian, uterine, litter observations)	Pregnancy was confirmed in 21, 24, 23, 24, and 21 females in the control, LD, MD and HD (SC) and in the HD (IV), respectively. No narsoplimab-related effects on any ovarian or uterine parameters (litter means for corpora lutea, implantations, percent preimplantation loss, viable and nonviable embryos, and percent postimplantation loss) at any dose level and no placenta abnormalities detected.
Necropsy findings	A single 300 mg/kg IV female presented a tan area in the liver left lateral lobe and caudate lobe and a large spleen. The relation of these findings to narsoplimab was unclear based on a single occurrence (1/24 pregnant females).
Toxicokinetics	Systemic exposure to OMS721 following SC administration generally increased with increasing dose in a dose proportional manner, except for males between 50

Parameters	Major Findings
	and 150 mg/kg SC and between 50 and 300 mg/kg SC on SD 57, where exposure was less than dose proportional.
	Following repeated dosing, accumulation was observed for males following both routes of administration. For females, accumulation was observed at 50 mg/kg SC and at 300 mg/kg IV.
	Exposure was similar among genders and it was higher for both sexes after IV compared to the SC route on all occasions. The absolute bioavailability was similar between males and females and ranged from 47.1% to 68.3% for AUC _(0-t) .

Table 64. Summary of Narsoplimab TK Parameters in Mice During the FEED Study (Excerpted From Submission)

Route	Sex	Dose (mg/kg)	Day	C ₀ (µg/mL)	T _{max} (hr)	C _{max} (µg/mL)	AUC ₍₀₋₇₂₎ (hr*µg/mL)	AUC ₍₀₋₁₆₈₎ (hr*µg/mL)	RAUC ₇₂ ^a	RAUC ₁₆₈ ^b
SC	Male	50	1	-	72	32.9	1350	3890	-	-
			57	-	24	84.6	5600	12800	-	3.30
		150	1	-	2	124	5100	9900	-	-
			57	-	24	143	9300	19800	-	2.00
		300	1	-	24	114	6690	14300	-	-
			57	-	24	207	13500	28000	-	1.97
	Female	50	1	-	168	30	603	3080	-	-
			DG 0	-	73.4	52.1	3390	NC	5.62	-
		150	1	-	72	102	5550	12100	-	-
			DG 0	-	24	123	7720	NC	1.39	-
		300	1	-	24	223	10200	16800	-	-
			DG 0	-	24	280	14600	NC	1.43	-
IV	Male	300	1	1030	2	877	18900	26000	-	-
			57	2240	2	1820	34600	47400	-	1.82
	Female	300	1	995	2	840	17900	24600	-	-
			DG 0	2050	2	1680	31200	34100	1.74	-

^aRAUC₇₂= DG 0 AUC₍₀₋₇₂₎/ Day 1 AUC₍₀₋₇₂₎

^bRAUC₁₆₈= Day 57 AUC₍₀₋₁₆₈₎/ Day 1 AUC₍₀₋₁₆₈₎

SC = Subcutaneous; IV = Intravenous (bolus); - = Not applicable; NC = Not Calculated

Antidrug antibody assessments	The incidence of confirmed positive samples was higher in females than males receiving SC doses which could be, in part, explained to the high serum concentrations of narsoplimab observed in male mice, which may have interfered with detection of ADA. ADA generally was associated with lower OMS721 serum concentrations compared to dose-matched mice.

Table 65. Anti-Narsoplimab Antibody Assessment, Mice FEED Study

ADA Results	OMS721 (mg/kg)									
	SC								IV	
	0		50		150		300		300	
Gender	M	F	M	F	M	F	M	F	M	F
No. of animals positive	3	1	2	9	1	10	0	9	0	4
% positive	9.4	3.1	5.1	23.1	2.5	26.3	0	22.5	0	11.1
Titers	50 to 12800		100 to 3200		50 to 102400		50 to 12800		50 to 12800	

Parameters	Major Findings
Pharmacodynamic activity – inhibition of the lectin pathway	Narsoplimab–related inhibition occurred at all time points and lasted through the end of the study.

Table 66. Narsoplimab-Related C4 Inhibition (%) in Mice FEED Study

		OMS721 (mg/kg)							
		SC						IV	
Time		0		50		150		300	
Gender		M	F	M	F	M	F	M	F
SD 1									
0				46	4	-19	7	34	-3
2				76	37	78	80	73	68
24	-5	35		40	53	93	31	91	88
72				75	83	51	83	73	87
168				39	61	88	75	85	77
SD 57									
0				51	62	87	59	82	81
2				69	63	92	67	96	90
24	15	-24		97	44	89	85	94	95
72				83	86	82	93	86	80
168				65	96	47	79	82	60

Source: Study Report # 20050868

Abbreviations: ADA, antidrug antibody; FEED, fertility and early embryonic development; GD, gestation day; HD, high dose; IV, intravenous(ly); LD, low dose; MD, mid dose; SC, subcutaneous; SD, study day; TK, toxicokinetic

Embryo Fetal Development

Study Number/Title: 20050865 / Narsoplimab: An Embryo-Fetal Development Study by Subcutaneous and Intravenous Injection in Pregnant Mice

GLP compliance: Yes

Reviewer's Comment

Subcutaneous administration provided the more relevant data as it utilized the clinical route of administration and achieved a modest ~3-fold multiple of clinical AUC exposure. The intravenous route led to maternal and fetal toxicity associated with a very high C_{max} and AUC relative to clinical exposure and to mice from SC dosing.

Key study findings:

Subcutaneous administration:

- There were no clear drug-related adverse findings in dams or fetuses with subcutaneous administration.
- The maternal and fetal NOAEL at 300 mg/kg SC provided ~3-times the exposure at the MRHD, narsoplimab based on extrapolated AUC_{0-168h}.

Intravenous administration

- Lower gestational weight gain and a single early decedent (gestation day (GD) 15) found with a litter of 13 dead fetuses suggests maternal toxicity was present at the 300 mg/kg IV dose (~22-times AUC and ~150-times C_{max} relative to MRHD)
- Embryofetal loss is indicated by findings of 13 dead fetuses from the early decedent female, a ~2-fold higher percent postimplantation loss, and a lower number of live fetuses.
- Surviving fetuses had lower body weight (-5.1% males, -3.8% females) and an increased number with cleft palate which exceeded the historical control data.

Table 67. Methods, Embryo-Fetal Developmental (EFD) Study in Mice

Parameter	Method Details
Dose and frequency of dosing:	SC: 0, 50, 150 or 300 mg/kg/dose; IV: 0 or 300 mg/kg/dose GD 6, 9, 12 and 15
Route of administration:	SC or IV
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, and 0.01% (v/v) Tween® 80 in sterile water for injection, USP, pH 5.0
Species/strain:	Mouse / CrI:CD1(ICR)
Number/sex/group:	25 females pre-mated/group
Satellite groups:	TK: 6/control, 18/SC groups, 27/IV group
Study design:	Standard EFD study design based on ICH S5(R3) included PD and ADA assessments
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Study Report # 20050865

Abbreviations: ADA, antidrug antibody; EFD, embryo-fetal development; GD, gestation day; ICH, International Council for Harmonisation; IV, intravenous; PD, pharmacodynamic; SC, subcutaneous; TK, toxicokinetic

Table 68. Observations and Results, Embryo-Fetal Developmental (EFD) Study in Mice

Parameters	Major Findings
Mortality	A 50 mg/kg SC female delivered on GD 18 and it was subsequently euthanized. This female received all 4 doses of narsoplimab, gained weight during the study, did not present clinical signs prior to parturition neither abnormalities at necropsy examination. The litter consisted of 15 live fetuses and 1 early resorption in utero. One fetus presented a supernumerary rib, a common variation. A 300 mg/kg IV female was found dead after dose administration on GD 15. This dam received all 4 doses of narsoplimab, gained weight during the study, did not present clinical signs prior to death neither abnormalities at necropsy examination. The litter consisted of 13 dead fetuses and one late resorption in utero. The viability of fetuses at the time of early maternal death could not be determined.
Clinical signs	No narsoplimab–related clinical signs occurred on study.
Body weights	Mean maternal body weight gains during the interval of GD 6 through 18 were +5%, +7%, +12%, and -5% compared to controls in the 50, 150, and 300 mg/kg SC and the 300 mg/kg IV dose group, respectively. Transient decreased maternal body weight gains were observed in 300 mg/kg IV individual dams at 5.8-times the exposure at the MRHD.
Necropsy findings Cesarean section data	No narsoplimab–related maternal gross findings.
Laparohysterectomy Evaluations	There were no differences on the number and litter averages for corpora lutea and number of implantations; however, pregnant mice receiving narsoplimab at 300 mg/kg IV delivered a lower number of live fetuses and the mean percent postimplantation loss was increased ~2-fold.

Parameters	Major Findings				

Table 69. Summary of Laparohysterectomy and Litter Evaluations, EFD Study in Mice

OMS721	SC/IV	SC			IV
Dose (mg/kg/day)	0	50	150	300	300
Number of females tested	25	25	25	25	25
Number of females pregnant (%)	23 (92)	21 (84)	24 (96)	20 (80)	23 (92)
Unscheduled euthanasia	0	1	0	0	0
Found dead w/ all dead or reabsorbed	0	0	0	0	1
Early delivery	0	1	0	0	0
Number of surviving pregnant females/Placenta normal	23	20	24	20	22
Dams with any resorptions N (%)	15 (65.2)	11 (52.4)	11 (45.8)	9 (45.0)	17 (73.9)
Corpora lutea	332	303	361	298	327
Mean number per litter	14.4	14.4	15.0	14.9	14.2
Implantations	326	301	361	298	325
Mean number per litter	14.2	14.3	15.0	14.9	14.1
Preimplantation loss	6	2	0	0	2
Mean percent preimplantation loss	1.8	0.7	0	0	0.6
Live fetuses	303	285	350	288	280
% difference vs. controls		-5.9	+15.5	-5.0	-7.6
Dead fetuses	0	0	0	0	13
Mean number of live fetuses (±SD)	13.2 (2.3)	13.5 (1.9)	14.6 (1.7)	14.4 (2.3)	12.7 (1.9)
% difference from control		2.5	10.7	9.3	-3.4
Sex distribution					
Males	166	139	183	163	136
Females	137	146	167	135	144
Mean percent male fetuses per litter	54.8	46.2	52.3	56.6	48.6
Mean fetal body weight (g) per litter	1.35	1.35	1.33	1.33	1.29 (-4.5) ^a
Male fetuses	1.38	1.37	1.35	1.36	1.31 (-5.1)
Female fetuses	1.31	1.32	1.31	1.30	1.26 (-3.8)
Postimplantation loss					
Number early resorptions	20	12	9	7	23
Mean	0.9	0.6	0.4	0.4	1.0
Number late resorptions	3	4	2	3	9
Mean	0.1	0.2	0.1	0.2	0.4
Mean percent postimplantation loss	7.1	5.3	3.1	3.4	13.9
% difference		-25.4	-56.3	-52.1	+95.8

^a Percent mean fetal body weight compared to control

Percent preimplantation loss = [(# corpora lutea - # implantations) / # corpora lutea] x 100

Percent postimplantation loss = [(# implantations - # live fetuses) / # implantations] x 100

Mean number early/late resorptions = number / number of litters (1 litter/dam e.g., #females pregnant)

Parameters Major Findings

Necropsy findings Offspring

Fetal Malformations/ Variations (External, Visceral, Skeletal)

The number of fetuses with cleft palate malformation but not the number of litters in which it was observed in the 300 mg/kg IV were outside the historical control data for the Testing Facility (Fetuses:0-2, range 0-1.7; Litters:0-2, range 0-13.6).

Table 70. OMD721-Related External Malformations (Excerpted From Submission)

Exam Type: External		0 mg/kg/ day Group 1	50 mg/kg/ day Group 2	150 mg/kg/ day Group 3	300 mg/kg/ day Group 4	300 mg/kg/ day Group 5
Number of Fetuses Examined:		303	285	350	288	280
Number of Fetuses Evaluated:		303	285	350	288	280
Number of Litters Examined:		23	21	24	20	22
Number of Litters Evaluated:		23	21	24	20	22
General						
General, Mechanical damage-Incidental	Foetuses N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(9.1)
Limb						
Hindlimb, Malrotated-Malformation	Foetuses N(%)	1(0.3)	0(0.0)	1(0.3)	0(0.0)	0(0.0)
	Litters N(%)	1(4.3)	0(0.0)	1(4.2)	0(0.0)	0(0.0)
Mouth						
Palate, Cleft-Malformation	Foetuses N(%)	0(0.0)	0(0.0)	2(0.6)	1(0.3)	3(1.1)
	Litters N(%)	0(0.0)	0(0.0)	1(4.2)	1(5.0)	3(13.6)

Soft Tissue Examination

No historical control data for the Testing Facility was provided for the absent kidney malformation in the 300 mg/kg IV. The Applicant considered this finding not related to narsoplimab based on the single fetus occurrence. The dilated renal pelvis was within historical control data.

Table 71. OMD721-Related Soft-Tissue Malformations (Excerpted From Submission)

Exam Type: Wilsons		0 mg/kg/ day Group 1	50 mg/kg/ day Group 2	150 mg/kg/ day Group 3	300 mg/kg/ day Group 4	300 mg/kg/ day Group 5
Number of Fetuses Examined:		120	108	133	104	104
Number of Fetuses Evaluated:		303	285	350	288	280
Number of Litters Examined:		19	17	19	15	17
Number of Litters Evaluated:		23	21	24	20	22
Kidney						
Kidney, Absent-Malformation	Foetuses N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.0)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
Renal pelvis, Dilated, Severe-Variation	Foetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(1.0)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(6.7)	0(0.0)

Skeletal Examination

Skeletal abnormalities observed were not considered OMS721-related based on: 1. the abnormality occurred in a single fetus; 2. the litter incidence was not dose-dependent; 3. the fetal and/or litter incidence and/or the percentage of litters affected was within the range of historical control data for the Testing Facility and/or 4. the litter incidence was highest in the control group or comparable to the litter incidence in the control group.

Parameters	Major Findings

Toxicokinetics

Systemic exposure to narsoplimab, as measured by C_{max} and $AUC_{(0-72)}$, generally increased with increasing dose from 50 to 300 mg/kg SC but the increases were less than dose-proportional and exposure values decreased on GD 15 compared to GD 6. Narsoplimab exposure after 300 mg/kg IV administration was at least 7-fold increase compared to the SC administration. There were no signs of accumulation after four doses.

Table 72. Summary of OMS721 Toxicokinetic Parameters in Pregnant Female CrI:CD1(ICR) Mice (Excerpted From Submission)

Dose (mg/kg)	DG	T _{max} (hr)	C ₀ (µg/mL)	C _{max} (µg/mL)	C _{max} /D (µg/mL/(mg/kg))	AUC ₍₀₋₇₂₎ (hr*µg/mL)	AUC ₍₀₋₇₂₎ /D (hr*µg/mL/ (mg/kg))	T _{1/2} (hr)	R _{AUC}
50 SC	6	24	-	51.5 ± 13.5	1.03	2650 ± 630	53.0	NC	NA
	15	24	-	33.3 ± 0.795	0.666	1690 ± 142	33.8	NC	0.638
150 SC	6	24	-	81.0 ± 38.0	0.540	4760 ± 1340	31.7	NC	NA
	15	24	-	74.1 ± 4.13	0.494	3320 ± 242	22.1	NC	0.696
300 SC	6	24	-	158 ± 14.0	0.527	8050 ± 529	26.8	NC	NA
	15	24	-	51.6 ± 25.8	0.172	2880 ± 945	9.60	NC	0.358
300 IV	6	0.0833	4080	3790 ± 858	12.6	19700 ± 1290	65.7	*	NA
	15	0.167	5490	4820 ± 389	16.1	22000 ± 2200	73.3	*	1.12

DG = Day of gestation; SC = Subcutaneous; IV = Intravenous; NC = Not Calculated; NA = Not Applicable

* Result not reported because extrapolation exceeds 20%, or R-squared is less than 0.800

^a R_{AUC} = DG 15 AUC₍₀₋₇₂₎ / DG 6 AUC₍₀₋₇₂₎

Antidrug Antibody Assessments No ADA positive samples were found

Pharmacodynamic Evaluation – Inhibition of the Lectin Pathway

Narsoplimab-related inhibition (range 49.3% to 97.8%) of the complement lectin pathway activation occurred at all SC doses and the IV dose. The inhibition was observed at all timepoints tested and lasted until the end of the study (72 hours post last injection).

Table 73. Narsoplimab-Related C4 Inhibition (%) in Mice EFD Study (Excerpted From Submission)

Group ID	Parameter	DG 6				DG 15				
		5 m	2 h	24 h	72 h	0 h	5 m	2 h	24 h	72 h
Group 2 50 mg/kg SC	Mean MFI	-	2330	2892	905	3751	-	-	395	587
	% inhibition	-	76.4	70.7	90.8	61.9	-	-	96.0	94.0
Group 3 150 mg/kg SC	Mean MFI	-	4998	2061	2183	1724	-	-	840	1347
	% inhibition	-	49.3	79.1	77.8	82.5	-	-	91.5	86.3
Group 4 300 mg/kg SC	Mean MFI	-	1210*	1358	478	1432	-	-	3101	572
	% inhibition	-	87.7	86.2	95.2	85.5	-	-	68.5	94.2
Group 5 300 mg/kg IV	Mean MFI	324	680	1674	235	1158	395	473	1516	217
	% inhibition	96.7	93.1	83.0	97.6	88.2	96.0	95.2	84.6	97.8
Control	Mean MFI	9851								

* Unexpected low results were obtained for 2 of the 3 animals despite their low levels of OMS721 measured in the serum.

Source: Study Report # 20050865

Abbreviations: ADA, antidrug antibody; EFD, embryo-fetal development; GD, gestation day; IV, intravenous; MRHD, maximum recommended human dose; SC, subcutaneous

BLA 761152
Narsoplimab-wuug

Study Number 20050867 / NARSOPLIMAB: An Embryo-Fetal Development Study by Subcutaneous and Intravenous Injection in Pregnant Rabbits

GLP compliance: Yes

Reviewer's Comment

A staggered dosing design was employed to accommodate a robust antidrug antibody (ADA) response identified in preliminary studies. Lectin inhibition by narsoplimab was confirmed in the course of the definitive study. Subcutaneous administration provided the more relevant data as it utilized the clinical route of administration and achieved an ~8-fold multiple of clinical AUC exposure. The intravenous route did not result in clear maternal toxicity but was potentially associated with an increase in postimplantation loss associated with a very high C_{max} and AUC relative to clinical exposure.

Key study findings:

Subcutaneous administration:

- There were no clear drug-related adverse findings in dams or fetuses with subcutaneous administration. Transient reductions in maternal weight gain were not considered as indicative of maternal toxicity by the reviewer.
- The maternal and fetal NOAEL at 150 mg/kg SC provided ~8-times the exposure at the MRHD, narsoplimab based on extrapolated AUC_{0-168h}.

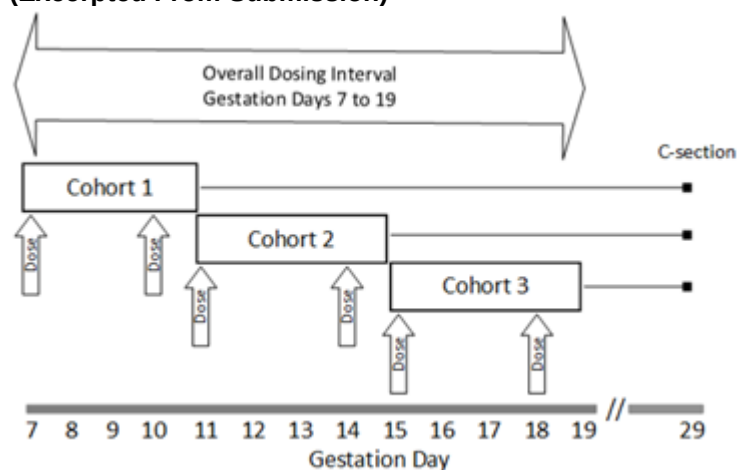
Intravenous administration:

- Increased postimplantation loss occurred on GD 7/10 (+88%) and GD 11/14 (+41%) but not on GD 15/18 at ~91- times the exposure at the MRHD (AUC). This finding is consistent with a drug action during early gestation.

Table 74. Methods, Embryo-Fetal Developmental (EFD) Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing:	SC: 0, 50, 150 mg/kg/dose; IV: 0 or 150 mg/kg/dose Cohort 1: GD 7 and 10; Cohort 2: GD 11 and 14; Cohort 3: GD 15 and 18
Route of administration:	SC or IV
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, and 0.01% (v/v) Tween® 80 in sterile water for injection, USP, pH 5.0
Species/strain:	Rabbit / New Zealand White [HraNZW]SPF]
Number/sex/group:	20 pre-mated females/dose group/cohort
Satellite groups:	3 pre-mated females /dose group/cohort
Study design:	3 cohorts with 20 dams/dose plus 3 dams/dose for TK dosed to cover the gestation period GD 6 to GD 18. Laparohysterectomy on GD 29

Figure 13. Experimental Design, Rabbit Definitive EFD Study (Excerpted From Submission)



Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Study Report # 20050867

Abbreviations: GD, gestation day; IV, intravenous(ly); SC, subcutaneous; TK, toxicokinetic; USP, United States Pharmacopeia

Table 75. Observations and Results, Embryo-Fetal Developmental (EFD) Study in Rabbits

Parameters	Major Findings
Mortality	<u>Cohort 1 Dosed GD 7 and 10</u> A 50 mg/kg/dose SC aborted on GD 23 and then euthanized. Litter of 14 conceptuses (14 empty implantation sites were observed due to abortion). The Applicant considered this abortion not narsoplimab-related since it occurred at the low dose, was not dose-dependent, and the single event was within historical data for the Testing Facility. <u>Cohort 2 Dosed GD 11 and 14</u> No abortions or mortality occurred. <u>Cohort 3 Dosed GD 15 and 18</u> A 150 mg/kg SC dam aborted on GD 28 and then euthanized. Litter of 9 live and 1 dead fetuses. All fetuses appeared normal at gross external examination. The dead fetus had a small right eye, a dilated aortic arch, a ventricular septal defect proximal to the semilunar valves, and a narrow pulmonary trunk at soft tissue examination. It also had an enlarged frontal suture, fused 4th and 5th sternebra, and a misshapen 1st sternebra. One of the live fetuses had unossified pubis at skeletal examination. All other fetuses appeared normal at soft tissue and skeletal examination. The Applicant considered this abortion as not narsoplimab-related since the occurrence was not dose-dependent and the single event was within historical data for the Testing Facility.
Clinical signs	<u>Cohort 1 Dosed GD 7 and 10</u> The 50 mg/kg SC rabbit that aborted on GD 23 presented ungroomed fur (GD 17 through 23), absent feces (GD 18 through 20), decreased fecal output (GD 21 through 23), and aborted red tissue and red liquid in the cage pan (GD 23). Narsoplimab-related clinical signs occurred at 150 mg/kg SC and at 300 mg/kg IV and included soft feces (MD 4/20; HD 3/20), liquid feces (HD 2/20), reduced fecal size (MD & HD 1/20), decreased fecal output (LD 1/20; MD 7/20; HD 2/20), and absent feces (LD & HD single dams). These clinical signs occurred after dose administration and were transient (up to 4 days). Decreased fecal output and absent feces were also observed in one 50 mg/kg SC dam. <u>Cohort 2 Dosed GD 11 and 14</u> No narsoplimab-related clinical signs occurred. <u>Cohort 3 Dosed GD 15 and 18</u> No adverse clinical signs were observed in the 150 mg/kg SC rabbit that aborted on GD 28. No narsoplimab-related clinical signs occurred in other rabbits.

Parameters	Major Findings
Body weights	<i>Note from Reviewer:</i> The Applicant called for (b) (4) based on the transient lower mean body weight gain that corresponded with reduction in mean maternal food consumption during the dosing period. The reviewer considered this is not the case based on the nature of rabbit's food consumption, lower mean body weight gain before dosing that occurred in Cohorts 2 and 3, the sporadic lower mean food consumption before, during and after the dosing period at different dose levels and cohorts, and the similar final mean body weight among all groups compared to controls on GD 29, see Tables 76-81 below. (b) (4)

Overall Percent Change Body Weight Gain in Rabbits EFD Study

Cohort 1 Dosed GD 7 and 10

Table 76. Overall Percent Change Body Weight Gain in Rabbits EFD Study, Cohort 1 Dosed GD 7 and 10

Dose Level (mg/kg)	Route	Change Day Intervals							Mean Body Weight (g) Day 29
		7-11	11-14	7-14	15-18	18-21	21-24	7-29	
0	SC/IV	48.81 ^a	75.43 ^a	124.24 ^a	41.21 ^a	47.91 ^a	54.34 ^a	371.63 ^a	3636.0
50	SC	↓42	↓17	↓27	↓5	↑21	↓56	↓15	3617.4
150	SC	↓66	↓16	↓36	↑46	↓46	↓36	↓17	3580.0
150	IV	↑62	↓16	↑9	↓18	↓30	↓22	--	3692.3

^a Control Mean body weight gain

Cohort 2 Dosed GD 11 and 14

Table 77. Overall Percent Change Body Weight Gain in Rabbits EFD Study, Cohort 2 Dosed GD 11 and 14

Dose Level (mg/kg)	Route	Change Day Intervals							Mean Body Weight (g) Day 29
		7-11	11-14	11-15	15-18	18-21	21-24	7-29	
0	SC/IV	42.32 ^a	85.40 ^a	104.15 ^a	30.09 ^a	43.46 ^a	48.68 ^a	340.43 ^a	3689.3
50	SC	↓39	↑8	↑19	↓60	↓42	↓51	↓19	3609.2
150	SC	↓35	↑27	↑29	↓20	↑44	↓100	↓25	3670.0
150	IV	↓35	↑16	↑24	↓88	↑32	↓82	↓19	3596.5

^a Control Mean body weight gain

Cohort 3 Dosed GD 15 and 18

Table 78. Overall Percent Change Body Weight Gain in Rabbits EFD Study, Cohort 3 Dosed GD 15 and 18

Dose Level (mg/kg)	Route	Change Day Intervals						Mean Body Weight (g) Day 29
		7-15	15-18	15-19	15-21	21-24	7-29	
0	SC/IV	123.05 ^a	60.86 ^a	67.16 ^a	106.05 ^a	50.55 ^a	335.10 ^a	3773.2
50	SC	↓43	↑6	↓8	↓15	↓6.0	↓24	3697.4
150	SC	↓20	↓24	↓24	↓18	↓11	↓20	3768.9
150	IV	↓12	↓25	↓46	↓48	↑19	↓16	3714.3

^a Control Mean body weight gain

Parameters Major Findings

Food Consumption

Cohort 1 Dosed GD 7 and 10

Table 79. Food Consumption, Cohort 1 Dosed GD 7 and 10 (Excerpted From Submission)

Group No.	Dose Level (mg/kg)	Route		Gestation Interval / Period				
				7 to 11	7 to 14	15 to 29	11 to 29	7 to 29
1	0	SC/IV	Abs. Wgt ^a	149.0	140.8	130.2	130.2	133.7
2	50	SC	Abs. Wgt ^a	162.1	155.4	131.6	134.3	139.3
			% diff	8.8	10.4	1.0	3.2	4.2
3	150	SC	Abs. Wgt ^a	153.5	142.5	128.2	127.2	131.1
			% diff	3.0	1.2	-1.6	-2.4	-1.9
4	150	IV	Abs. Wgt ^a	166.0	157.7	122.9	127.8	134.8
			% diff	11.4	12.1	-5.6	-1.9	0.9

Abs. Wgt = absolute weight; % diff = percent difference from control; SC = subcutaneous; IV = intravenous

^a Group mean in grams is shown.

Cohort 2 Dosed GD 11 and 14

Table 80. Food Consumption, Cohort 2 Dosed GD 11 and 14 (Excerpted From Submission)

Group No.	Dose Level (mg/kg)	Route		Gestation Interval / Period						
				7 to 10	7 to 11	11 to 15	11 to 18	18 to 29	15 to 29	7 to 29
1	0	SC/IV	Abs. Wgt ^a	148.7	149.0	140.6	141.8	116.2	122.0	130.3
2	50	SC	Abs. Wgt ^a	141.4	141.7	138.0	131.9	105.6	109.6	120.6
			% diff	-4.9	-4.9	-1.8	-7.0	-9.0	-10.2	-7.5
3	150	SC	Abs. Wgt ^a	152.0	151.1	148.0	145.7	100.7	109.7	124.2
			% diff	2.2	1.5	5.3	2.7	-13.3	-10.1	-4.7
4	150	IV	Abs. Wgt ^a	147.3	146.0	141.3	138.5	113.1	117.7	127.1
			% diff	-0.9	-2.0	0.5	-2.4	-2.6	-3.5	-2.5

Abs. Wgt = absolute weight; % diff = percent difference from control; SC = subcutaneous; IV = intravenous

^a Group mean in grams is shown.

Cohort 3 Dosed GD 15 and 18

Table 81. Food Consumption, Cohort 3 Dosed GD 15 and 18 (Excerpted From Submission)

Group No.	Dose Level (mg/kg)	Route		Gestation Interval / Period					
				7 to 15	15 to 19	19 to 29	15 to 21	21 to 29	7 to 29
1	0	SC/IV	Abs. Wgt ^a	141.8	157.5	117.4	155.6	108.8	133.6
2	50	SC	Abs. Wgt ^a	131.1	149.0	119.9	149.5	112.2	129.3
			% diff	-7.5	-5.4	2.1	-3.9	3.1	-3.2
3	150	SC	Abs. Wgt ^a	133.5	147.7	109.6	147.4	99.3	127.0
			% diff	-5.9	-6.2	-6.6	-5.3	-8.7	-4.9
4	150	IV	Abs. Wgt ^a	129.4	134.4	108.7	132.7	103.5	120.8
			% diff	-8.7	-14.7	-7.4	-14.7	-4.9	-9.6

Abs. Wgt = absolute weight; % diff = percent difference from control; SC = subcutaneous; IV = intravenous

^a Group mean in grams is shown.

Parameters	Major Findings
Necropsy findings Cesarean section data	<u>Cohort 1 Dosed GD 7 and 10</u> A single 150 mg/kg SC dam presented both kidneys with clear, fluid-filled cysts that were too numerous to count ranging in size from pinpoint to 0.4 cm x 0.5 cm x 0.2 cm. The cysts extended into the renal parenchyma. This gross lesion did not affect pregnancy (9 live fetuses) and was not considered related to OMS721 based on a single incidence in the absence of dose-relationship. <u>Cohort 2 Dosed GD 11 and 14</u> A single incidence of reduced to a ligament of the right uterine horn in a 50 mg/kg SC dam was not considered narsoplimab-related based on the single incidence and lack of dose-relationship. <u>Cohort 3 Dosed GD 15 and 18</u> No maternal gross observations occurred in cohort 3.
Laparohysterectomy evaluations	<u>Cohort 1 Dosed GD 7 and 10</u> The number and percentage of dams with any resorptions was increased at the HD (9/47 vs. Control 4/20) but it did not affect the mean number of live fetuses in narsoplimab-treated rabbits. The mean percent implantation loss was increased at the 50 mg/kg SC (+124%) and 150 mg/kg IV (+88%) but it was lower than control at the 150 mg/kg SC (-33%); the relation of implantation loss to narsoplimab administration is unclear based on the lack of dose-response for SC administration but the increased postimplantation loss at 150 mg/kg IV was considered related to narsoplimab. <u>Cohort 2 Dosed GD 11 and 14</u> Narsoplimab-treated rabbits presented a better profile compared to control except for an increased mean percent postimplantation loss (+41%) at 150 mg/kg IV that was considered narsoplimab-related. <u>Cohort 3 Dosed GD 15 and 18</u> Narsoplimab-treated rabbits presented a better profile compared to control except for lower number of females pregnant at 150 mg/kg SC (18/20) and a lower number of live fetuses at the 50 mg/kg SC (153, -20.7%) and 150 mg/kg SC (167, -13.5%) compared to control that corresponded with lower number of corpora lutea (177 and 180 vs. 216) and implantations (162 and 172 vs. 208) although values were within the historical control data range.
Necropsy findings Offspring	<u>Fetal Malformations/ Variations (external, visceral, skeletal)</u> No narsoplimab-related gross external, soft tissue, or skeletal abnormalities occurred at any dose in all Cohorts in rabbits. All ossification site averages were similar across all dose groups, including controls.

Parameters	Major Findings

Toxicokinetics

Increases in exposure were less than dose-proportional after the first dose and close to dose proportional after the second dose. The mean exposures were comparable among the 3 TK cohorts at both SC dose levels. OMS721 exposure after 150 mg/kg IV administration was ≥ 5 -fold increases compared to the SC administration. Exposure after the second dose increased only in TK cohort 2.

Narsoplimab half-life of 57.7 hours was estimated for the SC route from the first TK cohort and between 14.5 and 22.4 hours for the IV route from all three TK cohorts. Bioavailability (%F) based on AUC(0-72) ranged from 6.77 to 9.27% following the first 150 mg/kg SC dose and ranged from 8.59 to 18.7% following the second SC dose.

Table 82. Summary of OMS721 Toxicokinetic Parameters in Pregnant Female Rabbits (Excerpted From Submission)

Route	Dose	DG	T _{max} (hr)	C ₀ (µg/mL)	C _{max} (µg/mL)	AUC ₍₀₋₇₂₎ (hr*µg/mL)	AUC ₍₀₋₇₂₎ (hr*µg/mL)	R _{AUC} (RATIO)	T _{1/2} (hr)	CL (mL/hr/kg)	Vd (mL/kg)
Cohort 1											
SC	50	7	72 (72 - 72)	-	26.9	1420	1420	-	NR	-	-
	50	10	72 (24 - 72)	-	49.7	4460	3130	2.23	NR	-	-
	150	7	24 (24 - 72)	-	68.7	3940	3940	-	NR	-	-
	150	10	24 (24 - 24)	-	149	17900	8990	2.27	57.7	-	-
IV Bolus	150	7	0.15 (0.08 - 0.2)	2910	2870	46500	46500	-	15.2	3.04	66.9
	150	10	0.08 (0.08 - 0.08)	3060	3040	52700	50800	1.09	14.5	2.98	61.4
Cohort 2											
SC	50	11	72 (72 - 72)	-	34.3	1820	1820	-	NR	-	-
	50	14	24 (24 - 24)	-	35.7	2770	2310	1.73	NR	-	-
	150	11	24 (24 - 72)	-	97.1	5380	5380	-	NR	-	-
	150	14	24 (24 - 24)	-	153	8500	7770	1.49	NR	-	-
IV Bolus	150	11	0.08 (0.08 - 0.08)	3470	3440	58000	58000	-	15.7	2.80	63.5
	150	14	0.08 (0.08 - 0.08)	6360	6300	92200	90500	1.64	22.4	1.70	53.5
Cohort 3											
SC	50	15	72 (72 - 72)	-	35.4	1930	1930	-	NR	-	-
	50	18	24 (24 - 24)	-	51.7	3100	3100	1.68	NR	-	-
	150	15	72 (24 - 72)	-	73.5	4030	4030	-	NR	-	-
	150	18	24 (24 - 24)	-	229	11100	11100	2.85	NR	-	-
IV Bolus	150	15	0.08 (0.08 - 0.08)	3920	3890	59500	59500	-	NR	-	-
	150	18	0.08 (0.08 - 0.08)	3840	3810	59400	59400	1.04	14.9	2.53	54.2

^a T_{max} is presented as median (min - max); - = Not applicable; R_{AUC} = AUC₍₀₋₇₂₎ on day of last dose divided by AUC₍₀₋₇₂₎ on day of first dose; NR = Not reported due to insufficient sampling timepoint or R-square less than 0.800 at the terminal elimination phase.

Parameters	Major Findings
Antidrug antibody assessments	<u>Summary of ADA response</u> • Across all TK Cohorts, 9 of 26 pregnant narsoplimab-treated animals were ADA positive at the last sample evaluated (72 or 96 hours after the last dose). • Across all main cohorts, 12 of 173 pregnant narsoplimab--treated animals were ADA positive at the prefirst dose time point. • None of 173 pregnant narsoplimab--treated animals were ADA positive at 24-hour post second dose • On DG 29, 11 to 19 days after the last dose (depending on cohort), 167 of 173 pregnant narsoplimab--treated animals were ADA positive. • Confirmed positive ADA responses detected at 72 hours after the second dose were generally associated with a decreased serum narsoplimab concentrations and samples were excluded from TK analysis. • Pregnant females positive for ADA at 72 hours presented decreased in pharmacodynamic activity. • Maternal ADA response did not appear to affect fetal narsoplimab serum concentrations in both SC and IV bolus groups.

Parameters	Major Findings
Pharmacodynamic Evaluation – Inhibition of the Lectin Pathway	

According to the Applicant, the measured pharmacodynamic activity correlated well with the serum narsoplimab concentrations. The inhibition of the lectin complement pathway was maintained through 24 hours after the second dose but there was loss of inhibition by 72 hours Cohort 2 and 3 at 50 mg/kg SC/TK

Table 83. Narsoplimab–Related C4 Inhibition (%) in Rabbits EFD Study (Excerpted From Submission)

Group ID	Cohort ID	Group Mean Inhibition of the Lectin Complement Pathway (%)			
		24 hr Post First Dose	72 hr Post First Dose	24 hr Post Second Dose	72 hr Post Second Dose
Group 2 50 mg/kg (SC)	Main Study 1	-	-	70.3	-
	Main Study 2	-	-	78.7	-
	Main Study 3	-	-	74.9	-
	TK 1	68.1	69.9	72.5	72.0
	TK 2	68.6	70.7	70.5	53.2
	TK 3	68.6	70.5	74.3	43.3
Group 3 150 mg/kg (SC)	Main Study 1	-	-	80.2	-
	Main Study 2	-	-	81.4	-
	Main Study 3	-	-	85.0	-
	TK 1	70.1	68.0	70.5	71.5
	TK 2	83.6	82.3	84.3	73.4
	TK 3	78.3	79.6	84.8	76.4
Group 4 150 mg/kg (IV)	Main Study 1	-	-	85.2	-
	Main Study 2	-	-	87.1	-
	Main Study 3	-	-	89.3	-
	TK 1	84.9	79.4	83.6	68.8
	TK 2	89.6	85.9	90.7	82.1
	TK 3	80.9	75.7	83.9	74.5

TK: Toxicokinetic animals
-: Not assessed

Source: Study Report # 20050867

Abbreviations: ADA, antidrug antibody; EFD, embryo-fetal development; GD, gestation day; HD, high dose; IV, intravenous(ly); LD, low dose; MD, mid dose; SC, subcutaneous; TK, toxicokinetic

Prenatal and Postnatal Development (PPND)

Study Number/Title: 20113153 / NARSOPLIMAB: A Developmental and Perinatal/Postnatal Reproduction Study by Subcutaneous and Intravenous Injection in the Mouse, Including a Postnatal Behavioral/Functional Evaluation

GLP compliance: Yes

Reviewer Comment

No clear adverse effects were observed in dams or in F1 offspring after administering narsoplimab to dams during gestation and lactation by either the IV or SC routes. Signals of embryofetal toxicity (e.g., cleft palate, fewer live fetuses/litter) observed at 300 mg/kg IV in the definitive embryo-fetal development study were not observed at the same IV dose in this study, for uncertain reasons.

Key study findings:

- Narsoplimab–related effects in F0 generation mice were limited to transient and nonadverse reductions in maternal body weight and gestational weight gain at 300 mg/kg IV and 150 mg/kg SC.
- There was no effect on litter parameters including body weight and viability indices, and no necropsy findings in preweaning F1 offspring.
- No narsoplimab–related effects on growth, sexual maturation, or neurobehavioral or reproductive function in the F1 generation at any dose level evaluated.
- Narsoplimab was present in serum of F1 offspring, presumably via transfer during the lactation period. Levels of narsoplimab in maternal milk were not measured.
- A NOAEL was defined as 300 mg/kg IV and 150 mg/kg SC.

Table 84. Methods, Prenatal and Postnatal Developmental Study in Mice, Study 20113153

Parameter	Method Details
Dose and frequency of dosing:	SC: 0 or 150 mg/kg/dose; IV: 0, 150, or 300 mg/kg/dose BIW, Gestation: GD 6, 9, 12, 15, and GD 19, and 22 (mice that did not deliver) Lactation: LD 1, 4, 7, 10, 13, 16, and 19 (for mice that deliver a litter)
Route of administration:	SC or IV
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, and 0.01% (v/v) Tween® 80 in sterile water for injection, USP, pH 5.0
Species/strain:	Mouse / Crl:CD1(ICR)
Number/sex/group:	25 females/group; F0 generation virgin female mice, 70 or 71 days of age, were cohabitated maximum 4 or 5 days with untreated breeder male mice of the same source and strain, one male mouse per female mouse.
Lactation	Day 1 of lactation (postnatal) was defined as the day of birth and was also the first day on which all pups in a litter were individually weighed. Litters were not culled during the lactation period because random selection of pups for culling could result in potential biases in pup viabilities and body weight gains during this period.
Weaning	All F1 generation mice were weaned on PND 21. A table of random units was used to select 25 male and 25 female pups per group, total of 200 F1 generation mice (100 per sex) chosen for continued evaluation. The remainder of the pups were either euthanized or assigned to toxicokinetic sample collection.
Satellite groups:	TK; 8/control; 16/SC 150 mg/kg; 24/ IV groups
Study design:	Standard PPND study design based on ICH S5(R3) included PD and ADA assessments

Parameter	Method Details
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Study Report # 20113153

Abbreviations: ADA, antidrug antibody; BIW, twice a week; GD, gestation day; ICH, International Council for Harmonisation; IV, intravenous(ly); LD, lactation day; PD, pharmacodynamic; PND, postnatal day; PPND, prenatal and postnatal development; SC, subcutaneous; TK, toxicokinetic; USP, United States Pharmacopeia

Table 85. Observations and Results, Study 20113153

Parameters	Major Findings
Mortality	All F0 generation female mice survived to scheduled euthanasia.
Clinical signs	No narsoplimab-related clinical signs.
Maternal body weight gain & food consumption during gestation	Transient sometimes significant lower mean body weight gain, including the predose interval, occurred at some intervals during gestation without an impact on overall body weight gain or mean body weight on GD 18.

Table 86. Percent Change Body Weight Gain in Mice PPND Study During Gestation, Study 20113153

Dose Level (mg/kg)	Route	Change Gestation Day Intervals							Mean Body Weight (g) Day 18
		0-6	6-9	9-12	12-15	15-18	6-18	0-18	
0	SC/IV	4.4 ^a	2.7 ^a	5.7 ^a	8.4 ^a	11.0 ^a	27.7 ^a	32.1 ^a	59.6
150	SC	↓7	↓11	↑23	↑10	↑2	↑8	↑6	61.5
150	IV	↓9	↓22 **	↑9	↓1	↓6	↓2	↓3	58.8
300	IV	↓5	↓26 **	↑12	↓2	↓19 **	↓8	↓8	57.1

^a Control Mean body weight gain

Decreases in mean maternal food consumption were observed in the 300 mg/kg IV compared to controls during GD 6 to GD 18 (-9.1%) with no impact on overall mean body weight.

Maternal body weight gain & food consumption during lactation	No narsoplimab-related effects at any dose levels.
Maternal necropsy	No macroscopic observations noted for F0 females at necropsy.
Natural delivery	No narsoplimab-related effects on any natural delivery parameter at any dose level.
Litter observations	No narsoplimab-related effects on any litter parameter.
Prewaning F1 generation (birth to PND 21) clinical signs	No narsoplimab-related clinical signs occurred.
Pup necropsy	Necropsy was conducted on 1, 3, and 3 F1 generation pups that were found dead or stillborn in the control, 150, and 300 IV mg/kg dose groups, respectively. Two pups from the 150 and 300 mg/kg IV groups did not have milk present in the stomach.
Postweaning F1 generation mortality	All F1 generation male and female mice survived to scheduled euthanasia, except for one control female mouse.
Clinical signs, body weight, body weight gain and food consumption	No narsoplimab-related effects on these parameters were observed.
Sexual maturation	Achieved from 25.5 to 26.8 days for male balano-preputial separation and from 25.8 to 26.4 days for female vaginal patency. Mean body weight at sexual maturation was similar among the four dose groups.

Parameters	Major Findings
Behavioral assessments passive avoidance, acoustic startle habituation, Morris water maze	No narsoplimab-related effects on these parameters were noted.
Reproductive capacity mating and fertility F1 generation	F1 mice were 94 to 98 days of age at the initiation of the cohabitation period which ranged from 2.4 to 3.3 days. The mating index was 95.8% (controls) or 100% (narsoplimab groups). Male and female fertility index (number of pregnancies / number of pairs that mated) was 92% to 100%.
Necropsy observations, terminal body weights and reproductive organ weights	No narsoplimab-related macroscopic observations or effects on body or organ weights were noted.
Ovarian and uterine examination F1 generation	Pregnancy was confirmed in 23 (95.8%), 23 (92.0%), 25 (100.0%), and 24 (96.0%) F1 generation females in the control, 150 mg/kg/dose SC, 150 and 300 mg/kg/dose IV groups, respectively. All ovarian and uterine examination parameters were similar among the groups.

Toxicokinetics

Systemic exposure to narsoplimab on GD 15 increased with increasing IV BIW doses from 150 to 300 mg/kg in a dose proportional manner. The half-life was estimated between 13.8 and 16.2 hours. The V_d suggested that narsoplimab was distributed beyond the vasculature.

Table 87. Narsoplimab TK Parameters in Mice PPND Study During Gestation (Excerpted From Submission), Study 20113153

Route	Dose (mg/kg)	T_{max} (hr)	C_{max} (μ g/mL)	C_0 (μ g/mL)	$AUC_{(0-72)}$ (hr* μ g/mL)	$AUC_{(0-72)/D}$ (hr* μ g/mL/ (mg/kg))	$T_{1/2}$ (hr)	CL (mL/hr/kg)	V_d (mL/kg)
Subcutaneous	150	24	41.1	NC	2200	14.7	NC	NC	NC
IV Bolus	150	0.083	1740	1850	8810	58.8	16.2	17.0	399
IV Bolus	300	0.083	4280	4580	18800	62.6	13.8	16.0	317

NC = Not Calculable

Parameters	Major Findings
Maternal and Fetal Narsoplimab Serum Concentrations	

Narsoplimab was present in offspring when F0 generation mice were administered narsoplimab during the gestation and lactation periods. Higher fetal than maternal serum concentrations were measured when using the SC route and similar fetal and maternal serum concentration when using the IV route.

Table 88. Narsoplimab Maternal and Fetal Serum Concentrations in Mice PPND Study, Study 20113153

Narsoplimab (mg/kg/dose)	Mean	GD 18	LD 1	LD 21
150 SC	Maternal (F0)	16.2 ^a	14.5 ^a	83.4 ^a
	Fetal (F1)	32.4 ^a	76.2 ^a	60.0 ^a
	Ratio	2.3	5.7	1.2
150 IV	Maternal (F0)	15.7 ^a	40.3 ^a	69.6 ^a
	Fetal (F1)	20.7 ^a	33.6 ^a	39.8 ^a
	Ratio	1.5	0.8	0.8
300 IV	Maternal (F0)	20.2 ^a	64.2 ^a	76.1 ^a
	Fetal (F1)	34.4 ^a	51.9 ^a	59.6 ^a
	Ratio	1.9	0.8	1.0

^a mean serum concentrations (ng/mL); Ratio = F1 / F0 serum concentrations

Source: Study Report # 20113153

Abbreviations: BIW, twice a week; GD, gestation day; IV, intravenous(ly); LD, lactation day; PPND, prenatal and postnatal development; SC, subcutaneous; TK, toxicokinetic

Juvenile Animal Studies

Study Number/Title: 9000601: A 13-Week Subcutaneous Injection Toxicity Study of in the Juvenile Mouse with a 16-Week Recovery

Key study findings:

- Narsoplimab-related nonadverse increases in neutrophil counts at ≥ 50 mg/kg corresponded with nonadverse microscopic findings of eosinophilic infiltration in the bone marrow, injection site, and inguinal skin. All changes were resolved at the end of recovery except for lower incidence of findings at the injection site.
- Elevated IgE plasma levels occurred at all dose levels with partial reversibility at the end of the recovery period indicative of an immunological sensitization of juvenile mice to narsoplimab. T-cell dependent antibody response assessment shows juvenile mice successfully mounted an immune response to keyhole limpet hemocyanin.
- Substantial (>70%) and similar inhibition of the complement lectin pathway was observed at all narsoplimab dose levels. The inhibition was sustained beyond 28 days after the last dose. Results indicate narsoplimab inhibition was achieved at the lowest dose tested.
- Antidrug antibody response onset occurred after the last dose and did not interfere with toxicokinetic assessments of narsoplimab in juvenile mice.
- NOAEL was 300 mg/kg/dose SC at 2-times the exposure at the MRHD (AUC, conservatively corrected for a 4-fold potency difference).

Table 89. Methods for Juvenile Mice Study, Study 9000601

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 50, 150, or 300 mg/kg SC / untreated control BIW for 8 injections (PND 4, 7, 10, 14, 17, 21, 24 and 28; preweaning period) Q1W for 9 injections (PND 35 to 91; postweaning period). Total 17 SC doses.
Route of administration:	SC. Subcutaneous injection sites were rotated between 3 different sites: interscapular, lumbar left and lumbar right.
Formulation/vehicle:	20mM sodium acetate, 50 mg/mL sorbitol, and 0.01% (v/v) Tween® 80 in sterile water for injection, USP, pH 5.0
Species/strain:	Mouse / Crl:CD1(ICR)
Number/sex/group:	Control: 95/sex Narsoplimab groups: 140/sex/group Untreated: 8/sex
Age at start of experiment:	4 days
Satellite groups:	Include TK groups. Control 6/sex; narsoplimab treated 15/sex
Parameters and key endpoints evaluated:	Clinical pathology, PD inhibition of the complement lectin pathway, plasma biomarker (IgE) concentration, T-cell dependent antibody response (TDAR), phenotyping of blood lymphocytes, antidrug-antibody (ADA) analysis, gross and histopathologic evaluation, organ weights, and bone measurements.
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Study Report # 9000601

Abbreviations: BIW, twice a week; GLP, good laboratory practice; PD, pharmacodynamic; PND, postnatal day; Q1W, once a week; SC, subcutaneous; TK, toxicokinetic

Table 90. Observation and Results, Study 9000601

Parameters	Major Findings
<u>Mortality</u>	

Early deaths (11 found dead, 1 unscheduled euthanasia) occurred randomly among all groups at low incidence (12/1030) and with no dose-dependent pattern noted. These early decedents appeared not related to narsoplimab, see [Table 91](#).

Table 91. Mortality in in Mice JAS (Excerpted From Submission), Study 9000601

Animal No.	Sex	PND	Dose Group	Subset	Demise Status	Pathology Examination	Cause of Death
Preweaning Period^a							
273-6	F	19	2	Immunophenotyping Recovery	Found dead	NA	Undetermined ^b
292-6	F	19	2	Hematology	Found dead	Gross	Undetermined ^b
382-6	F	19	3	Recovery	Found dead	Gross/microscopic	Undetermined
484-3	M	12	4	Hematology	Found dead	Gross	Undetermined
494-5	F	19	4	TK (PND 91)	Found dead	Gross	Undetermined
Postweaning Period							
1013	M	56	1	Main	Found dead	Gross/microscopic	Renal amyloid
1065	M	58	1	Immunophenotyping Recovery	Found dead	Gross	Undetermined
1550	F	200	1	TDAR Recovery	Unscheduled euthanasia	Gross	Left eye lesion
2063	M	191	2	Immunophenotyping Recovery	Found dead	Gross	Possible renal obstruction
2514	F	66	2	Main	Found dead	Gross/microscopic	Renal amyloid
2571	F	56	2	TK (PND 91)	Found dead	Gross	Accidental ^c
4113	M	125	4	TK (PND 91)	Found dead	Gross	Thymic mass

NA = Not applicable. A cause of death was not investigated since necropsy was not performed as per existing version of the Study Plan;

^a The adult numbers assigned to these animals were stated in [Section 4.9](#) (No. 2566 for 273-6, No. 2640 for 292-6, No. 3530 for 382-6, No. 4137 for 484-3, and No. 4602 for 494-5).

^b Early death possibly associated with the stress caused by the tattooing procedures.

^c Animal found with head stuck between food hopper and top of bin/rack.

TK=Toxicokinetic; TDAR=T-Cell Dependent Antibody Response.

Clinical signs	None
Body weights	None
Ophthalmoscopy	None
ECG	No conducted
<u>Hematology</u>	

Preweaning period (PND 29): decreases in neutrophil, lymphocyte, monocyte, and/or WBC in males and females at ≥ 50 mg/kg, and minimal transient decreases in eosinophil counts in males at 300 mg/kg and females at ≥ 150 mg/kg were noted.

Postweaning period (PND 95): changes observed at PND 29 were resolved. However, neutrophil counts increased at ≥ 50 mg/kg and corresponded with microscopic findings of eosinophilic infiltration in the bone marrow, injection site and inguinal skin.

End of recovery (PND 207): Full resolution of all changes noted.

Parameters	Major Findings

Table 92. Narsoplimab–Related Changes in Hematology Parameters in Mice JAS (Excerpted From Submission), Study 9000601

Group Dose (mg/kg/dose) Sex	1		2		3		4	
	0 M	0 F	50 M	50 F	150 M	150 F	300 M	300 F
NEUT (10³/uL)								
PND 29	0.628	0.423	0.361	0.368	0.291	0.272	0.281	0.289
Diff (% or fold)			-42%	—	-54%	-36%	-55%	-32%
LYMPH (10³/uL)								
PND 29	2.790	1.920	1.799	1.392	1.854	1.342	1.486	1.476
Diff (% or fold)			-36%	-27%	-34%	-30%	-47%	-23%
MONO (10³/uL)								
PND 29	0.108	0.069	0.073	0.049	0.066	0.033	0.031	0.030
Diff (% or fold)			-33%	-29%	-39%	-52%	-71%	-56%
WBC (10³/uL)								
PND 29	3.661	2.528	2.331	1.910	2.326	1.719	1.873	1.876
Diff (% or fold)			-36%	-24%	-36%	-32%	-49%	-26%
EOS (10³/uL)								
PND 29	0.100	0.101	0.076	0.089	0.096	0.058	0.054	0.062
Diff (% or fold)			—	—	—	-43%	-46%	-39%
PND 95	0.091	0.123	0.212	0.329	0.246	0.225	1.136	0.202
Diff (% or fold)			2.33x	2.67x	2.70x	+83%	+50%	+64%

M = Males F = Females

A dash (—) indicates absence of change. Numerical values indicate fold change or % change of the OMS721-dosed group mean value relative to the control group value. **Bolded** values indicate mean values were statistically different from controls at P ≤ 0.05.

Clinical Chemistry

Postweaning period (PND 95): Narsoplimab–related changes in serum chemistry parameters were minimal and occurred at ≥50 mg/kg in albumin (ALB), triglyceride (TRIG), globulin (GLOB) and/or albumin/globulin (A/G) ratio.

End of recovery (PND 207): Full resolution of all changes noted.

Table 93. Narsoplimab–Related Changes in Clinical Chemistry Parameters in Mice JAS (Excerpted From Submission), Study 9000601

Group Dose (mg/kg/dose) Sex	1		2		3		4	
	0 M	0 F	50 M	50 F	150 M	150 F	300 M	300 F
TRIG (mg/dL)								
PND 95	184.1	135.3	160.0	170.8	221.1	176.0	261.8	168.4
Diff (%)			—	+26%	+20%	+30%	+42%	+25%
GLOB (g/dL)								
PND 95	1.92	1.58	1.97	1.78	2.12	1.77	2.13	1.76
Diff (%)			—	+13%	+10%	+12%	+11%	+11%
ALB (g/dL)								
PND 95	3.07	3.50	3.02	3.43	2.89	3.38	2.88	3.36
Diff (%)			—	-	-6%	-	-6%	-
A/G								
PND 95	1.60	2.31	1.54	1.95	1.37	1.93	1.39	1.93
Diff (%)			—	-16%	-14%	-16%	-13%	-16%

M = Males F = Females

A dash (—) indicates absence of change. Numerical values indicate % change of the OMS721-treated group mean value relative to the control group mean value. **Bolded** values indicate mean values were statistically different from controls at P ≤ 0.05.

Urinalysis

At the end of the postweaning period, a mild trend for a decrease in urine pH in HD males (5.5-7.0 / control 6.0-8.5) and females (5.0-6.5 / control 5.5-7.0) was noted with values similar to control groups by the end of the recovery period.

Parameters	Major Findings
<u>Plasma IgE Biomarker of Allergic Reaction</u>	

Dose-related increases in IgE levels at 150 and 300 mg/kg/dose reached statistical significance on PND 29. Levels continued increasing through the postweaning period and reached statistical significance at ≥ 50 mg/kg on PND 95 with a maximal fold change of 36.2-fold for one female at 300 mg/kg and of 49.5-fold for one male at 50 mg/kg.

Partial recovery of the increased IgE concentrations was observed on PND 207.

Elevated IgE plasma levels were indicative of an immunological sensitization of the mice to narsoplimab.

Table 94. Narsoplimab–Related Changes in IgE Biomarker of Allergic Reaction (Excerpted From Submission), Study 9000601

Group Dose (mg/kg/dose) Sex	1		2		3		4	
	0 M	0 F	50 M	50 F	150 M	150 F	300 M	300 F
IgE (ng/mL)								
PND 29	0.64	1.43	6.55	6.46	7.91	14.9	12.1	16.4
Diff (fold)			10.2x	4.5x	12.4x	10.4x	18.8x	11.4x
PND 95	3.06	3.96	124	208	103	194	91.0	232
Diff (fold)			40.4x	52.6x	33.4x	49.1x	29.7x	58.7x
PND 207	4.71	6.16	57.0	192	29.1	224.8	35.5	154
Diff (fold)			12.1x	31.2x	6.2x	36.5x	7.6x	25.0x

M = Males F = Females

Numerical values indicate the fold change of OMS721-dosed group mean value relative to the control group mean value. Bold numbers indicate significantly different from control (Group 1) value.

Immunotoxicity Assessment

Peripheral Blood Immunophenotyping

No narsoplimab–related differences in cell counts. A trend for decrease in mean NK cell counts occurred at ≥ 50 mg/kg although there is high interanimal variability in this small cell counts.

Blood Phenotyping Last Week of Dosing in Mice JAS

Table 95. Blood Phenotyping Last Week of Dosing in Mice JAS, Males, Study 9000601

Narsoplimab (mg/kg/dose)	Summary Info	Total Lymphocyte Count	Total T Lymphocytes (CD3+)	Helper T Lymphocytes (CD3+/CD4+)	Cytotoxic T Lymphocytes (CD3+/CD8a+)	B Lymphocytes (CD3-/CD19+)	Natural-Killer Cells (CD3-/NK1.1+)
Control	Mean	4197	1355	999	348	2575	177
50	Mean	5313	1638	1166	445	3433	136
	% Diff	27	21	17	28	33	-23
150	Mean	5049	1781	1267	505	2985	154
	% Diff	20	31	27	45	16	-13
300	Mean	3758	1353	969	377	2245	81
	% Diff	-10	0	-3	8	-13	-54

All cell type counts (cells/ μ L); Percent Difference compared to Control

Table 96. Blood Phenotyping Last Week of Dosing in Mice JAS, Females, Study 9000601

Narsoplimab (mg/kg/dose)	Summary Info	Total Lymphocyte Count	Total T Lymphocytes (CD3+)	Helper T Lymphocytes (CD3+/CD4+)	Cytotoxic T Lymphocytes (CD3+/CD8a+)	B Lymphocytes (CD3-/CD19+)	Natural-Killer Cells (CD3-/NK1.1+)
Control	Mean	3469	1419	1021	384	1846	142
50	Mean	4591	1798	1326	462	2502	214
	% Diff	32	27	30	20	36	51

Parameters		Major Findings					
150	Mean	4056	1581	1147	401	2256	119
	% Diff	17	11	12	4	22	-16
300	Mean	4037	1572	1107	444	2249	132
	% Diff	16	11	8	16	22	-7

All cell type counts (cells/ μ L); Percent Difference compared to Control

T-cell dependent antibody response (TDAR) assessment	Keyhole limpet hemocyanin (KLH) solution was administered on PNDs 81 and 88 (14 and 7 days before the scheduled euthanasia) by intraperitoneal injection to two cohorts of TDAR animals (10/sex/group/cohort). The kinetics of the anti-KLH IgM and IgG responses indicate that these animals successfully mounted an immune response to KLH.
Sexual maturation and reproductive capacity	No effects on the development of hallmarks for physical development of preputial separation in males and vaginal opening in females at all dose levels.
CNS/ neurobehavioral assessment	Functional observation battery (FOB) assessments were conducted on a subset of mice assigned for recovery on PND 59, 60, or 61, and at the end of the recovery period on PND 199, 200, or 201. No narsoplimab-related effects on qualitative and quantitative parameters evaluated at any dose level.
Bone evaluation	No changes in bone measurements including right femoral length and width.
Gross pathology	None
Organ weights	None

Histopathology

Adequate battery: Yes

End of Dosing

Bone marrow: minimal to mild increased cellularity in eosinophils without a dose-response at ≥ 50 mg/kg in both sexes with an increased incidence and severity in HD females compared to males.

Injection site: minimal to mild eosinophilic infiltration and mononuclear cell infiltration in control and narsoplimab-treated animals that were considered narsoplimab-related based on the increased incidence and severity compared to controls.

Skin: higher incidence of subcutaneous eosinophilic infiltration, graded as minimal to mild, in females at ≥ 50 mg/kg and considered an extension of the findings at the injection site.

Parameters	Major Findings							

Table 97. Narsoplimab–Related Microscopic Findings in Mice JAS at the End of the Dosing Phase (Excerpted From Submission), Study 9000601

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg)	0	50	150	300	0	50	150	300
No. Animals Examined	19	20	20	20	20	19	20	20
Bone marrow (No. Examined)	19	20	20	20	20	19	20	20
Increased cellularity, eosinophilic	(5) ^a	(12)	(9)	(15)	(4)	(17)	(10)	(20)
Minimal	5	12	9	15	4	17	10	15
Mild	0	0	0	0	0	0	0	5
Injection site ^b (No. Examined)	19	20	20	20	20	19	20	20
Infiltration, eosinophilic	(4)	(16)	(17)	(18)	(12)	(18)	(20)	(20)
Minimal	4	16	17	16	12	13	13	10
Mild	0	0	0	2	0	5	7	10
Infiltration, mononuclear cell	(0)	(5)	(5)	(6)	(1)	(7)	(9)	(8)
Minimal	0	4	5	6	1	5	4	4
Mild	0	1	0	0	0	2	5	4
Skin (No. Examined)	19	20	20	20	20	19	20	20
Infiltration, eosinophilic	(6)	(9)	(7)	(7)	(5)	(10)	(8)	(16)
Minimal	6	9	7	7	5	10	8	14
Mild	0	0	0	0	0	0	0	2

^a Numbers in parentheses represent the number of animals with the finding.

^b Subcutaneous.

End of Recovery

Injection site: Partial recovery of narsoplimab-related mononuclear cell infiltration at the subcutaneous injection site at 300 mg/kg males and at ≥50 mg/kg females based on a decreased incidence and severity compared to the end of dosing.

Table 98. Narsoplimab–Related Microscopic Findings in Mice JAS at the End of the Recovery Phase (Excerpted From Submission), Study 9000601

Group	Males				Females			
	1	2	3	4	1	2	3	4
Dose (mg/kg)	0	50	150	300	0	50	150	300
No. Animals Examined	10	10	10	10	10	10	9	10
Injection site ^b (No. Examined)	10	10	10	10	10	10	9	10
Infiltration, mononuclear cell	(0) ^a	(0)	(0)	(2)	(0)	(5)	(6)	(4)
Minimal	0	0	0	2	0	5	6	3
Mild	0	0	0	0	0	0	0	1

^a Numbers in parentheses represent the number of animals with the finding.

^b Subcutaneous.

Parameters	Major Findings

Toxicokinetics

There was no significant increase in systemic exposure by increasing the dose from 150 to 300 mg/kg SC.

Narsoplimab accumulated after repeat-dose with ratios for AUC_(0-72h) averaging 5X for the 50 and 150 mg/kg and average of 3.7 for the 300 mg/kg but much lower accumulation at the end of the weekly dosing schedule for AUC_(0-168h) with average of 2.5X for the MD and <2X for the LD and HD.

Table 99. Summary of Narsoplimab TK Assessment in Juvenile Mice (Excerpted From Submission), Study 9000601

PND	Dose		T _{max} (hr)	C _{max} ±SE (µg/mL)	C _{max} /D ±SE (µg/mL/(mg/kg))		AUC ₍₀₋₇₂₎ ±SE (hr*µg/mL)		AUC _{(0-72)/D} ±SE (hr*µg/mL/(mg/kg))	
4	50		72.0	13.5 ± 0.634	0.269 ± 0.0127		756 ± 27.1		15.1 ± 0.541	
		150	72.0	26.7 ± 2.13	0.178 ± 0.0142		1500 ± 59.9		10.0 ± 0.399	
		300	24.0	42.2 ± 1.32	0.141 ± 0.00440		2460 ± 58.9		8.20 ± 0.196	
PND	Dose	Sex	T _{max} (hr)	C _{max} ±SE (µg/mL)	C _{max} /D ±SE (µg/mL/(mg/kg))		AUC ₍₀₋₁₆₈₎ ±SE (hr*µg/mL)		AUC _{(0-168)/D} ±SE (hr*µg/mL/(mg/kg))	
28	50	Male	72.0	34.7 ± 2.16	0.694 ± 0.0431		5150 ± 201		103 ± 4.02	
		Female	72.0	35.8 ± 3.81	0.716 ± 0.0763		5120 ± 342		102 ± 6.84	
		Combined	72.0	35.2 ± 0.770	0.705 ± 0.0154		5130 ± 15.7		103 ± 0.313	
	150	Male	72.0	41.8 ± 4.27	0.279 ± 0.0285		6660 ± 367		44.4 ± 2.45	
		Female	72.0	53.9 ± 6.48	0.359 ± 0.0432		7990 ± 558		53.3 ± 3.72	
		Combined	72.0	47.9 ± 8.52	0.319 ± 0.0568		7320 ± 944		48.8 ± 6.29	
	300	Male	72.0	67.5 ± 3.17	0.225 ± 0.0106		9750 ± 405		32.5 ± 1.35	
		Female	72.0	63.9 ± 8.00	0.213 ± 0.0267		9340 ± 702		31.1 ± 2.34	
		Combined	72.0	65.7 ± 2.55	0.219 ± 0.00851		9540 ± 292		31.8 ± 0.972	
PND	Dose	Sex	T _{max} (hr)	C _{max} ±SE (µg/mL)	C _{max} /D ±SE (µg/mL/(mg/kg))		AUC ₍₀₋₇₂₎ ±SE (hr*µg/mL)		AUC _{(0-72)/D} ±SE (hr*µg/mL/(mg/kg))	
91	50	Male	72.0	67.7 ± 6.66	1.35 ± 0.133		27700 ± 2170		553 ± 43.5	
		Female	72.0	62.0 ± 2.54	1.24 ± 0.0508		17300 ± 2420		346 ± 48.3	
		Combined	72.0	64.9 ± 4.02	1.30 ± 0.0805		22500 ± 7330		449 ± 147	
	150	Male	72.0	112 ± 26.3	0.749 ± 0.175		48200 ± 3430		322 ± 22.9	
		Female	24.0	181 ± 30.9	1.21 ± 0.206		45600 ± 5010		304 ± 33.4	
		Combined	48.0	147 ± 48.4	0.977 ± 0.323		46900 ± 1850		313 ± 12.3	
	300	Male	24.0	139 ± 12.1	0.464 ± 0.0402		57400 ± 3370		191 ± 11.2	
		Female	24.0	154 ± 12.8	0.513 ± 0.0425		44200 ± 2330		147 ± 7.78	
		Combined	24.0	147 ± 10.2	0.488 ± 0.0341		50800 ± 9300		169 ± 31.0	
PND	Dose	Sex	AUC ₍₀₋₁₆₈₎ (hr*µg/mL)	RAUC ₍₀₋₁₆₈₎ (RATIO)	T _{last} (hr)	AUC ₍₀₋₇₂₎ (hr*µg/mL)	RAUC ₍₀₋₇₂₎ (RATIO)	Vd/F (mL/kg)	CL/F (mL/hr/kg)	T _{1/2} (hr)
91	50	Male	9320	1.81	2016	3670	-	4540	13.6	231
		Female	8780	1.71	1344	3980	-	2590	12.6	143
		Combined	9050 ± 387	1.76 ± 0.0699	1680	3830 ± 213	5.07	3560 ± 1380	13.1 ± 0.730	187 ± 62.7
	150	Male	16100	2.42	2016	7130	-	7090	21.0	234
		Female	21300	2.66	1344	10600	-	3300	14.2	161
		Combined	18700 ± 3630	2.54 ± 0.168	1680	8850 ± 2430	5.90	5190 ± 2680	17.6 ± 4.83	197 ± 51.3
	300	Male	16900	1.73	2688	8040	-	13500	37.3	251
		Female	19700	2.11	1344	10200	-	9570	29.3	226
		Combined	18300 ± 1970	1.92 ± 0.265	2016	9140 ± 1550	3.72	11500 ± 2780	33.3 ± 5.66	239 ± 17.4

Parameters	Major Findings
Antidrug-antibody response	No ADA was detected predose on PNDs 4, 28, or 91, or following administration of narsoplimab on PND 28. On PND 91, ADA positive responses were confirmed in 7/89, 8/90, and 3/87 mice at 50, 150, and 300 mg/kg, respectively. The onset of ADA positive samples was on or after 1344 hours following the last dose, for which all their corresponding TK samples had nonquantifiable concentrations of serum narsoplimab. Therefore, all ADA confirmed positive results had no impact on the overall TK interpretation and no serum narsoplimab concentrations were excluded from TK analysis.
Pharmacodynamic assessment – inhibition of the lectin pathway	In general, narsoplimab inhibition was similar in male and female juvenile mice. Inhibition of >70% was frequently observed in all groups after dose administration on PND 91 and was sustained up to 28 days (672 hours) into the recovery period. Inhibitory activity decreased overtime, but it was ≥50% at the end of the 16-week recovery period (2688 hours). Narsoplimab inhibition of the complement lectin pathway was similar at the LD of 50 mg/kg/dose compared to the MD and HD of 150 and 300 mg/kg/dose.

Source: Study Report # 9000601

Abbreviations: ADA, antidrug antibody; HD, high dose; JAS, juvenile animal studies; LD, low dose; MD, mid dose; NK, natural killer; PND, postnatal day; SC, subcutaneous; TK, toxicokinetic

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

None.

14.2. In Vivo Studies

Narsoplimab IV and SC Single Ascending Dose (OMS721-NHV-001)

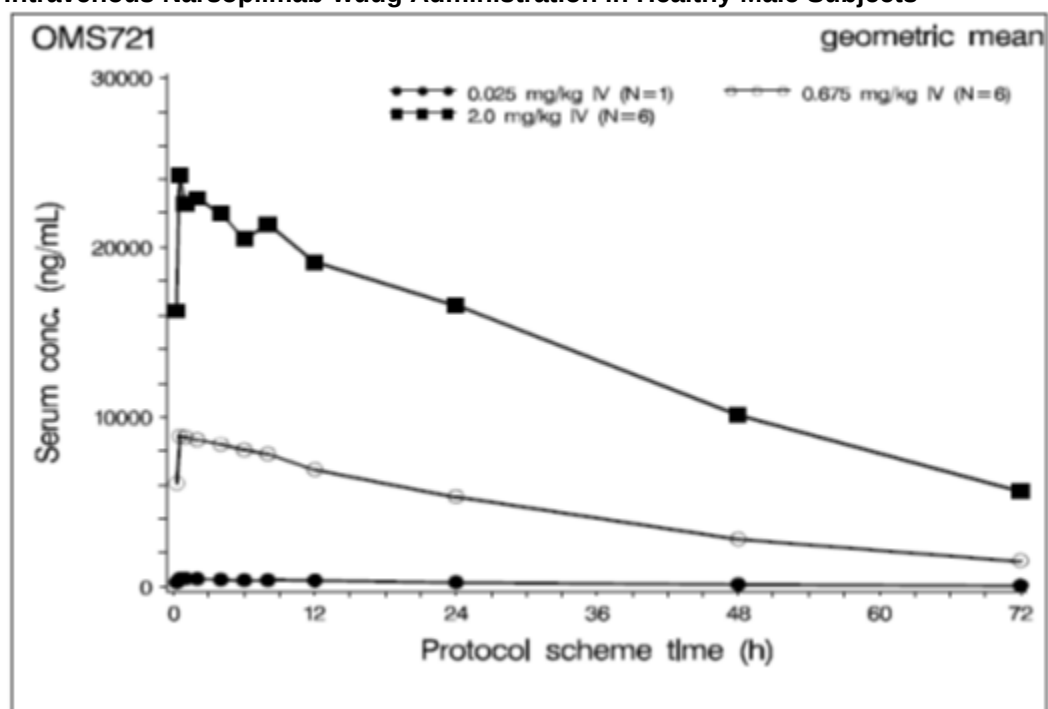
Study Design

Study OMS721-NHV-001 was a Phase 1, sequential, single dose, escalation study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and ADA response of narsoplimab-wuug or placebo given via IV and SC administration in healthy male subjects.

There were 7 cohorts with weight-based dosing of narsoplimab-wuug administered via IV infusion (30 min) or SC injection. The doses were 0.025, 0.675, and 2 mg/kg for IV administration and 0.075, 0.225, 0.675, and 2 mg/kg for SC administration.

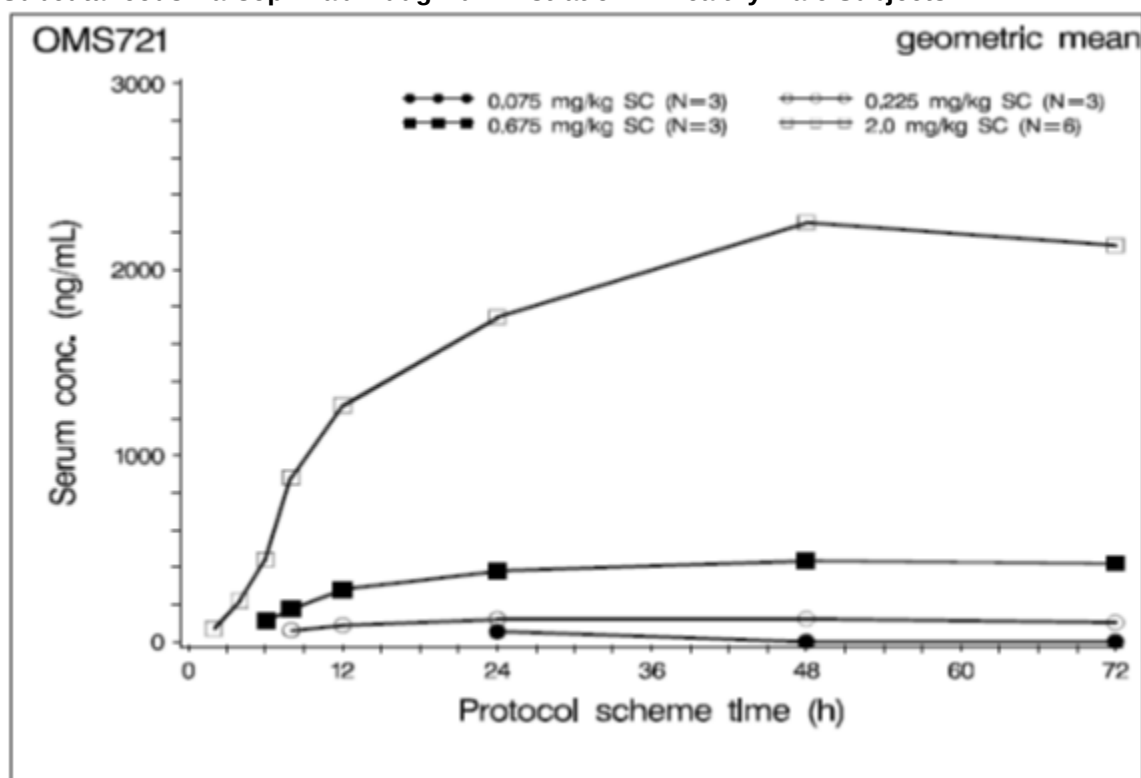
Results

Figure 14. Mean Narsoplimab-wuug Concentration-Time Profile Following Single Dose Intravenous Narsoplimab-wuug Administration in Healthy Male Subjects



Source: Applicant's Figure 14.2.3

Figure 15. Mean Narsoplimab-wuug Concentration-Time Profile Following Single Dose Subcutaneous Narsoplimab-wuug Administration in Healthy Male Subjects



Source: Applicant's Figure 14.2.3

Table 100. Summary of Pharmacokinetic Parameters Following Single Dose Intravenous and Subcutaneous Administration of Narsoplimab-wuug in Healthy Male Subjects

Summary Statistics of Serum PK Parameters for OMS721 Administered IV and SC (Geometric Mean; Min-Max)							
Route	Treatment	N	C _{max} (µg/mL)	t _{max} * (h)	AUC _{0-inf} (µg.h/mL)	CL (L/h)	t _{1/2} (h)
IV	0.025 mg/kg (IV1)	1	0.499	1.00	21.3	0.111	31.5
	0.675 mg/kg (IV2)	6	9.10	0.74	430	0.120	37.5
			(7.47-10.8)	(0.48-6.02)	(375-541)	(0.103-0.151)	(33.8-53.0)
	2.0 mg/kg (IV3)	6	24.8	0.48	1410	0.123	78.9
			(21.7-30.3)	(0.48-8.00)	(1004-2192)	(0.0864-0.161)	(44.4-104)
SC	0.075 mg/kg (SC1)*	2	0.126	348.00			
			(0.0642-0.247)	(24.00-672.00)			
	0.225 mg/kg (SC2)	3	0.128	48.00	18.0	1.20	69.9
			(0.0900-0.207)	(24.00-48.00)	(12.4-22.2)	(0.864-2.18)	(53.5-110)
	0.675 mg/kg (SC3)	3	0.440	48.07	117	0.484	180
			(0.290-0.673)	(24.03-72.00)	(71.1-169)	(0.341-0.679)	(143-282)
	2.0 mg/kg (SC4)	6	2.36	48.00	453	0.364	163
			(0.626-5.39)	(24.00-72.00)	(165-979)	(0.171-0.867)	(130-205)

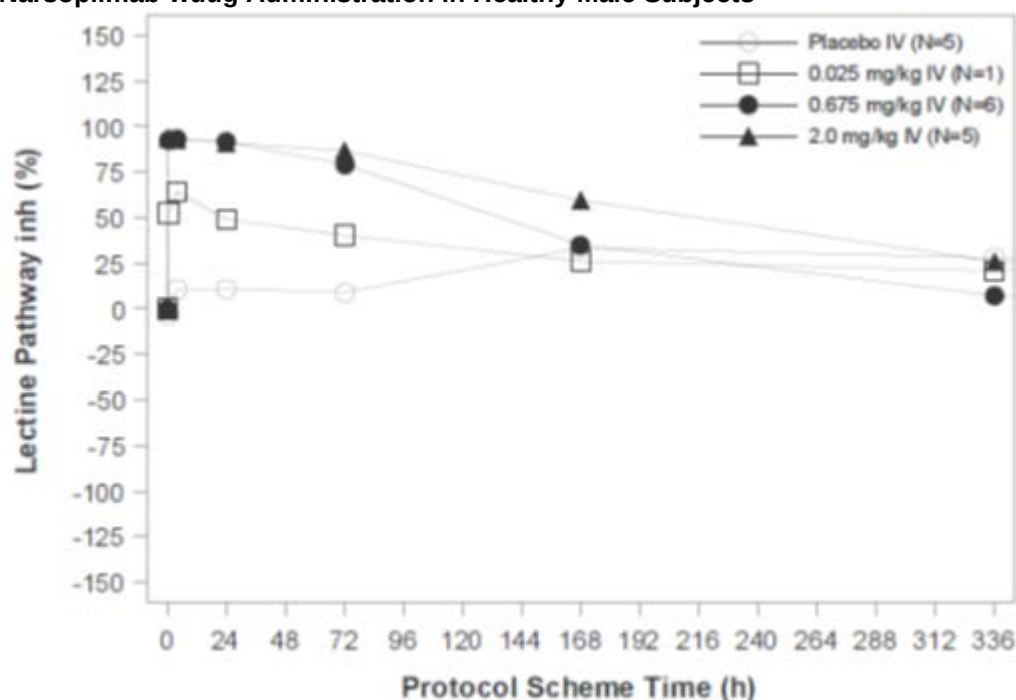
IV = intravenous; Max = maximum; Min = minimum; N = number of subjects; PK = pharmacokinetic; SC = subcutaneous.

*For t_{max} the median (range) is presented.

*For the 0.075 mg/kg SC dose level, geometric mean AUC_{0-inf}, CL/F and t_{1/2} could not be determined.

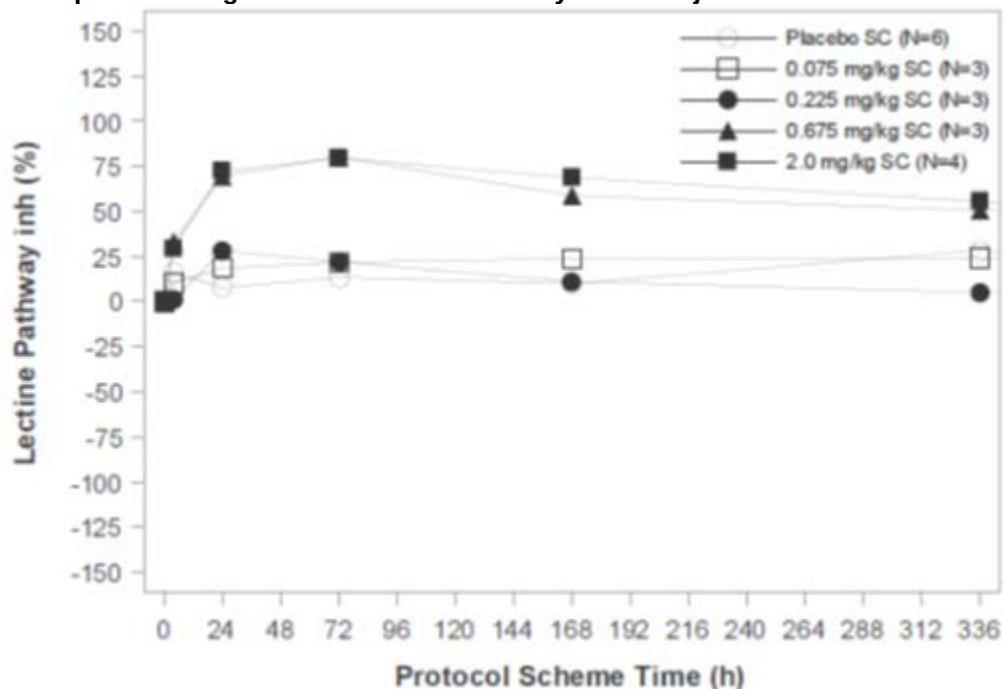
Source: Applicant's Table, page 10 of 1199 study report OMS721-nhv-001

Figure 16. Mean Lectin Pathway Inhibition, C4d Inhibition Following Single Dose Intravenous Narsoplimab-wuug Administration in Healthy Male Subjects



Source: Applicant's Figure 14.3.2

Figure 17. Mean Lectin Pathway Inhibition, C4d Inhibition Following Single Dose Subcutaneous Narsoplimab-wuug Administration in Healthy Male Subjects



Source: Applicant's Figure 14.3.2

Conclusions

For the IV route, there was approximately dose proportional increases in C_{max} and AUC_{0-inf} . Clearance (CL) was the same for the three IV doses evaluated. For the SC route of administration, there was greater than dose proportional increase for AUC_{0-inf} and dose proportional for C_{max} .

For highest single dose 2 mg/kg narsoplimab-wuug IV, the median (range) T_{max} was approximately 0.5 (0.5-8.0) h and mean (range) half-life was 79 (44-104) h. At the 2 mg/kg dose, IV administration resulted in approximately 3.1-fold higher exposure (AUC_{0-inf}) and approximately 10-fold higher maximum concentration (C_{max}), compared to SC administration.

Inhibition of the lectin pathway as assessed by C4d inhibition was considered high (80% from baseline) for 0.675 and 2 mg/kg for up to 72 h postdose and highest (~100%) 0.5 to 4 h postdose. The inhibition following lowest IV dose of 0.25 mg/kg was moderate (50-80% inhibition) on Day 1 and declined to baseline afterwards. SC administration resulted in a lower C4 inhibition, compared to IV dosing.

Narsoplimab-wuug IV and SC Multiple Ascending Dose (OMS721-NHV-002)

Study Design

Study OMS721-NHV-002 was a Phase 1, placebo-control, sequential, multiple dose escalation study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and ADA response of narsoplimab-wuug or placebo given via IV and SC administration in about 90 healthy male and female subjects. The objectives of the study were to characterize multiple dose pharmacokinetics, assess safety, pharmacodynamic markers of lectin pathway inhibition, and development of antidrug antibody.

The purpose of including both daily and weekly administration regimens was to assess the potential of providing trough serum narsoplimab-wuug concentrations that can adequately inhibit the lectin pathway. The Applicant anticipated that once daily administration would result in higher trough and lower peak serum narsoplimab-wuug concentrations and a decrease in intersubject variability, compared to weekly administration.

There were 10 cohorts, two dosing schemes (weight-based dosing or fixed dosing), and two routes of administration (IV or SC).

Cohorts 1-6 received **IV or SC once weekly** administration of narsoplimab-wuug or placebo for 6 weeks:

- Cohort 1: IV once weekly doses of 2 mg/kg narsoplimab-wuug or placebo
- Cohort 2: IV once weekly doses of 4 mg/kg narsoplimab-wuug or placebo
- Cohort 3: SC once weekly doses of 2 mg/kg narsoplimab-wuug or placebo
- Cohort 4: SC once weekly doses of 4 mg/kg narsoplimab-wuug or placebo

- Cohort 5: SC once weekly doses of 6 mg/kg narsoplimab-wuug or placebo
- Cohort 6: SC once weekly doses of 8 mg/kg narsoplimab-wuug or placebo

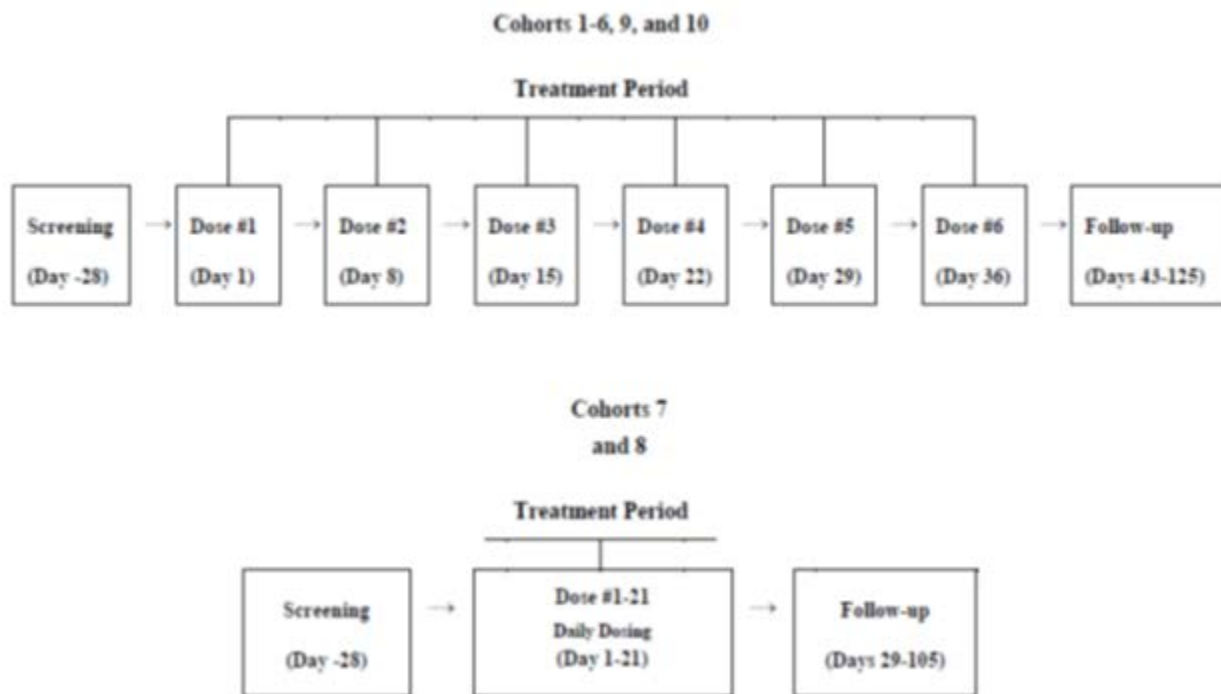
Cohorts 7 and 8 received SC daily with fixed doses administration narsoplimab-wuug or placebo for 3 weeks

- Cohort 7: SC daily doses of 50 mg narsoplimab-wuug or placebo
- Cohort 8: SC daily doses of 150 mg narsoplimab-wuug or placebo

Cohorts 9 and 10 received SC once weekly with fixed doses administration of narsoplimab-wuug or placebo for 6 weeks

- Cohort 9: SC once weekly doses of 370 mg narsoplimab-wuug or placebo
- Cohort 10: SC once weekly doses of 740 mg narsoplimab-wuug or placebo

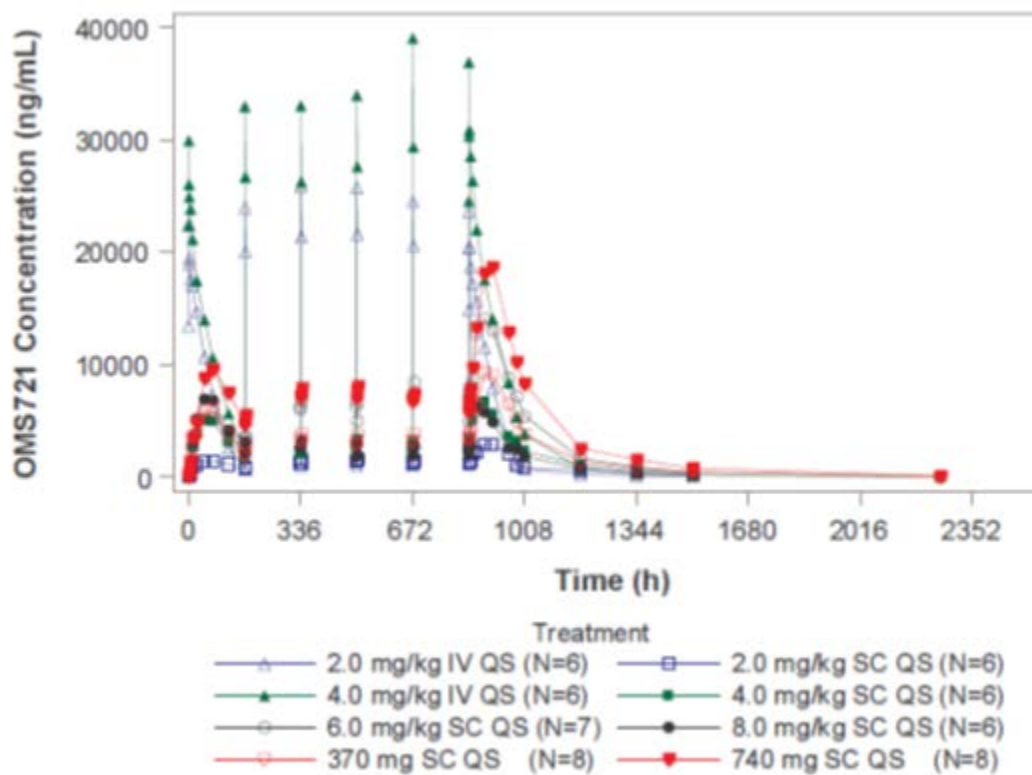
Figure 18. Schematic of Study Design



Source: Applicant's Figure 1

Results

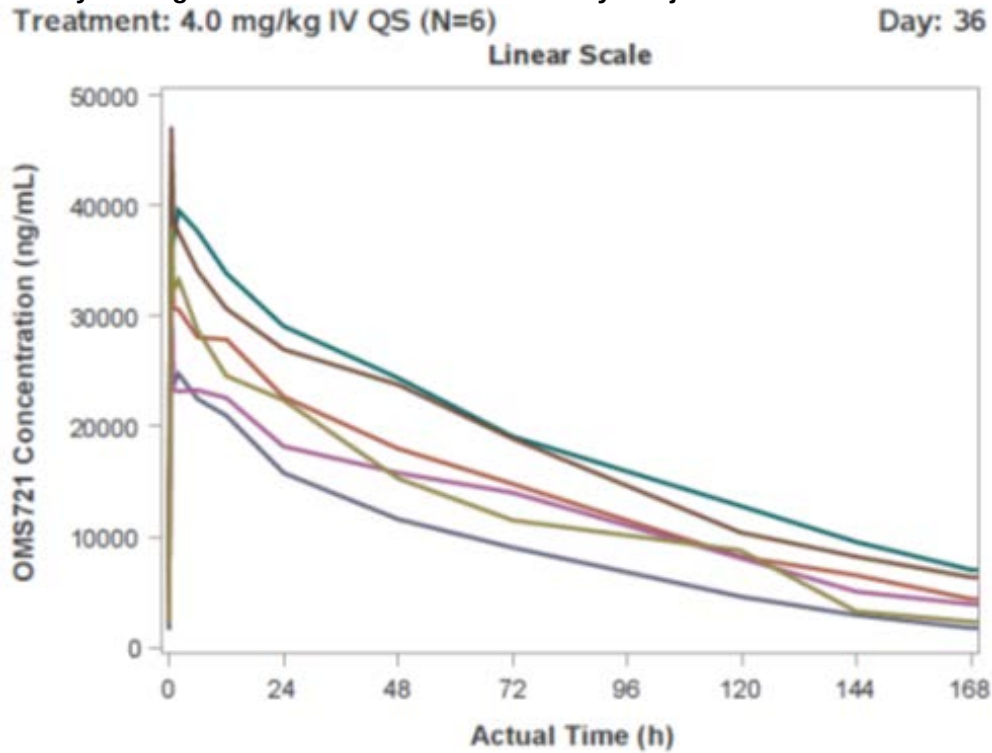
Figure 19. Mean Narsoplimab-wuug Concentration Versus Time Profiles Following Narsoplimab-wuug Intravenous and Subcutaneous Once Weekly Dosing in Healthy Subjects



Source: Applicant's Figure 15.2.3

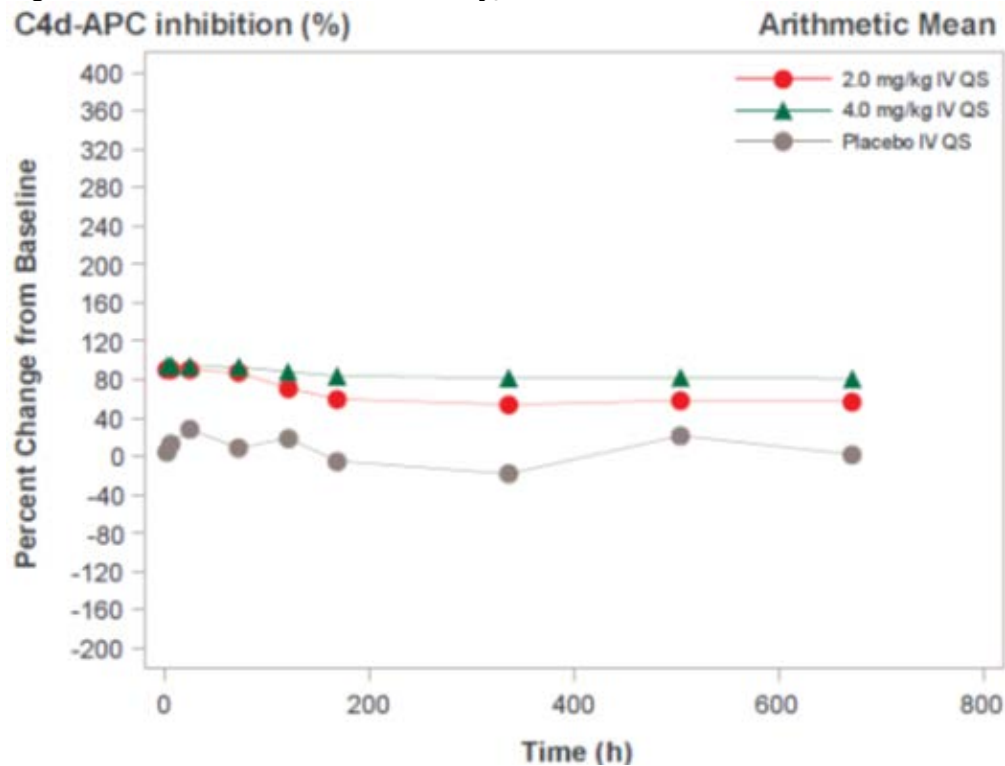
Abbreviations: IV, intravenous; SC, subcutaneous; QS, once weekly

Figure 20. Narsoplimab-wuug Concentration versus Time Profile Following 4 mg/kg IV Once Weekly Dosing for 6 Weeks in Individual Healthy Subjects



Source: Applicant's Figure 15.2.4
Abbreviations: IV, intravenous; QS, once weekly

Figure 21. Inhibition of Lectin Pathway, Mean % Inhibition of C4d From Baseline



Source: Applicant's Figure 15.3.4

Conclusions

Steady-state serum narsoplimab-wuug concentrations were reached by the third (Day 15) IV once weekly injection of 4 mg/kg narsoplimab-wuug. Mean (range) accumulation ratio for 4 mg/mL IV once weekly was 1.3 (1.0-1.8) based upon Day 36/Day1 serum concentrations.

Narsoplimab-wuug 2 and 4 mg/kg administered intravenously once weekly (represented as blue and green triangles in [Figure 20](#)) resulted in the greatest serum concentration over the 6 weeks of treatment. Subcutaneous dosing with fixed doses or weight-based dosing resulted in lower systemic exposure.

The Applicant postulated that inhibition of C4d is representative of lectin pathway inhibition. With 2 mg/kg administered once weekly by intravenous infusion, C4d inhibition of approximately 90% was achieved after the first dose and later in the treatment (~Day 36); however, it was not maintained (>80%) over each dosing period during the 6-week treatment period.

With 4 mg/kg administered once weekly by intravenous infusion, C4d inhibition of approximately 95% was achieved and a high level was maintained (>80%) over each dosing period during the 6-week treatment period. Compared to 2 mg/kg IV, the higher 4 mg/kg once weekly IV dose exhibited greater C4d inhibition and was within the target to anticipate clinical benefit as per the Applicant.

Subcutaneous dosing regimens up to 8 mg/kg, 370 mg, 740 mg once weekly and 50 mg and 150 mg once daily were not able to maintain the same degree of persistent C4d inhibition as 4 mg/mL IV once weekly.

14.3. Pharmacometrics Review

In general, the Applicant's population PK-PD analysis is considered acceptable in describing the observed narsoplimab-wuug concentrations in healthy subjects and patients. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined below:

Table 101. Specific Comments on Applicant's Final Population PK and PD Model

Table 202: Specific Comments on Applicant's Final Population PK and PK-PD Model	
Utility of the Final Model	Reviewer's Comments
Support Applicant's proposed labeling statements (b) (4)	(b) (4)
Derive exposure metrics for exposure-response analyses	• PK model was used to predict C_{min}, C_{max}, AUC. • The PK-PD model was used to justify the selection of 4 mg/kg IV dosing in the Phase 2 studies as it was expected to maintain mean lectin pathway inhibition (using C4d as a marker) >80% up to 168 hours (proposed dosing interval). Complement 4d inhibition (C4d) is a pharmacodynamic marker and not an efficacy endpoint in evaluating treatment response. • The Applicant's final model is generally acceptable for generating exposure metrics. However, the PK modelling was not considered reliable for estimating the effect of plasma therapy on the drug's exposure. • No association was observed between narsoplimab-wuug trough concentrations or the level of mean C4d inhibition and the response to narsoplimab-wuug treatment in patients with HSCT-TMA. Therefore, the mechanistic role of C4d inhibition to predict treatment response is not clear.

Utility of the Final Model		Reviewer's Comments
Predict exposures at alternative dosing regimen	• No alternative dosing regimen were predicted via PK modeling. • The Applicant did not provide clinical justification or PK data (either through a dedicated study or PK modeling) to support the need for an additional narsoplimab-wuug dose of 2 mg/kg after each plasma therapy event.	• The PK modelling was not considered reliable for predicting the effect of plasma therapy on the drug's exposure. Therefore, the need as well as the strength and frequency of supplemental dosing post-plasma exchange could not be reliably evaluated. • Although the reviewer's PK simulation did not show plasma exchange to affect narsoplimab-wuug exposure, the data collected in clinical studies to evaluate the impact of plasma exchange on narsoplimab-wuug clearance is not adequate. As plasma exchange, in general, is known to remove monoclonal antibodies from plasma, we agree with the recommendation of a supplemental dose of 2 mg/kg following each plasma exchange. The supplemental dose of 2 mg/kg was administered in clinical trials and the safety is established. Nevertheless, a dedicated PK study to evaluate the impact of plasma exchange on narsoplimab-wuug clearance should be considered as a postmarketing requirement to accurately assess the need and the amount of supplemental dose required post-plasma exchange.

Source: FDA Reviewer
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma drug concentration; C_{min}, minimum plasma drug concentration; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous(ly); PD, pharmacodynamic; PK, pharmacokinetic

14.3.1. Applicant's Population PK Analysis

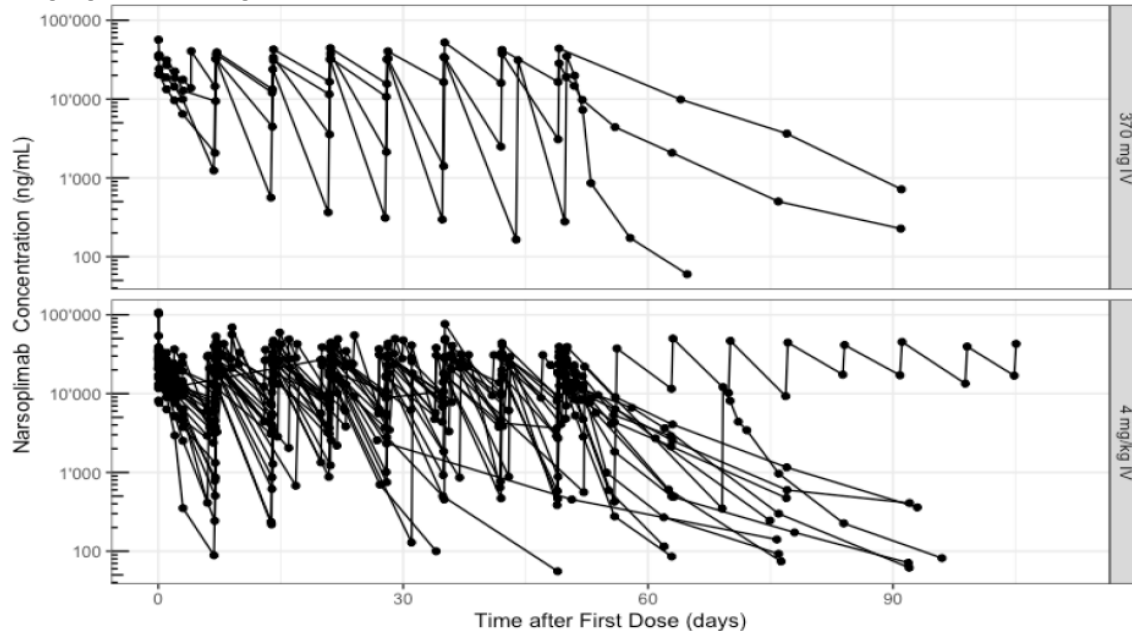
The population PK (popPK) analysis was based on PK data from 4 studies ([Table 102](#)): Two Phase 1 studies in healthy subjects (OMS721-NHV-001 and OMS721-NHV-002) and two Phase 2 studies in different patients' populations (OMS721-GNP-001 and TMA-001) with thrombotic microangiopathies (TMAs) or glomerulopathies (GNPs). Narsoplimab-wuug was administered by either an SC injection or 30-minute IV infusion in healthy subjects. In Phase 2 studies, Narsoplimab-wuug was administered as 30-minute IV infusion. Only narsoplimab-wuug serum concentration data from the IV arms were used for the popPK analysis.

The analysis dataset comprised of 3330 PK observations from 110 subjects, including 159 below quantification limit concentrations. The planned timing of blood samples for narsoplimab-wuug, ADA, and inhibition of *ex-vivo* lectin-mediated complement pathway activation (inhibition of complement component 4d - C4d - formation) measurements are presented in [Table 103](#).

The summary statistics for the continuous and categorical covariates are presented by study in [Table 104](#). Twenty-eight adult patients with HSCT-TMA were enrolled in Study TMA-001 and during the whole clinical development program of narsoplimab-wuug.

Twenty-four patients with HSCT-TMA (median [range] weight =69 kg [51 – 134 kg]) received a narsoplimab-wuug dose of 4 mg/kg and 4 patients with HSCT-TMA (weight =71 kg [52 – 83 kg]) received a dose of 370 mg/kg ([Figure 22](#)).

Figure 22. Observed Individual Narsoplimab-wuug Serum Concentration-Time Profiles Under 4 mg/kg and 370 mg in HSCT-TMA Patients



Source: Applicant's Summary of Clinical Pharmacology Studies, Figure 7, page 28.

Table 102. Summary of Narsoplimab-wuug Clinical Studies

Study Number	Study Objectives	Narsoplimab Dose Regimens	No of IV Narsoplimab-Treated Subjects/Patients	Narsoplimab Formulation
Phase 1 Studies				
OMS721-NHV-001	Safety, tolerability, PK, PD, and immunogenicity of single IV and SC administrations of narsoplimab in healthy male subjects	0.025 mg/kg, 0.675 mg/kg, and 2 mg/kg	N = 13 (1 at 0.025 mg/kg, 6 at 0.675 mg/kg, and 6 at 2 mg/kg)	100 mg/mL (batch # ORO503EC)
OMS721-NHV-002	Safety, tolerability, PK, PD, and immunogenicity of multiple IV and SC administrations of narsoplimab in healthy subjects	2 mg/kg qw total of 6 doses 4 mg/kg qw total of 6 doses	N = 12 (6 at 2 mg/kg and 6 at 4 mg/kg)	100 mg/mL (lot # 14MM-006) ¹
Phase 2 Studies				
OMS721-TMA-001	Safety, efficacy, PK, PD, immunogenicity of multiple IV administrations of narsoplimab in patients diagnosed with thrombotic microangiopathies	28 HSCT-TMA patients; 4 or 8 x 4 mg/kg qw IV infusions total or 4 or 8 x 370 mg qw IV infusions 5 TTP patients; 4 x 2 mg/kg qw IV or 4 or 8 x 4 mg/kg qw IV 25 aHUS patients; 4 x 0.675 mg/kg qw IV, or 4 x 2 mg/kg qw IV, or 4 x 4 mg/kg qw IV, or 12 or 24 x 4 mg/kg qw IV	N = 58 (HSCT-TMA; 24 at 4 mg/kg and 4 at 370 mg) (TTP; 1 at 2 mg/kg and 4 at 4 mg/kg) (aHUS; 3 at 0.675 mg/kg, 2 at 2 mg/kg, and 20 at 4 mg/kg)	100 mg/mL (lot # 14MM-041, 070I0915; 108I0316; 005I0316) 185 mg/mL (lot # 056I0616; 051I0517)
OMS721-GNP-001	Safety, efficacy, PK, PD, immunogenicity of multiple IV administrations of narsoplimab in patients diagnosed with complement-mediated glomerulonephropathy disorders	5 LN, 5 MN patients; 12 x qw IV at 4 mg/kg. 17 IgAN patients; 12 x qw IV at 4 mg/kg or 370 mg ²	N = 27	100 mg/mL (lot # 066I0715; 070I0915; 018I0316; 005I0316) 185 mg/mL (lot # 056I0616; 024I0418)

Abbreviations: aHUS = atypical hemolytic uremic syndrome; CTD = Common Technical Document; HSCT-TMA = hematopoietic stem cell transplant-associated thrombotic microangiopathy; IgAN = IgA nephropathy; IV = intravenous; LN = lupus nephritis; MN = membranous nephritis; N = number; No = number; PD = pharmacodynamic; PK = pharmacokinetic; qw = once weekly; SC = subcutaneous; TTP = thrombotic thrombocytopenic purpura.

¹ Subjects in the IV cohorts received the 100 mg/mL formulation. Subjects in the SC arms received the 185 mg/mL formulation.

² Eleven patients received 4 mg/kg (100 mg/mL formulation), 2 patients received 4 mg/kg x 12 followed by 370 mg (100 mg/mL formulation), 1 patient received 4 mg/kg (100 mg/mL formulation) followed by 370 mg (both the 100 mg/mL and 185 mg/mL formulations), 2 patients received D5W only, 5 patients received D5W followed by 370 mg (100 mg/mL formulation), 1 patient received D5W followed by 370 mg (both the 100 mg/mL and 185 mg/mL formulation), 6 patients received 370 mg (100 mg/mL formulation), and 1 patient received 370 mg (both 100 mg/mL and 185 mg/mL formulations).

Source: Applicant's Summary of Clinical Pharmacology Studies, Table 1, page 10

Table 103. Summary of Sampling Schedules

Studies	Samples	Sampling Times
OMS721-NHV-001	PK	Predose, at 15 min, 0.5, 1, 2, 4, 6, 8, 12, 24, 72 hours, Day 8, 15, 22, 29, 60, and 90 postdose.
	ADA	Predose and at Day 15, 29, 60, and 90.
	PD	Predose and at 4, 24, 72 hours, Day 8, 15, 22, 29, 60, and 90 postdose.
OMS721-NHV-002	PK	Predose, and at 15 min, 0.5, 1, 2, 6, 12, 24, 72, and 120 hours following the first dose (Day 1) and last dose (Day 36). Sparse sampling was conducted at predose, 0.5 and 2 hours postdose for each intervening IV infusion and then at Day 50, 57, 64, 95, and 125.
	ADA	Prior to each IV infusion and then at Day 50, 57, 64, 95, and 125.
	PD	Predose, and at 2, 6, 24, 72, and 120 hours after each IV infusion and then at Day 50, 57, 64, 95, and 125.
OMS721-TMA-001	PK	Predose, 5 min, 2, 24, 48, and 72 hours after the first dose, and at predose and 2 hours postdose for all subsequent IV infusions.
	ADA	Prior to each IV infusion and on study Day 57, 64, 78, and 92.
	PD	Prior to each dose and 2 hours after each dose.
OMS721-GNP-001	PK	Predose, 5 min, 2, 24, and 72 hours after the first dose, and at predose and 0.5 hours postdose for all subsequent IV infusions.
	ADA	Prior to each IV infusion and on study Day 85 and 148.
	PD	Prior to each dose and 2 hours after the first dose, and at predose and 0.5 hours postdose for subsequent IV infusions.

Source: Adapted from the Applicant's Integrated Summary of Immunogenicity (pages 16-17) and OMS721-GNP-001 Protocol (pages 69-73).

PD: inhibition of *ex-vivo* lectin-mediated C4d formation

Abbreviations: ADA, antidrug antibody; IV, intravenous(ly); PD, pharmacodynamic; PK, pharmacokinetic

Table 104. Summary of Demographic Characteristics

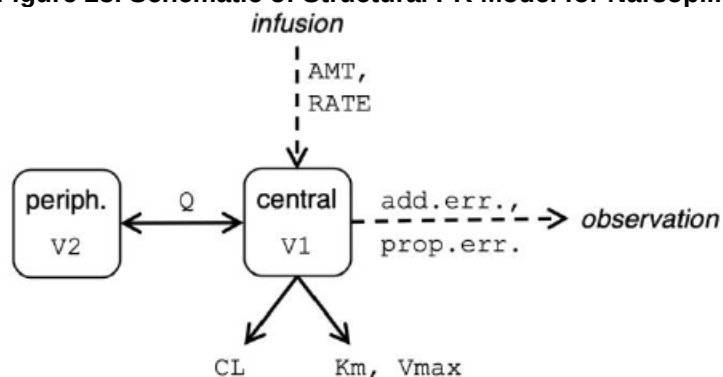
	OMS721-NHV-001 (N=13)	OMS721-NHV-002 (N=12)	OMS721-GNP-001 (N=27)	OMS721-TMA-001 (N=58)	Overall (N=110)
Study subjects					
Healthy	13 (100%)	12 (100%)	0 (0%)	0 (0%)	25 (22.7%)
IgAN	0 (0%)	0 (0%)	17 (63.0%)	0 (0%)	17 (15.5%)
other GNP	0 (0%)	0 (0%)	10 (37.0%)	0 (0%)	10 (9.1%)
aHUS	0 (0%)	0 (0%)	0 (0%)	25 (43.1%)	25 (22.7%)
HSCT_TMA	0 (0%)	0 (0%)	0 (0%)	28 (48.3%)	28 (25.5%)
TTP	0 (0%)	0 (0%)	0 (0%)	5 (8.6%)	5 (4.5%)
Age (years)					
Mean (SD)	34.0 (13.7)	39.3 (11.6)	41.0 (14.2)	46.7 (16.3)	43.0 (15.5)
Median [Min, Max]	27.0 [20.0, 53.0]	41.0 [22.0, 54.0]	35.0 [24.0, 76.0]	48.0 [18.0, 84.0]	44.0 [18.0, 84.0]
Weight (kg)					
Mean (SD)	82.8 (9.05)	81.9 (14.7)	93.2 (27.1)	72.5 (18.7)	79.8 (21.5)
Median [Min, Max]	83.8 [67.1, 94.7]	79.3 [56.7, 109]	91.7 [47.9, 135]	67.7 [44.6, 134]	77.2 [44.6, 135]
BMI (kg/m2)					
Mean (SD)	25.2 (2.85)	25.6 (3.58)	32.3 (8.41)	25.3 (5.45)	27.0 (6.62)
Median [Min, Max]	24.6 [20.5, 31.1]	25.2 [19.3, 31.3]	32.0 [20.1, 49.2]	23.8 [16.7, 42.3]	25.2 [16.7, 49.2]
Baseline albumin (g/L)					
Mean (SD)	46.3 (2.02)	46.4 (1.83)	34.9 (5.20)	35.0 (6.46)	37.5 (7.22)
Median [Min, Max]	47.0 [43.0, 50.0]	46.5 [43.0, 49.0]	36.0 [22.0, 47.0]	34.0 [22.0, 52.0]	36.0 [22.0, 52.0]
Individual dose (mg)					
Mean (SD)	104 (69.2)	238 (71.0)	348 (72.8)	277 (107)	270 (115)
Median [Min, Max]	56.6 [2.36, 189]	222 [142, 335]	370 [188, 530]	276 [30.0, 540]	275 [2.36, 540]
Treatment arm					
0.025 mg/kg	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
0.675 mg/kg	6 (46.2%)	0 (0%)	0 (0%)	3 (5.2%)	9 (8.2%)
2 mg/kg	6 (46.2%)	6 (50.0%)	0 (0%)	3 (5.2%)	15 (13.6%)
4 mg/kg	0 (0%)	6 (50.0%)	15 (55.6%)	44 (75.9%)	65 (59.1%)
370 mg	0 (0%)	0 (0%)	12 (44.4%)	4 (6.9%)	16 (14.5%)
400 mg	0 (0%)	0 (0%)	0 (0%)	4 (6.9%)	4 (3.6%)
ADA status					
Negative	9 (69.2%)	9 (75.0%)	16 (59.3%)	47 (81.0%)	81 (73.6%)
Positive	4 (30.8%)	3 (25.0%)	11 (40.7%)	11 (19.0%)	29 (26.4%)
Plasma therapy					
no Plasma therapy	13 (100%)	12 (100%)	27 (100%)	51 (87.9%)	103 (93.6%)
Plasma exchange	0 (0%)	0 (0%)	0 (0%)	6 (10.3%)	6 (5.5%)
Plasma infusion	0 (0%)	0 (0%)	0 (0%)	1 (1.7%)	1 (0.9%)

Source: Reviewer's Summary from the Population PK datasets.

Base PK Model

The pharmacokinetics of narsoplimab-wuug following IV administration was described by a 2-compartment distribution model with parallel linear, and nonlinear Michaelis Menten elimination (Figure 23). The PK model was parameterized in terms of CL, central and peripheral volumes of distribution (V1 and V2 respectively), intercompartmental clearance (Q), maximum saturable elimination rate (V_{max}) and the Michaelis-Menten constant (K_m : Narsoplimab-wuug concentration that achieves half V_{max}). Between subject variability (BSV) was estimated on all parameters. The residual error model consisted of a combined additive and proportional error model.

Figure 23. Schematic of Structural PK Model for Narsoplimab-wuug



Source: Applicant's Population PK Report, Figure 8, page 37.

Covariates Analysis

A stepwise covariate modeling procedure was used in order to build the covariate model, with a significance level of 0.05 for the forward inclusion and 0.001 for the backward deletion step.

The following covariates were included in the final model:

- Baseline Body Weight on CL using a power model, centered at 77.2 kg.
- Albumin as a time varying covariate on CL using a proportional linear model, centered at 38 g/L.
- Baseline albumin on V1 using a power model, centered at 36 g/L.
- Dose on V1 using a power model, centered at 260 mg.
- Antidrug antibody positive status as a time varying covariate on V_{max} (using linear proportional model).
- Albumin as a time varying covariate on K_m using a power model, centered at 38 g/L.
- Health status on K_m and V_{max} (using proportional linear model).

Body weight was not found to be a statistically significant covariate on the volumes of distribution. A total of 7 patients from Study TMA-001 (n=58) received plasma therapy (PLT) on the day of narsoplimab-wuug treatment or later during narsoplimab-wuug treatment, with 6 of 58 patients receiving plasma exchange and 1 patient receiving plasma infusion. The frequency of

plasma therapy varied between patients (Table 104). The effect of plasma therapy on narsoplimab-wuug CL was evaluated in the PK model and deemed not clinically significant.

Final Model

The parameter estimates from the final popPK model for narsoplimab-wuug are listed in Table 105. For an average 77.2 kg patient with a baseline albumin level of 36 g/L, an average albumin over time of 38 g/L, and no ADA, treated with 4 mg/kg narsoplimab-wuug, the population estimates for narsoplimab-wuug CL, V1, V2, Q, Km and V_{max} are 0.12 L/h (2.9 L/day); 10.9 L, 4.64 L, 0.021 L/h (0.5 L/day), 5705 ng/mL, and 0.346 mg/h (8.31 mg/day). The interindividual random effect (ETA) shrinkage from the final popPK model was 10.3%, 7.5%, 22.8%, 32.8%, 32.6%, and 40.9% for CL, V1, Q, V2, Km and V_{max}.

Table 105. Parameter Estimates From Final Population PK Model

Param.	Role	Estimate	Fixed	Rel.Std.Err.	95% CI
CL	TV (L/h)	0.12	No	26.2%	[0.0583, 0.182]
	albumin over time slope (g/L / L/h)	-0.0136	No	2.1%	[-0.0141, -0.013]
	weight exponent	0.726	No	6.1%	[0.639, 0.813]
	BSV _a	0.438	No	10.0%	[0.352, 0.524]
V1	TV (L)	10.6	No	18.7%	[6.72, 14.5]
	baseline albumin exponent	-0.505	No	21.8%	[-0.721, -0.289]
	dose exponent	0.167	No	35.3%	[0.0514, 0.283]
	BSV _a	0.308	No	23.9%	[0.164, 0.452]
Q	TV (L/h)	0.0214	No	17.4%	[0.0141, 0.0288]
	BSV _a	1.31	No	13.7%	[0.962, 1.67]
V2	TV (L)	4.64	No	36.8%	[1.29, 7.99]
	BSV _a	0.545	No	1.1%	[0.533, 0.557]
Km	TV (ng/mL)	4872	Yes	—	—
	% change for patients	17.1	No	27.2%	[7.97, 26.2]
	albumin over time exponent	-2.96	No	49.8%	[-5.85, -0.0712]
	BSV _a	1.51	No	2.8%	[1.42, 1.59]
Vmax	TV (mg/h)	0.433	Yes	—	—
	% change for patients	-20	No	5.9%	[-22.3, -17.7]
	% change for ADA-positive	143	No	0.4%	[142, 144]
	BSV _a	0.697	No	0.6%	[0.689, 0.705]
RV	prop.err.	26.3	No	11.9%	[20.1, 32.4]
	add.err. (%)	65.2	No	0.6%	[64.3, 66]

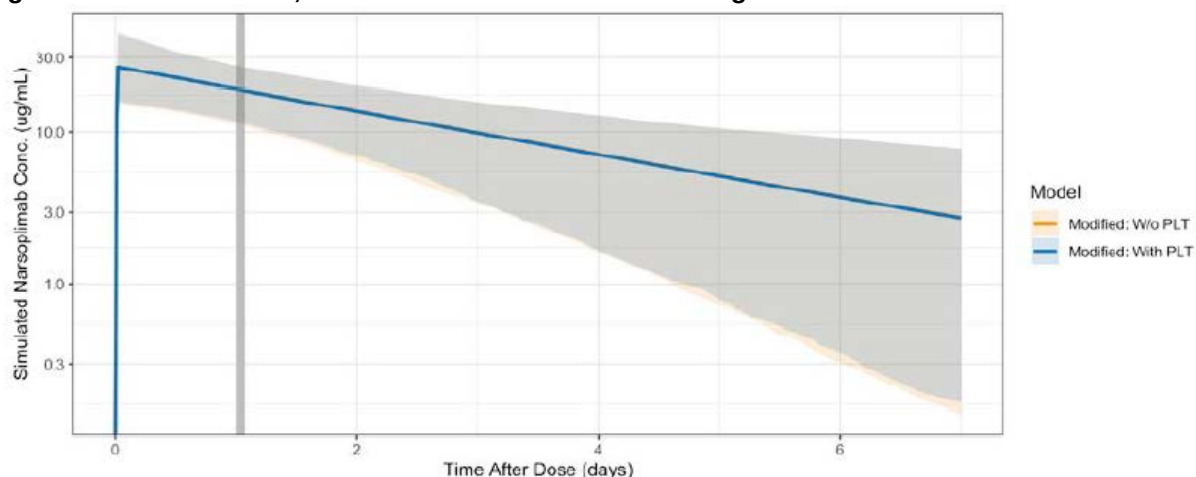
^a Estimates for between subject variability (BSV) parameters reported on SD scale.
Source: Applicant's Population PK Report, Table 14, page 43.

Albumin was identified as a major covariate explaining parts of the between subject variability on CL, V1, and Km. Further covariate effects were body weight on CL, dose on V1, ADA status on V_{max}, and health status on Km and V_{max}.

Most of patients who received plasma therapy on the day of treatment start or later (median plasma therapy duration of 1:75 h, ranging from 1 h to 2.87 h) received a supplemental narsoplimab-wuug dose of about 2 mg/kg after plasma therapy. The effect of plasma therapy on narsoplimab-wuug CL was never investigated in a dedicated study. Based on an information request, the Applicant assessed the effect of plasma therapy on CL using the developed final popPK model. The increase in narsoplimab-wuug clearance during plasma therapy was estimated to be 37.1% or 0.045 L/h for a typical patient. The modified popPK model could estimate the effect of plasma therapy on narsoplimab-wuug CL with reasonable precision (relative standard error of 19.9%), with a 95% confidence interval (CI) of the mean plasma effect ranging from 22.6% to 51.6%. However, the precision of the remaining PK parameters substantially decreased, indicating that the included outliers caused substantial numerical instabilities in the PK model. Based on a likelihood ratio test, the modified model was fitting the data significantly better (p -value=0.025) compared to the previously reported final popPK model. However, the addition of plasma therapy as covariate on CL did not reduce the unexplained BSV on CL. In addition, single 4 mg/kg dose PK simulations in a reference subject (70 kg, with median albumin concentrations and no ADA) without or with about 2 hours PLT after 24 hours of narsoplimab-wuug treatment initiation showed no noticeable difference in narsoplimab-wuug PK profile ([Figure 24](#)), with overlapping PK profiles. In view of these results the Applicant concluded that due to the modest effect size and short duration of PLT, no clinically meaningful effects of PLT on narsoplimab-wuug exposure could be identified that would support supplemental doses following plasma exchange.

The goodness-of-fit plots from the final popPK model (i.e., without PLT effect), are shown in [Figure 25](#). The plots of the observed concentrations versus population predicted as well as the individual predicted concentrations show random normal scatter around the identity lines, indicating absence of systematic bias except for very few large concentrations ($>100 \mu\text{g/mL}$) showing underprediction of these observations by the PK model. The population conditional and individual weighted residuals versus time after dose or versus population predicted concentrations also show random normal scatter around zero with no specific trend, indicating no apparent model misspecifications.

Figure 24. Simulation of Narsoplimab-wuug PK Profile After a Single 4 mg/kg Dose in a Typical 70 kg Patient With No ADA, Without and With Plasma Exchange



The figure shows medians and 90% prediction intervals of 1000 simulations per scenario. The plasma therapy is indicated as gray vertical bar.

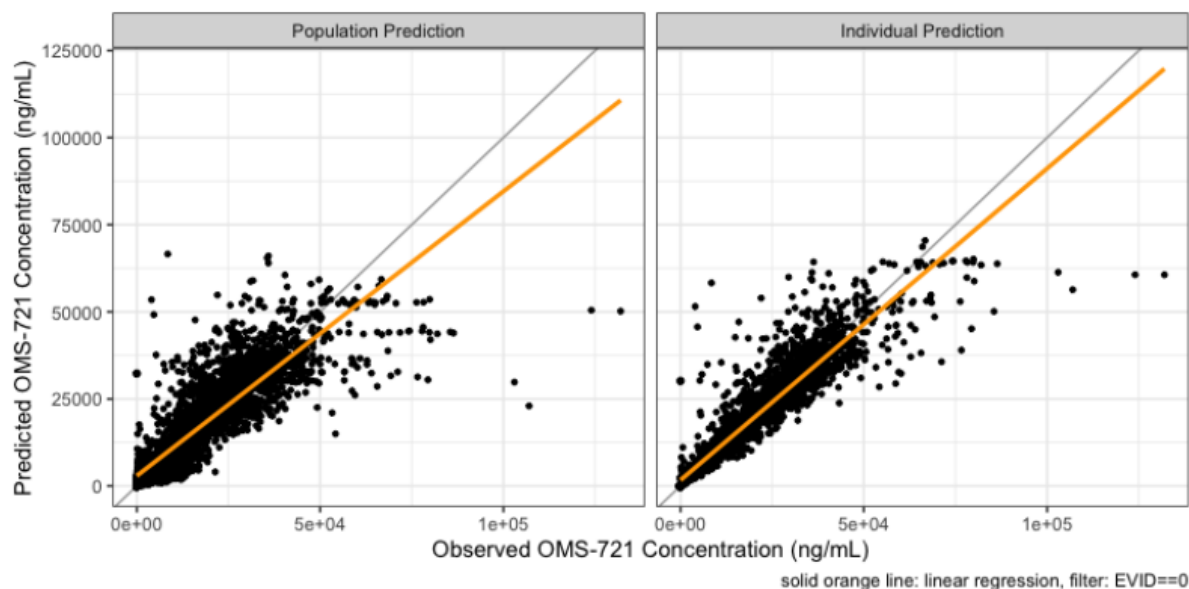
The orange Line and Shaded Area represent the median PK profile and 90% prediction interval in a typical patient without plasma therapy. Blue Line and Grey Shaded Area represent the median PK profile and 90% prediction interval in a typical patient with plasma therapy (2 Hours Plasma Exchange) simulated using the modified PK model.

Source: Applicant's Response to information request of May 13, 2021, Figure 5, page 9.

Reviewer comment

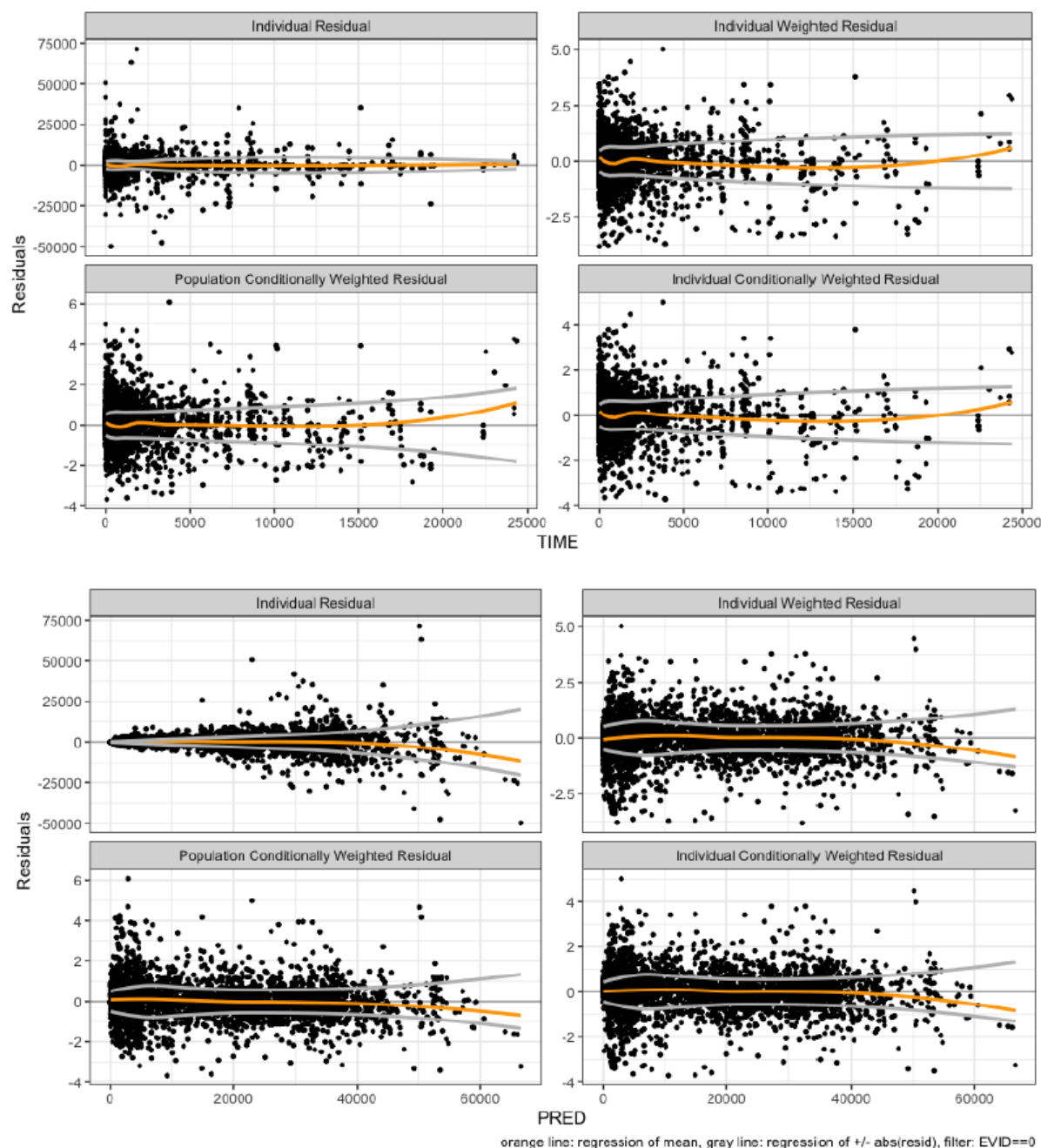
The orange line and shaded area is not clearly visible from the graph as it is overlapping with the blue line and grey shaded area.

Figure 25. Goodness-of-Fit Plots From the Final PK Model



Pairs of observed (DV) and predicted (left: PRED, right: IPRED) PK concentrations are shown as black dots. The gray line represents the line of identity, the orange line represents a linear regression.

[Figure 25](#) (continues)



Various residual types (individual residuals (IRES), individual weighted residuals (IWRES), population conditionally weighted residuals (CWRES), and individual conditionally weighted residuals (CIWRES)) were plotted over population predictions (PRED) in ng/mL. The orange line represents a local regression (loess) of the residuals and the gray lines represents a local regression (loess) of $\pm$ the absolute value of the residuals.

Source: Applicant's Population PK Report, Figure 13, Figure 14, and Figure 15, page 44 to 45.

The nonparametric bootstrap (500 replicates), to assess the robustness of the final PK model, found that the deviation between the final model parameter estimates and the mean bootstrap estimates were small (-4.6% to 10.5%), and the bootstrap 95% CI did not include 0 and were close to the original CIs based on final PK model reported standard errors. Overall, the parameter estimates were considered robust ([Table 106](#)).

Table 106. Bootstrap Results From Final PK Model

Param.	Role	Fixed	Original Estimate	Bootstrap		
				Mean	Rel.Std.Err.	95% CI
CL	TV	No	0.12	0.1197	1.9	[0.114, 0.125]
	albumin over time slope	No	-0.0136	-0.0139	10.1	[-0.0182, -0.013]
	weight exponent	No	0.702	0.6695	26	[0.279, 1.03]
	BSV _a	No	0.192	0.1864	10.6	[0.121, 0.199]
V1	TV	No	10.5998	10.5954	1.9	[10.2, 11.1]
	baseline albumin exponent	No	-0.5807	-0.6179	28.1	[-0.962, -0.247]
	dose exponent	No	0.1729	0.1762	28.3	[0.0744, 0.275]
	BSV _a	No	0.0949	0.0934	13.1	[0.0616, 0.104]
Q	TV	No	0.0215	0.0216	3.8	[0.0203, 0.0238]
	BSV _a	No	1.7262	1.7028	14.2	[1, 2.02]
V2	TV	No	4.6433	4.6826	5.2	[4.46, 5.21]
	BSV _a	No	0.2971	0.2936	12.2	[0.209, 0.332]
Km	TV	Yes				
	patient % change	No	17.087	18.8784	56	[12.1, 39.9]
	albumin over time exponent	No	-2.7451	-2.8537	32.2	[-4.86, -1.36]
	BSV _a	No	2.2668	2.2507	14.8	[1.39, 2.93]
Vmax	TV	Yes				
	patient % change	No	-20.0162	-20.3806	14.7	[-27.8, -15.7]
	ADA % change	No	143.298	143.7468	11.8	[114, 183]
	BSV _a	No	0.485	0.5212	33.3	[0.456, 0.986]
RV	prop.err.	No	26.2476	26.0677	4.6	[22.9, 28.7]
	add.err.	No	65.1518	66.5223	38.7	[41.1, 90.5]

^a Between subject variability (BSV) parameters are shown on variance scale. Bootstrap results were summarized as mean and standard deviation (SD). Relative standard errors (Rel.Std.Err) were derived as |SD|/mean. Shown bootstrap confidence intervals (CI) are non-parametric 2.5th to 97.5th percentiles. The bias was derived as the deviation between the original estimate and the bootstrap mean. TV stands for typical value.

Source: Applicant's Population PK Report, Table 16, pages 57-58.

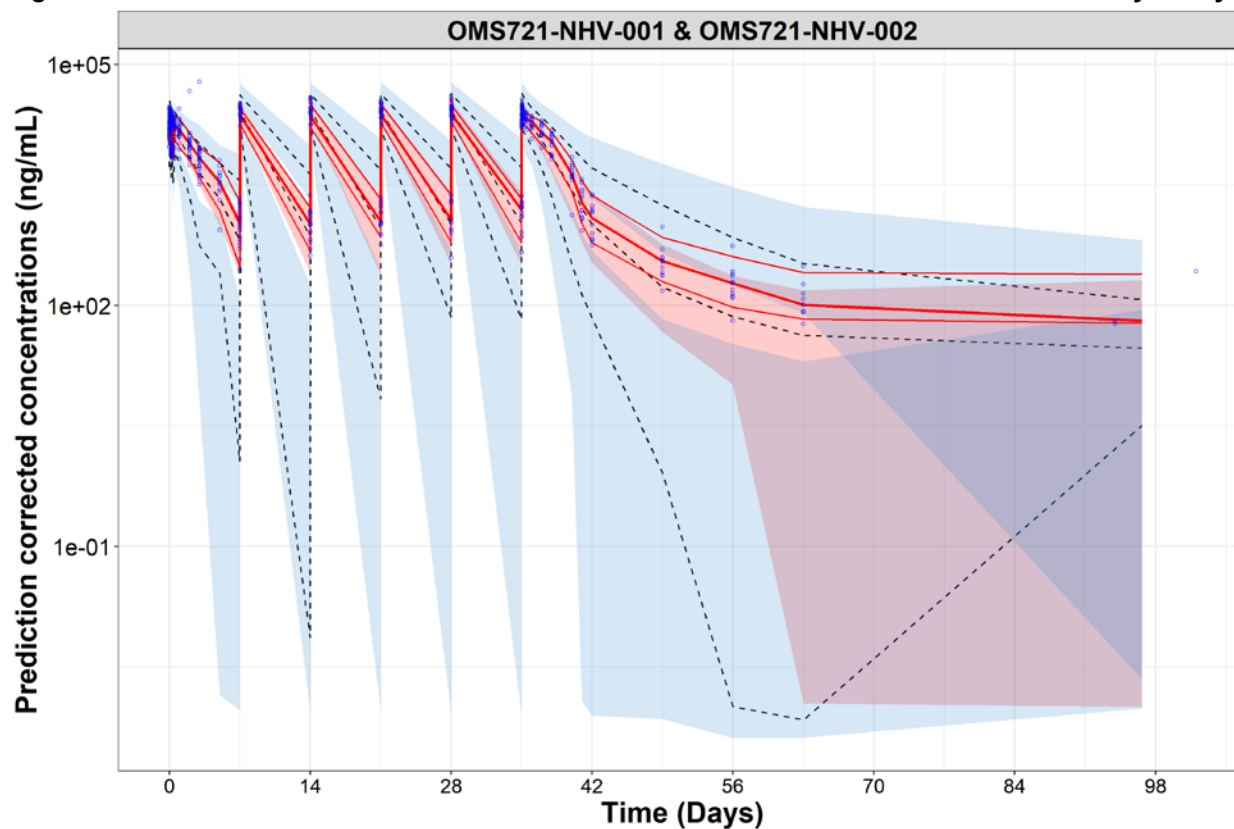
14.3.2. Reviewer's Assessment of the Population PK Analysis

Adequacy of Model in Describing the Data

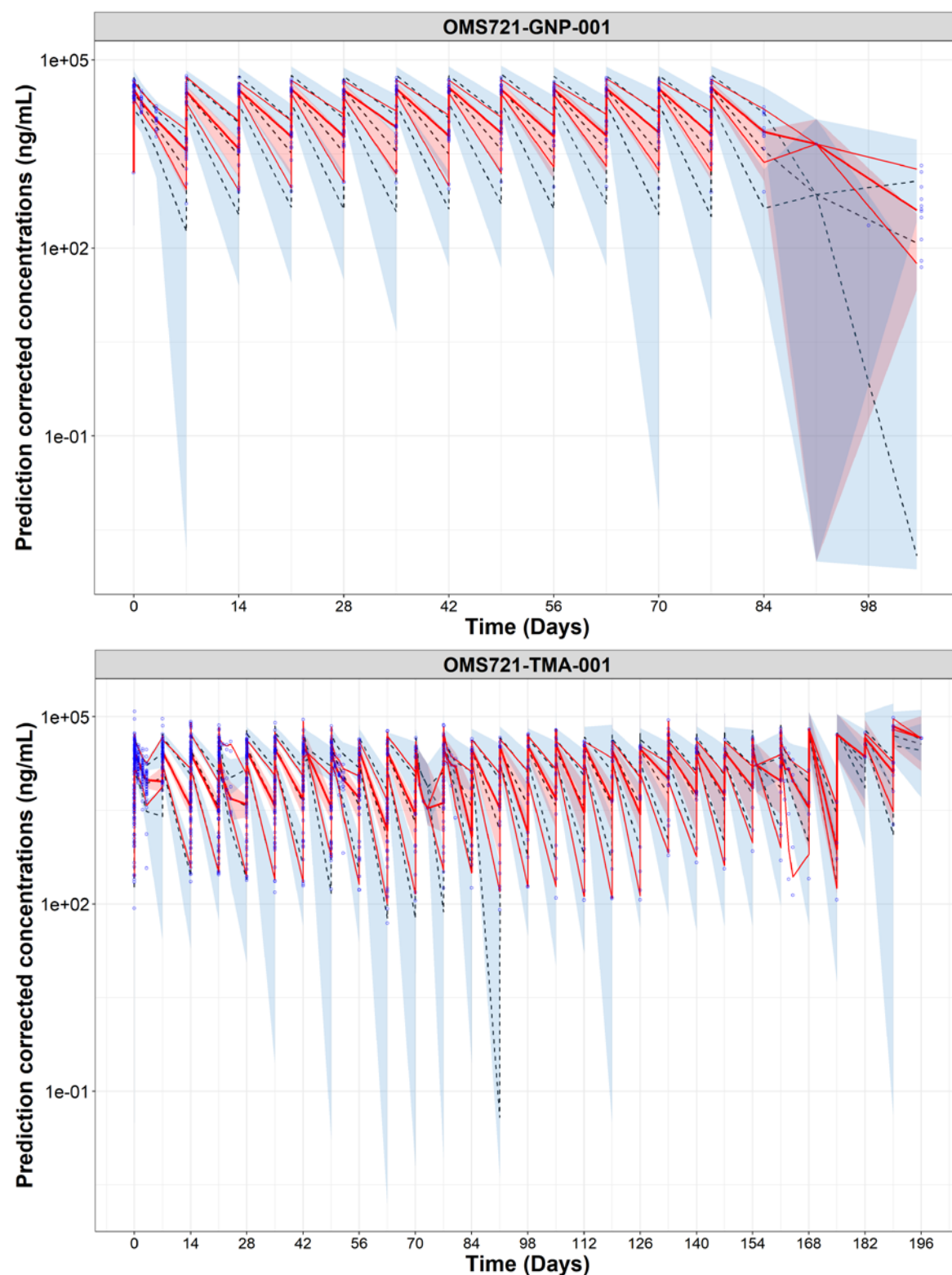
- The Applicant's PK model adequately describes the observed concentrations from narsoplimab-wuug clinical studies.
- The reviewer's evaluation of the model with the M3 method to handle values below quantification limit did not improve the model or affected the PK parameter estimates.
- The reviewer's prediction-corrected visual predictive check (pcVPC) shows that the model reasonably captured and predicted the observed mean PK profiles and the between-subject variability of narsoplimab-wuug concentrations, with the 5th, 50th and 95th percentiles of the prediction-corrected observed concentrations (red solid lines, [Figure 26](#)) are either overlaying with the 5th, 50th and 95th percentiles of the prediction-corrected simulated concentrations (black dashed lines) or encompassed within the confidence

intervals of the 5th, 50th and 95th percentiles of the prediction-corrected simulated concentrations (shaded area, [Figure 26](#)).

Figure 26. Prediction-Corrected Visual Predictive Check From Final PK Model Stratified by Study



(continued on next page)



Source: FDA Reviewer

Note: Open circles: prediction-corrected observed concentrations. Red solid lines: the 5th, 50th and 95th percentiles of the prediction-corrected observed concentrations. Black dashed lines: the 5th, 50th and 95th percentiles of the prediction-corrected simulated concentrations. Shaded areas represent the 95% confidence intervals for the 50th percentile (in red), and for the 5th and 95th percentiles (in blue) of the simulated concentrations (from 1000 dataset replicates).

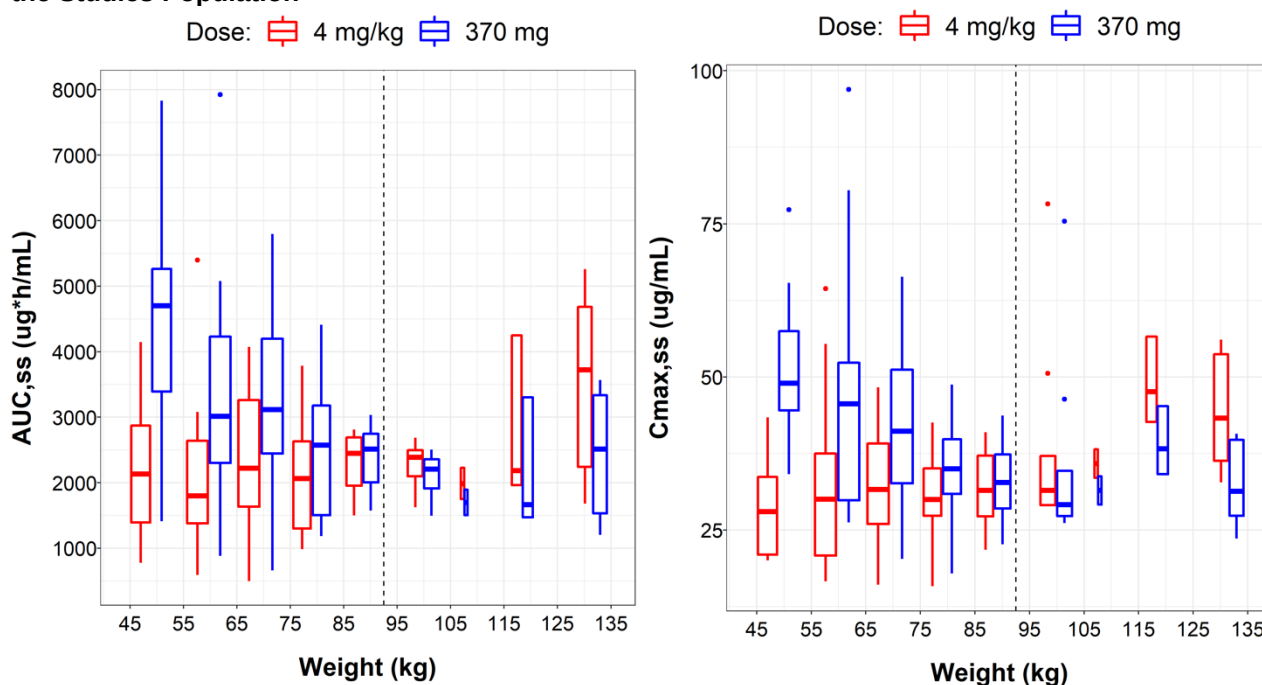
Adequacy of the Proposed Dosing to Standardize Exposure Between Patients Over the Body Weight Range

The proposed dosing of 4 mg/kg of narsoplimab-wuug capped to 370 mg is considered appropriate, as it provides comparable steady-state exposure (area under the concentration-time curve over the dosing interval: AUC_{ss}, maximum concentration: C_{max}, and trough concentration: C_{min}) across the body weight range. [Figure 27](#) shows the predicted steady-state exposure metrics from PK simulations using the clinical studies population and the estimated individual PK parameters from the PK model. The red boxplots represent the exposure metrics if all subjects received a 4 mg/kg narsoplimab-wuug dose (i.e., without dose capping) and the blue boxplots represent the exposure metrics if all subjects received a fixed narsoplimab-wuug dose of 370 mg.

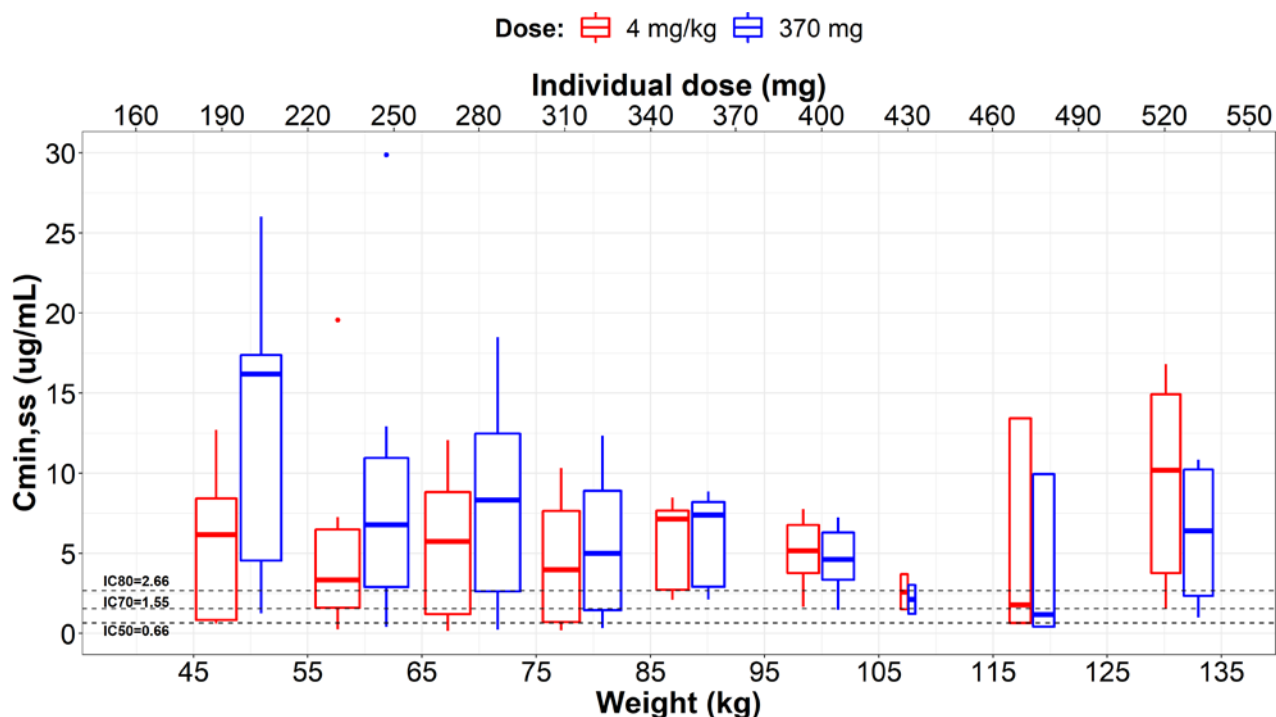
The PK simulations demonstrate that capping narsoplimab-wuug dosing to 370 mg, particularly in heavier subjects (weight >100 kg), provides consistent and comparable narsoplimab-wuug exposure (mainly C_{max,ss} and AUC_{ss}) to subjects with body weight below 92.5 kg and receiving 4 mg/kg of narsoplimab-wuug (red boxplots).

The administration of a 4 mg/kg narsoplimab-wuug dose in subjects with body weight above 100 kg (red boxplot) or the administration of a fixed dose of 370 mg in subjects with body weight below 70 kg (blue boxplot) is expected to result in relatively higher exposure compared to the studied and current proposed dosing.

Figure 27. Predicted Narsoplimab-wuug AUC_{ss}, C_{max,ss}, and C_{min,ss} Under 4 mg/kg and 370 mg in the Studies Population



[Figure 27](#) (continues)



Source: FDA Reviewer

Note: The vertical dashed line represents a body weight of 92.5 kg. The horizontal dashed lines represent the average narsoplimab-wuug concentrations responsible for 50%, 70%, and 80% of the maximum complement component 4d (C4d) inhibition effect (i.e., $IC_{50}=0.66 \mu\text{g/mL}$, $IC_{70}=1.55 \mu\text{g/mL}$ and $IC_{80}=2.66 \mu\text{g/mL}$, respectively, according to the Applicant's developed PK-PD model).

Assessment of the Covariate Analysis

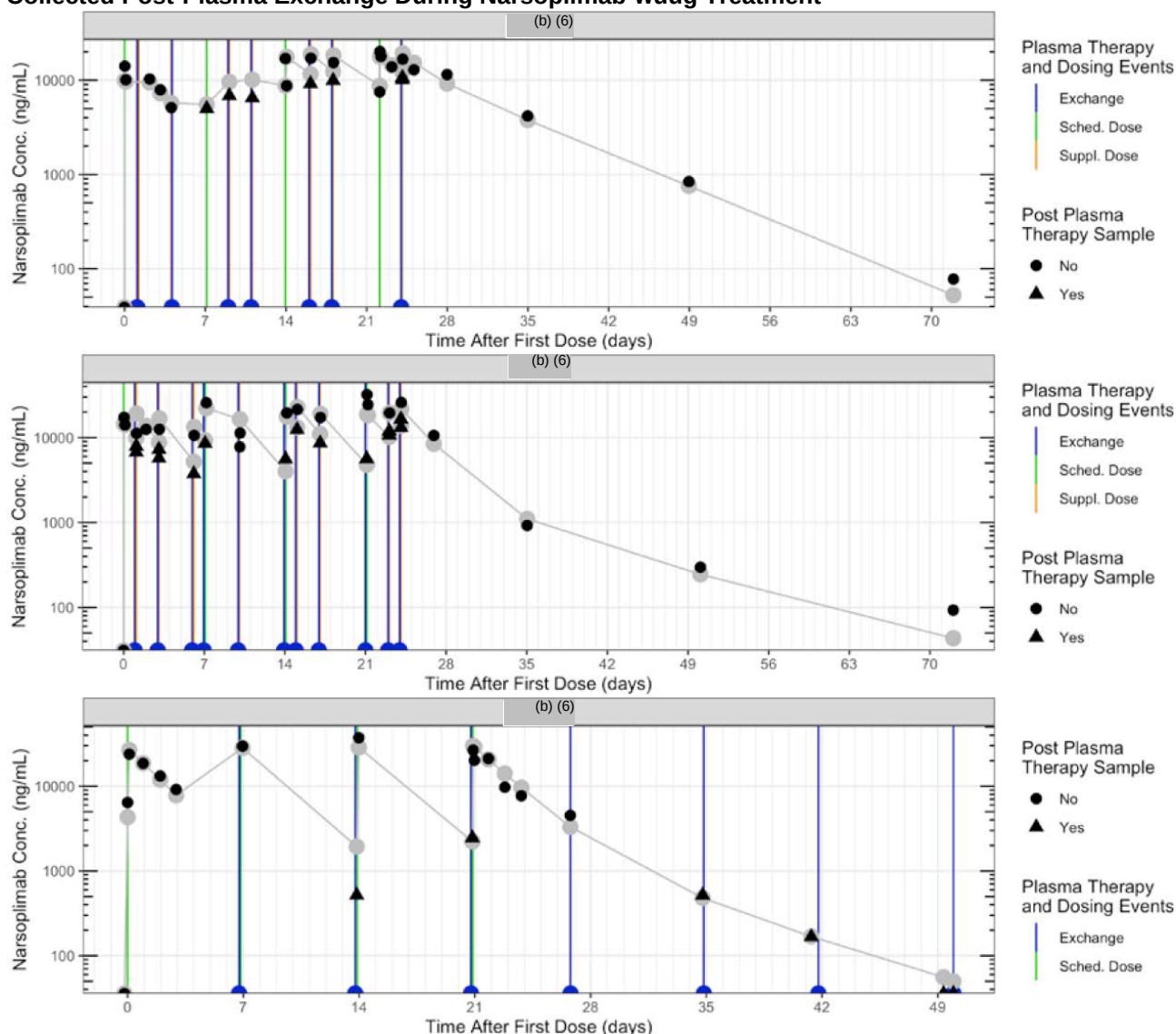
- The PK parameters from the final model and from the nonparametric bootstrap were estimated with acceptable precision, except for the estimated effect of health status on K_m . Deletion of health status as a covariate on K_m did not change the objective function value (OFV), with an OFV decrease of 0.7 points. The unexplained BSV on K_m remained unchanged as well, indicating that health status is likely not a relevant covariate on K_m . The effect of health status on $V_{\max}$ was found not statistically significant as well, after backward deletion of health status as a covariate on $V_{\max}$ from the Applicant full covariate model. The deletion of health status as a covariate on $V_{\max}$ increased the objective function by 2.8 points. The unexplained BSV on $V_{\max}$ remained unchanged.
- Among the PK parameters that are affected by the identified covariates, the ETA shrinkage was acceptable for reliable assessment of covariate effects. According to the base PK model, the ETA shrinkage was low and ranged from 3.7% to 17.7% for CL, V_1 and Q. The ETA shrinkage for the remaining parameters was relatively higher for V_2 (32.5%), K_m (41%) and $V_{\max}$ (38.7%), which makes the graphical assessment of covariate on these parameters less reliable.
- Individual dose was found to be a statistically significant covariate on the central volume of distribution (V_1) and was considered directly related to body weight as narsoplimab-wuug dosing was a weight-based dosing. The reviewer's evaluation of body weight (included as power model standardized to 77.2 kg) instead of dose as covariate on V_1 resulted in an increased OFV (by 34 points).

- The presence of ADA was estimated to increase V_{max} by 143% according to the popPK model, which is predicted to result at steady-state exposure in about 22% decrease in AUC_{ss} and 52% decrease in $C_{min,ss}$.
- PLT and more specifically plasma exchange (PE) is expected to remove large molecules such as proteins and monoclonal antibodies from the systemic circulation. Five patients received PE during narsoplimab-wuug treatment, and were used to evaluate the effect of PE on narsoplimab-wuug PK. The median duration of PE in these 5 patients was 1.8 h (ranging from 1.4 h to 2.9 h).

The reviewer's reassessment of the effect of PE on narsoplimab-wuug CL, after appropriate modification and rearrangement of the PK dataset, found that PE increased narsoplimab-wuug CL by an average of 47% (with an OFV decrease of 4.5 for 1 degree of freedom). However, the estimated effect on narsoplimab-wuug CL could not be precisely estimated, with a 95% CI of the mean effect ranging from 24% to 124% (determined from bootstrap, $n=200$). In addition, the covariate effect was sensitive to the initial value in the PK model.

The difficulty in reliably estimating the effect of PE on CL using the population PK model is most likely related to the lack of informative PK data. There was no PK sampling performed concurrently immediately pre- and post-PE amongst the 5 patients who received PE during narsoplimab-wuug treatment. The potential estimated effect of PE on the PK is likely driven by 3 of the 5 patients, who had post-PE PK samples collected ([Figure 28](#)). Besides, the duration of the procedure was not found to impact the estimated effect.

Figure 28. Overview of PK Data in Patients (b) (6) With PK Samples Collected Post-Plasma Exchange During Narsoplimab-wuug Treatment



Source: Applicant's Response to information request of February 23, 2021, Figure 5-7 page 16-17.

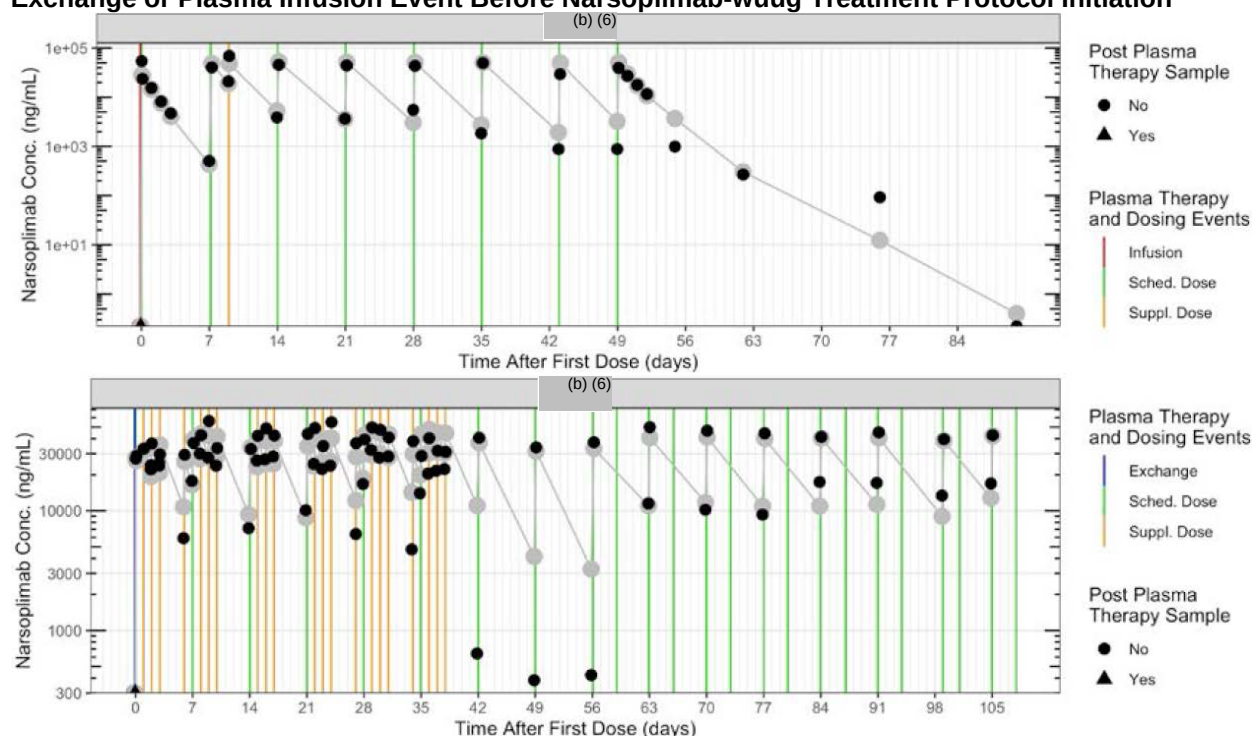
Note: Patient (b) (6) (aHUS patient, study arm: 2 mg/kg), (b) (6) (aHUS, 4 mg/kg), and (b) (6) (aHUS, 4 mg/kg). Grey line: PK model individual predicted concentrations. Black circles and triangles: observed plasma concentrations collected either post-plasma exchange or not. Blue line: Plasma exchange event. Green line: regular once weekly scheduled narsoplimab-wuug dose. Orange line: supplemental narsoplimab-wuug dose.

Assessment of the Need for Supplemental 2 mg/kg Narsoplimab-wuug Dose After Plasma Exchange

According to current PK data and the reviewer's PK simulations from the modified PK model (with its known limitations), 1) PE does not seem to have a relevant effect on narsoplimab-wuug PK despite the average 47% effect on CL and therefore 2) a supplemental narsoplimab-wuug of 2 mg/kg immediately post-PE does not seem to be needed to correct narsoplimab-wuug exposures.

In Study TMA-001, patients who received PLT during treatment received a supplemental narsoplimab-wuug dose of about 2 mg/kg after PLT. Two patients with HSCT-TMA, in Study TMA-001, received plasma exchange (b) (6) and plasma infusion (b) (6) before narsoplimab-wuug dose at the day of treatment initiation. These two patients would theoretically not need supplemental doses to correct for potential decrease in exposure. However, these patients received either a single supplemental dose (b) (6) or multiple supplemental doses (b) (6) in addition to unscheduled full narsoplimab-wuug doses during treatment (Figure 29), without clinical justification by the Applicant for these supplemental doses and unscheduled doses.

Figure 29. Overview of PK Data in HSCT-TMA Patients (b) (6) With Plasma Exchange or Plasma Infusion Event Before Narsoplimab-wuug Treatment Protocol Initiation



Source: Applicant's Response to information request of February 23, 2021, Figure 8-9 page 17-18.

Note: Patient (b) (6) (HSCT-TMA, 4 mg/kg). Grey line: PK model individual predicted concentrations. Black circles and triangles: observed plasma concentrations collected either post-plasma exchange or not. Blue line: Plasma exchange event. Red line: Plasma infusion event. Green line: regular once weekly scheduled narsoplimab-wuug dose. Orange line: supplemental narsoplimab-wuug dose.

The effect of PLT on narsoplimab-wuug CL and its overall exposure was not investigated in a dedicated study, and no justification for the selected supplemental narsoplimab-wuug dose of 2 mg/kg as well as the frequency of the supplemental dose administration was provided by the Applicant. Based on our information request, the Applicant estimated that PLT increased narsoplimab-wuug CL by 37.1% (using popPK modeling) and concluded that due to the modest effect size and short duration of PLT, no clinically meaningful effects of PLT on narsoplimab-wuug exposure could be identified that would support supplemental doses following plasma exchange.

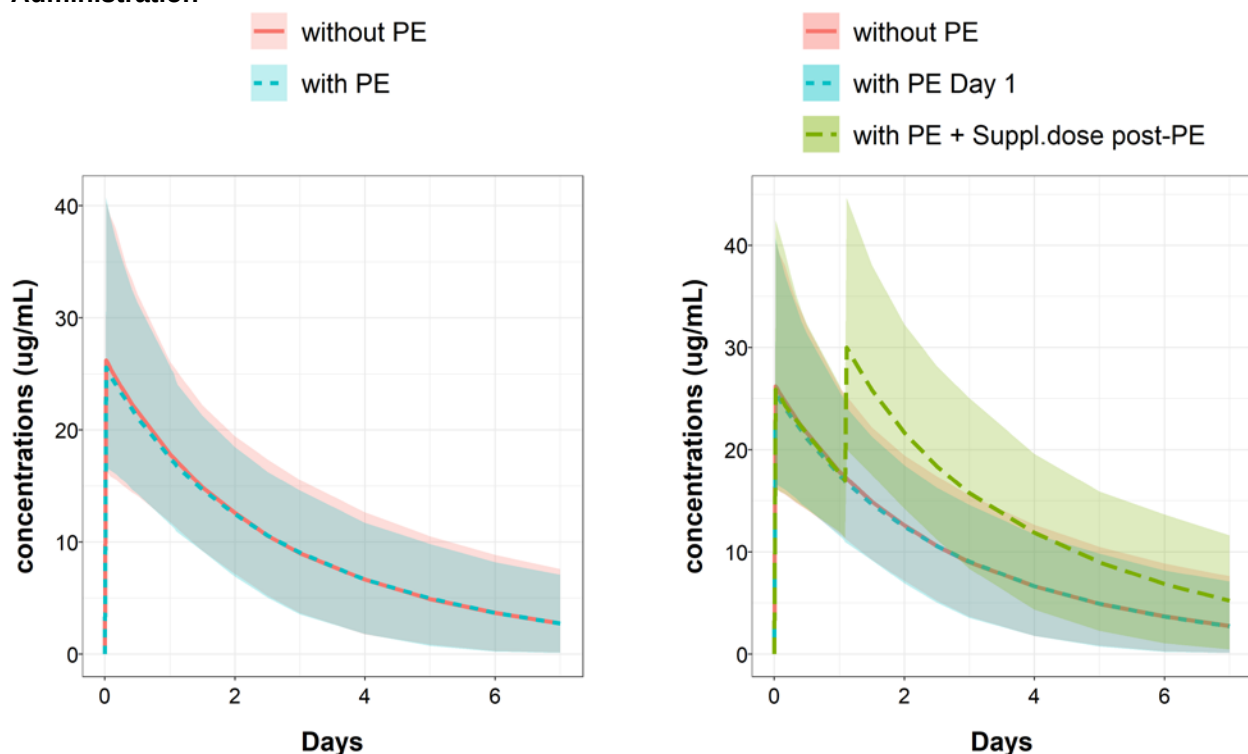
The reviewer's assessment of the effect of PE on narsoplimab-wuug CL, found that PE increased narsoplimab-wuug CL by an average of 47% during an average 2-hour PE window. However,

the estimated effect on narsoplimab-wuug CL could not be precisely estimated, with a 95% CI of the mean effect ranging from 24% to 124%. Although the PE effect on CL could not be reliably estimated (likely due to the lack of informative PK data), PK simulations were performed to evaluate the need for an additional supplemental dose of 2 mg/kg after PE to correct for potential change in narsoplimab-wuug exposure. Different scenarios and frequencies of PE were simulated during a dosing interval (i.e., one PE on Day 1, two PE on Day 1 and Day 2, two PE on Day 1 and Day 4, two PE on Day 5 and Day 6, three PE on Day 1, Day 3 and Day 6 post-Narsoplimab-wuug single dose administration, or PE on Day 7 before the second narsoplimab-wuug dose administration).

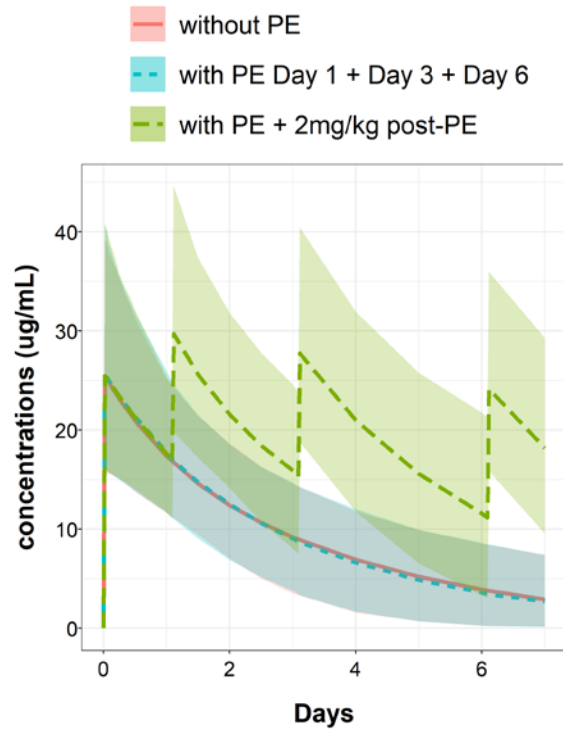
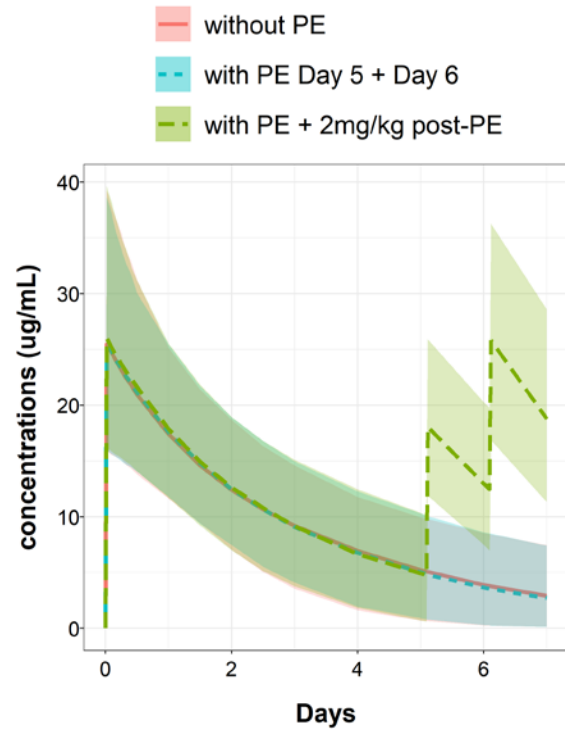
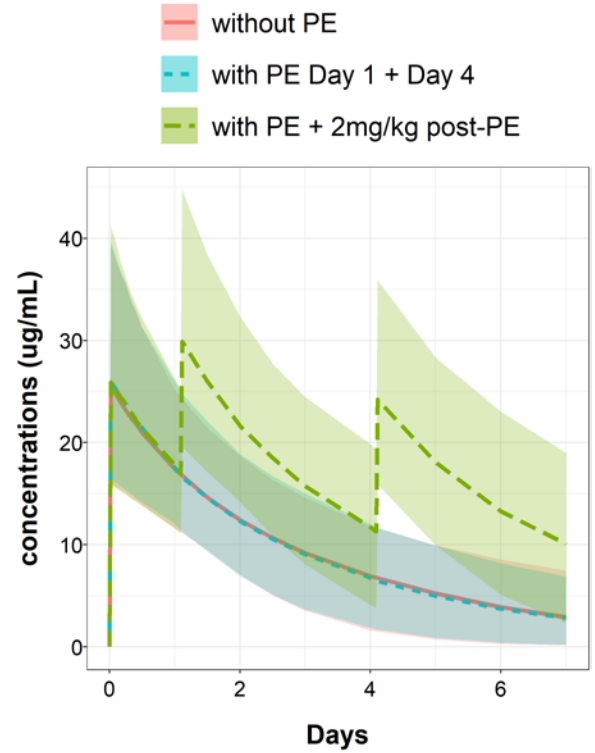
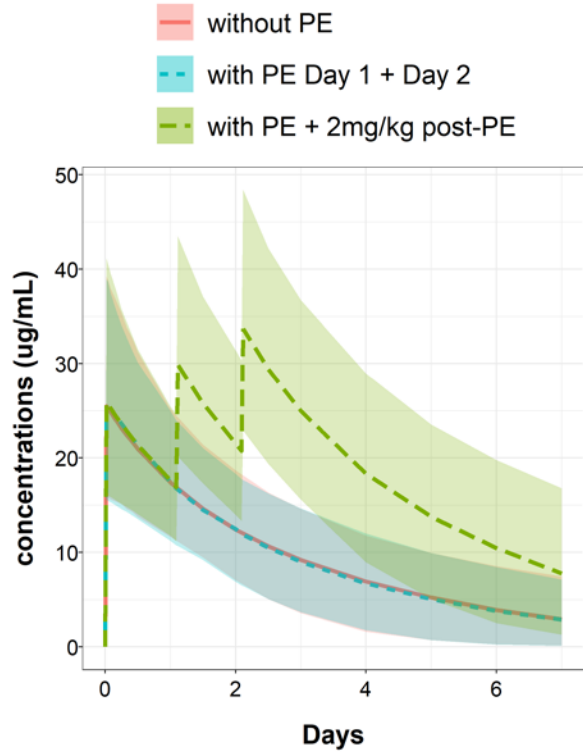
Single 4 mg/kg dose simulations using the modified PK model (with the estimated average 47% effect of PE on CL) failed to show difference in narsoplimab-wuug PK in a 70 kg subject without PE or receiving a 2-hour PE up to three times during a dosing interval of 7 days ([Figure 30](#), red or blue lines and shaded areas).

The simulated administration of a supplemental dose of 2 mg/kg immediately after each 2-hour PE event resulted generally in higher narsoplimab-wuug PK exposure and trough concentrations (green line and shaded area) compared to the absence of supplemental dose, particularly in case of more than one PE or PE occurring towards the end of dosing interval. In agreement with the observed PK data from the clinical studies, a peak of narsoplimab-wuug concentration occurs after each supplement narsoplimab-wuug dose post-PE, and these predicted peak concentrations were generally within the range of C_{max} expected from the conventional scheduled dose of 4 mg/kg.

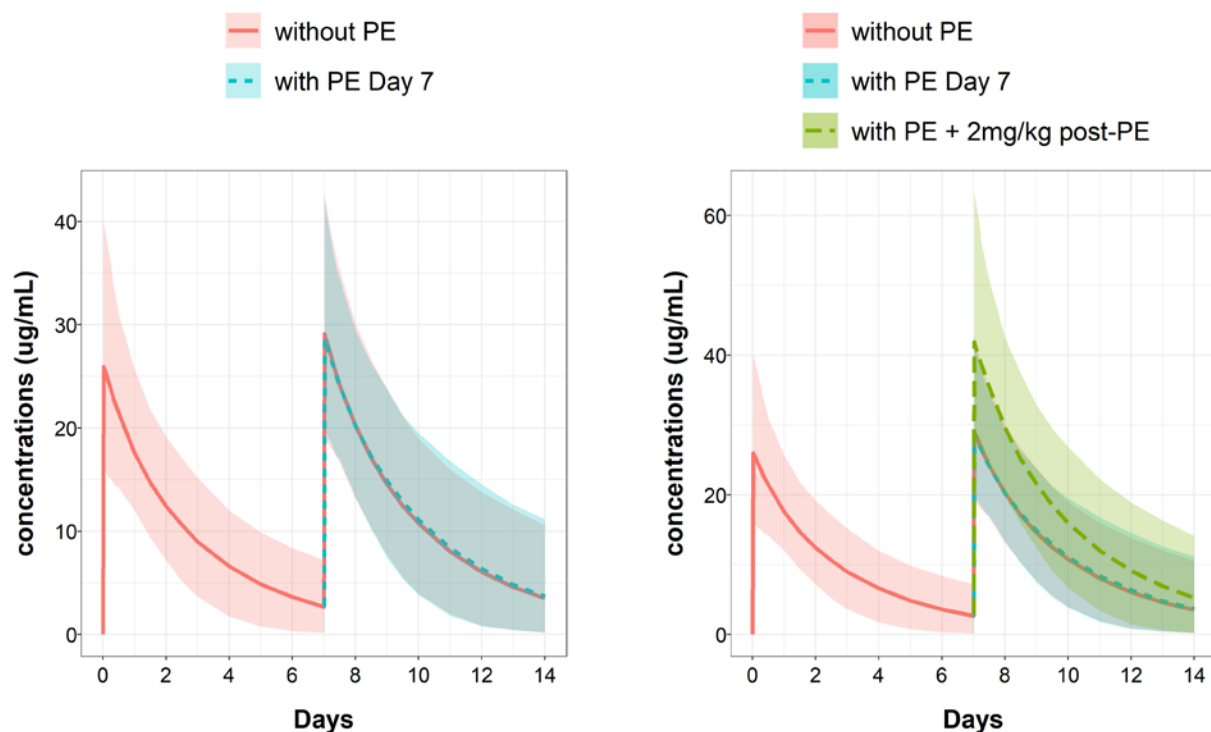
Figure 30. Predicted Typical Narsoplimab-wuug PK Profile in the Absence or Under Various Scenarios of Plasma Exchange Event's Frequencies, With or Without Supplemental Dose Administration



(continued on next page)



(continued on next page)



Source: FDA Reviewer

Note: PK simulations for a 70 Kg patient either without plasma exchange (PE) (red line and shaded area), or with PE in the absence of supplemental dose (blue line and shaded area), or with PE and supplemental dose immediately after each PE (green dashed line and shaded area). The figure shows the median and 90% prediction intervals of 1000 simulations per scenario.

14.3.3. Applicant's Population PK-PD (C4d Inhibition) Analysis

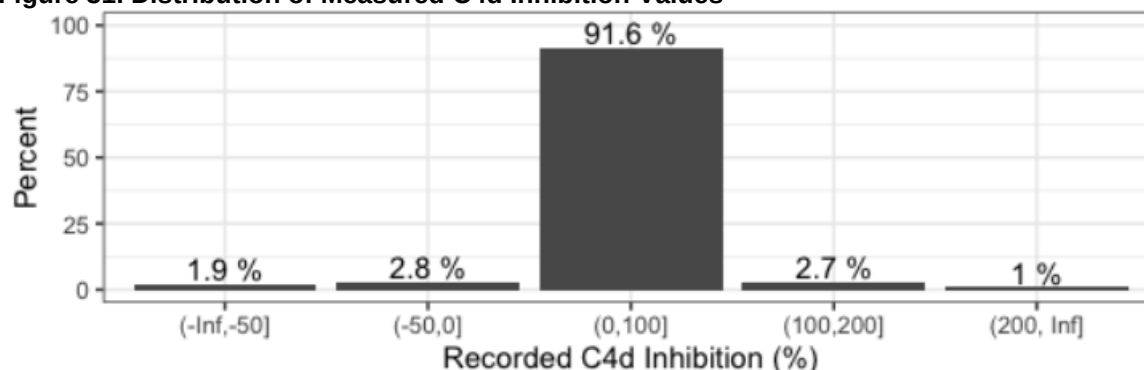
Narsoplimab-wuug is a human IgG4 monoclonal antibody that binds to and inhibits MASP-2. Inhibition of *ex-vivo* lectin-mediated C4d (complement component 4d) formation was assessed, as a PD biomarker of the mechanism of action, and the PK/C4d relationship across all studies was analyzed. The *ex-vivo* assay of C4d inhibition was used to justify the selection of 4 mg/kg IV dosing in the Phase 2 studies as it was expected to maintain mean lectin pathway inhibition >80% for about 168 hours, the proposed dosing interval. However, C4d inhibition was not used as an efficacy endpoint in evaluating treatment response.

The majority of the C4d inhibition records had a time-matched PK observation, and the observed PK data were used to characterize C4d inhibition, rather than model predicted concentrations. PK concentrations below the limit of quantification were set to lower limit of quantification (LLOQ)/2 (25 ng/mL). The C4d assay depends on the availability of mannan-binding lectin. In 4 subjects

(b) (6) the baseline mannan-binding lectin levels were below the limit of quantification (<35.2 ng/mL). These subjects were excluded from the subsequent PK/PD model development, as the C4d assay depends on the availability of mannan-binding lectin. Some C4d inhibition values were measured outside of the stability window of 836 days. These records were flagged and tested for exclusion during model development. Recorded C4d values were capped at -50% or +200% to reduce the huge variability in these data and improve the PK-

PD model stability. C4d observations ranged from -1359% to +2430%, however large values were relatively rare ([Figure 31](#)).

Figure 31. Distribution of Measured C4d Inhibition Values



Source: Applicant's Population PK Report, Figure 29, page 80

Base PK-PD Model

A direct link $E_{\max}$ model was used to describe the relationship between narsoplimab-wuug concentrations and C4d inhibition. The $E_{\max}$ model was parameterized in terms of baseline C4d inhibition at zero narsoplimab-wuug concentration (E_0), maximum C4d inhibition response ($E_{\max}$), and narsoplimab-wuug concentration required to achieve half (50%) of the maximum C4d inhibition effect or change from baseline (EC_{50}). A Hill coefficient or shape parameter (Gamma) was estimated to be close to 1 and subsequently fixed to 1. BSV was estimated on all parameters, except for Gamma, with an additive random effect of E_0 and $E_{\max}$ and exponential random effect on EC_{50} . The residual error model consisted of an additive error model. The parameter estimates from the base PK-PD model are listed below in [Table 107](#).

Table 107. Parameter Estimates of Base Population PK-PD Model

Parameter	Role	Estimate	Fixed	Rel.Std.Err.	95% CI
E0	TV (%)	21.5	No	19.2%	[13.4, 29.6]
	BSV _a (%)	33.9	No	11.5%	[26.3, 41.5]
EC50	TV (ng/mL)	658	No	13.4%	[485, 831]
	BSV _a	1.04	No	11.9%	[0.795, 1.28]
EMAX	TV (%)	95.5	No	0.4%	[94.8, 96.2]
	corr(EC50) _a	0.843	No	16.5%	[0.571, 1.12]
	BSV _a (%)	1.94	No	31.3%	[0.749, 3.13]
GAMMA	TV	1	Yes	—	—
Residual Error	additive	7.74	No	6.6%	[6.73, 8.75]

^a Estimates for between subject variability (BSV) parameters reported on SD scale.

Parameter estimates and limits of the approximate 95% confidence intervals (CI) were rounded to 3 significant digits.

Relative standard errors (Rel.Std.Err.) were rounded to 1 decimal digit. corr(EC50) represents the BSV correlation term between EC50 and Emax.

Source: Applicant's Population PK Report, Table 36, page 80.

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic

Covariates Analysis

A stepwise covariate modeling procedure was used in order to build the covariate model, with a significance level of 0.05 for the forward inclusion and 0.001 for the backward deletion step. Tested potential covariates were gender, patient or health status, diseases, race, ethnicity, ADA status, age, body weight, baseline albumin, creatinine concentration, and platelet counts

The following covariates were included in the final model:

- Body weight on $E_{\max}$, as power function centered at 77.2 kg
- Body weight on E_0 , as proportional linear function centered at 77.2 kg
- Baseline albumin on E_0 , as power function centered at 36 g/L
- Health status on E_0 , as percent difference using proportional linear model
- IgAN (IgA Nephropathy) disease on E_0 , as percent difference using proportional linear model

Final Model

The parameter estimates from the final PK-PD model are listed in [Table 108](#), and the model-predicted C4d inhibition versus narsoplimab-wuug concentrations is presented in [Figure 32](#). According to the model, Narsoplimab-wuug plasma concentration responsible for 50% of the maximum C4d inhibition effect (EC_{50}) was estimated to be 664 ng/mL (0.664 μ g/mL). Typical parameters were estimated with good precision while covariate effect parameters had standard errors up to 40% and 57.9% in the case of albumin on E_0 . The ETA shrinkage ranged from 10.4 to 11.1% and the residual error (Epsilon) shrinkage was 4.2%.

The goodness-of-fit plots from the final PK-PD model, are shown in [Figure 33](#). The plots of the observed C4d inhibition versus the population predicted or the individual predicted C4d inhibition show random normal scatter around the identity lines, indicating absence of systematic bias. The population and individual conditionally weighted residuals versus population predicted C4d inhibition also show random normal scatter around zero with no specific trend, indicating no apparent model misspecifications.

Table 108. Parameter Estimates of Final Population PK-PD Model

Parameter	Role	Estimate	Fixed	Rel.Std.Err.	95% CI
E ₀	TV (%)	30.2	No	22.8%	[16.7, 43.7]
	weight effect (slope in %/kg)	0.0332	No	39.7%	[0.00738, 0.0589]
	albumin effect (exponent)	2.65	No	57.9%	[-0.356, 5.66]
	% change for healthy volunteers	-88.5	No	6.5%	[-99.8, -77.2]
	% change for IgAN patients	-87.1	No	17.7%	[-117, -56.9]
	BSV _a (%)	28.7	No	8.6%	[23.9, 33.6]
EC ₅₀	TV	664	No	13.5%	[488, 840]
	BSV _a	1.06	No	11.5%	[0.824, 1.3]
E _{max}	TV	95.5	No	0.4%	[94.8, 96.2]
	weight effect (exponent)	-0.0394	No	35.4%	[-0.0667, -0.012]
	corr(EC50) _a	1	No	0.0%	[1, 1]
	BSV _a (%)	1.64	No	31.5%	[0.627, 2.65]
Residual Error	additive (%)	7.74	No	6.4%	[6.77, 8.72]

^a Estimates for between subject variability (BSV) parameters reported on SD scale.

Parameter estimates and limits of the approximate 95% confidence intervals (CI) were rounded to 3 significant digits.

Relative standard errors were rounded to 1 decimal digit. corr(EC50) represents the BSV correlation term between EC50 and E_{max}.

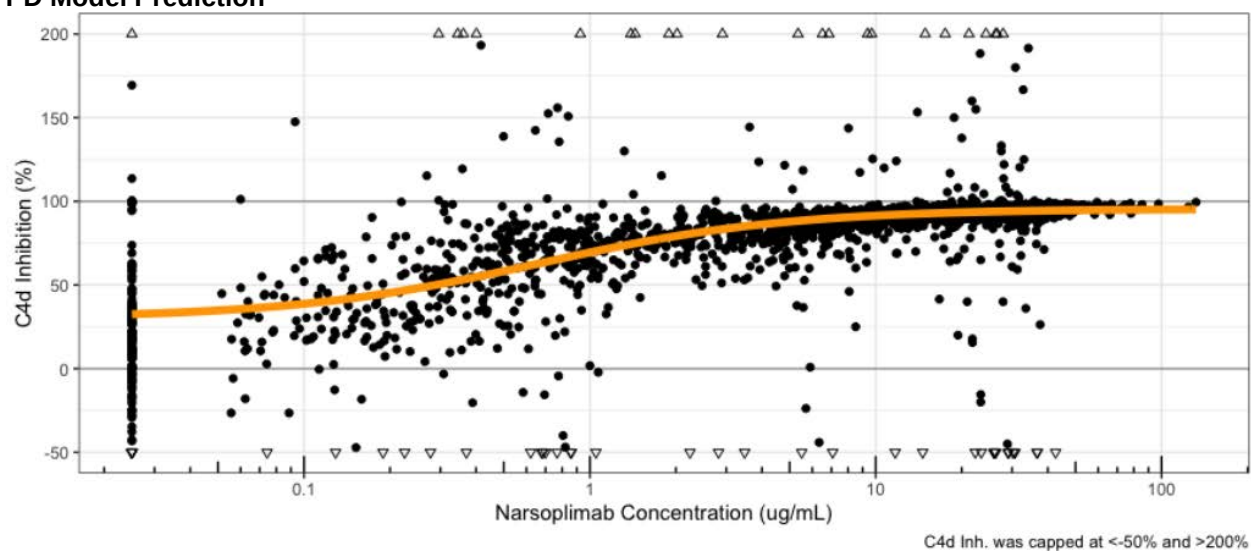
Source: Applicant's Population PK Report, Table 37, page 83.

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic

Reviewer comment

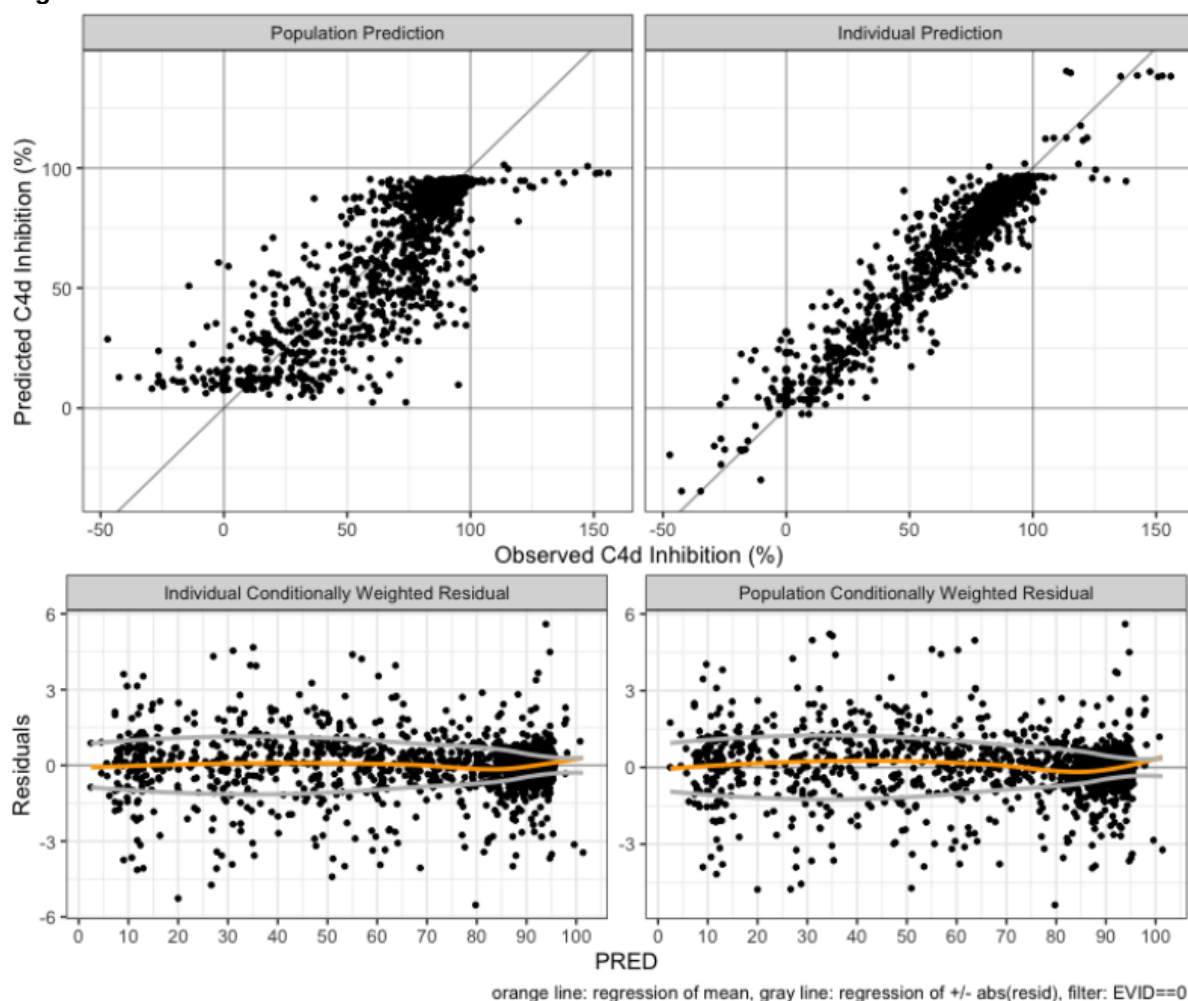
In [Table 108](#), the BSV for EC₅₀, estimated as an exponential random effect is the standard deviation and do not represent a coefficient of variation expressed in %CV. The BSV for E₀ and E_{max}, estimated as an additive random effect in the PK-PD model, are expressed in their respective units (i.e., inhibition of C4d in %) and do not represent a %CV.

Figure 32. Narsoplimab-wuug PK Concentrations Versus C4d Inhibition, Overlaid by Typical PK-PD Model Prediction



Source: Applicant's Population PK Report, Figure 32, page 82.

Figure 33. Goodness of Fit Plots of Final PK-PD Model



Various residual types (conditionally weighted residuals (CWRES), and individual conditionally weighted residuals (CIWRES)) were plotted over population predictions (PRED) in %. The orange line represents a local regression (loess) of the residuals and the gray lines represents a local regression (loess) of $\pm$ the absolute value of the residuals.

Source: Applicant's Population PK Report, Figure 34-35, page 84-85.

The nonparametric bootstrap (500 replicates), to assess the robustness of the final PK model, found that the deviation between the final model parameter estimates and the mean bootstrap estimates were small (-16.8% to 0%). The bootstrap 95% CI were close to the original CIs based on standard errors, except for the estimated effects of baseline albumin and IgAN disease as covariates on E_0 for which the 95% CI included 0 ([Table 109](#)).

Table 109. Bootstrap Results of Final PK-PD Model

Param.	Role	Original Estimate	Bootstrap		Bias	
			Mean	95% CI	Absolute	Percent
E ₀	TV (%)	30.2326	29.6016	[12.7, 41.2]	-0.63104	-2.1
	weight effect (slope in %/kg)	0.0331	0.0296	[0.00119, 0.0552]	-0.00350	-10.6
	albumin effect (exponent)	2.6499	2.2055	[-1.21, 6.4]	-0.44443	-16.8
	% change for healthy volunteers	-88.5009	-83.2704	[-96.2, -46.8]	5.23049	-5.9
	% change for IgAN patients	-87.0884	-79.8410	[-99.9, 6.18]	7.24741	-8.3
	BSV (%)	824.3650	767.9432	[519, 1060]	-56.42183	-6.8
EC ₅₀	TV	664.0160	665.7120	[514, 836]	1.69605	0.3
	BSV	1.1322	1.0774	[0.593, 1.55]	-0.05481	-4.8
E _{max}	TV	95.5188	95.4933	[94.9, 96.1]	-0.02555	0.0
	weight effect (exponent)	-0.0394	-0.0351	[-0.0614, -0.00657]	0.00426	-10.8
	corr(EC ₅₀) _a	1.7423	1.5833	[0.351, 2.84]	-0.15902	-9.1
	BSV (%)	2.6815	2.6658	[0.186, 6.01]	-0.01562	-0.6
Residual Error	additive (%)	7.7442	7.6963	[6.71, 8.77]	-0.04789	-0.6

Parameter estimates and limits of the approximate 95% confidence intervals (CI) were rounded to 3 significant digits.

Relative standard errors were rounded to 1 decimal digit. corr(EC₅₀) represents the BSV correlation term between

EC₅₀ and E_{max}.

Source: Applicant's Population PK Report, Table 40, page 89.

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic

Reviewer comment

In [Table 109](#), the Applicant's reported BSV values are the variances and not the standard deviations. The reported corr(EC₅₀) is not the correlation but the actual covariance between EC₅₀ and E_{max} random effects.

14.3.4. Reviewer's Assessment on the PK-PD Model

Adequacy of the PK-PD Model in Describing PD Data

- The Applicant's PK-PD model adequately describes the measured C4d inhibition from the narsoplimab-wuug clinical studies.
- The Applicant's PK-PD modeling was not a simultaneous or sequential modeling PK-PD approach. The measured PK data were used directly to characterize the PD model, since the majority of the C4d inhibition records had a time-matched PK observation (the below quantification limit PK values were set to LLOQ/2). The reviewer re-evaluated the PK-PD model using a sequential PK-PD modeling approach, where the individual predicted PK concentrations (estimated using the developed PK model) were used to characterize the PD model. The PK-PD model parameters using either the observed PK data (i.e.,

Applicant's model) or the individual predicted PK data (i.e., reviewer's model) were comparable, when considering the base and the full covariate model.

- The recorded C4d inhibition data were highly variable, and the Applicant truncated the C4d values at -50% or +200% to reduce the huge variability in the data and improve the PK-PD model stability. The reviewer re-evaluated the PK-PD model using after considering the C4d inhibition values between 0 and 100% only. The resulting PK-PD model parameter estimates were comparable to those observed from the Applicant's PK-PD model.
- There was no observed delay in the C4d inhibition response, with maximum C4d inhibition occurring around peak narsoplimab-wuug concentrations. In addition, the evaluation of an effect compartment in the PK-PD model did not improve the model.

Assessment of the Covariate Analysis

- Among the PD model parameters that are affected by the identified covariates, the ETA shrinkage was acceptable for reliable assessment of covariate effects. According to the Applicant's base PK-PD model, the ETA shrinkage was 7.8%, 12.5%, and 25.6% for E_0 , EC_{50} and E_{max} , respectively.
- The PD parameters from the Applicant's final PK-PD model and from the nonparametric bootstrap were estimated with acceptable precision, except for the estimated effect of baseline albumin and IgAN disease on E_0 , with the bootstrap 95% CI including 0. The precision around the estimated mean effect of body weight on E_0 and E_{max} was relatively high (>30%).

The evaluation of the individual ETA for E_0 versus covariate plot from the base model did not show a trend between E_0 and baseline albumin. No clinical justification was provided for including the effect of albumin on the baseline levels of C4d inhibition (E_0). The deletion of baseline albumin as a covariate on E_0 from the final model did not result in a statistically significant change of the OFV at a 0.001 significance level (OFV increased by 5.8 points for 1 degree of freedom).

The univariate deletion of IgAN or health status as a covariate on E_0 from the final model resulted in a statistically significant change of the OFV at a 0.001 significance level (OFV increased by 16.8 and 18.5 points for 1 degree of freedom, respectively). The covariate plot from the base model showed a slightly lower median E_0 in healthy subjects and IgAN patients compared to the other disease conditions. However, these differences in E_0 were not expected to be clinically relevant given the high and overlapping variability in E_0 between healthy subjects and patients, as well as between the various disease conditions among patients. In addition, if we consider the mechanism of action of the drug, baseline C4d inhibition (i.e., in the absence of drug) would be anticipated to be either lower in patients compared to healthy subjects or comparable to healthy subject due to other standard of care procedure pre-enrollment.

Although, body weight remained statistically significant covariates on E_0 and E_{max} , after univariate deletion from the Applicant's full covariate model, the ETA versus covariate plots for E_0 and E_{max} did not show a trend with body weight. In addition, the estimated effect of body

weight on E_0 and $E_{\max}$ has low precision (35.4% and 39.7% respectively) and were close to zero. Therefore, body weight is not expected to be clinically relevant covariate on E_0 and $E_{\max}$.

Finally, the univariate covariate analysis using the Applicant's base model found that only health status on E_0 and body weight on $E_{\max}$ were statistically significant at a 0.05 significance level (decrease in OFV by -4.2 and -10.3 for 1degree of freedom, respectively).

- Covariate analysis performed on the reviewer's PK-PD model, which linked the individual predicted PK concentrations (from the developed PK model) instead to the current observed concentrations to C4d inhibition, found that baseline albumin on E_0 and body weight on $E_{\max}$ were not statistically significant covariates at a 0.001 significance level after univariate deletion from the full covariate model (in agreement with the ETA versus covariate plots showing the absence of trends).

This was also in agreement with the univariate covariate analysis using the reviewer's base model, which found that only health status on E_0 and body weight on $E_{\max}$ were statistically significant at a 0.05 significance level (decrease in OFV by -4.9 and -6.4 for 1degree of freedom, respectively), but were not statistically significant at significance level <0.01.

In conclusion, the investigated covariates on the Applicant's and the reviewer's base PK-PD models are not considered clinically relevant due to:

- The weak statistical significance of the included covariates in the Applicant's and the reviewer's full covariate PK-PD models.
- The absence of a relationship between the PD parameters and the covariates from the ETA versus covariate plots from the Applicant's and the reviewer's base PK-PD models.
- The absence of clear physiological relevance of these covariates.

[Table 110](#) provides the parameter estimates from the reviewer's PK-PD base model.

Table 110. Parameter Estimates of Reviewer's Base Population PK-PD Model Using Individual Predicted PK Data Instead of Observed PK Data

Parameter	Description	Estimate [% RSE]	Between-Subject Variability [% RSE]
E_0	Baseline measured C4d inhibition (%)	24 [16%]	31.5 [11%]
EC_{50}	Narsoplimab-wuug concentration half of maximum C4d inhibition effect (ng/mL)	779 [12%]	94.7 (%CV) [14%]
$E_{\max}$	Maximum measured C4d inhibition response (%)	95.9 [0.4%]	1.70 [42%]
Additive residual error (% C4d inhibition)		8.56 [7%]	-

Source: FDA Reviewer

Note: Estimates for the between-subject variability were reported as the square root of variance and expressed as %CV for the log-normally distributed parameter EC_{50} . %RSE is the relative standard error expressed in percentage. The $E_{\max}$ model for the PD response (the measured C4d inhibition in %) was model as:

$$Response = E_0 + \frac{(E_{\max} - E_0) \times [Narsoplimab\ concentration]^{\gamma}}{EC_{50}^{\gamma} + [Narsoplimab\ concentration]^{\gamma}}$$

where the hill coefficient (γ) was fixed to 1. The reviewer's assessment of an alternative $E_{\max}$ model with a proportional increase in maximum effect from baseline (E_0) did not improve the fit.

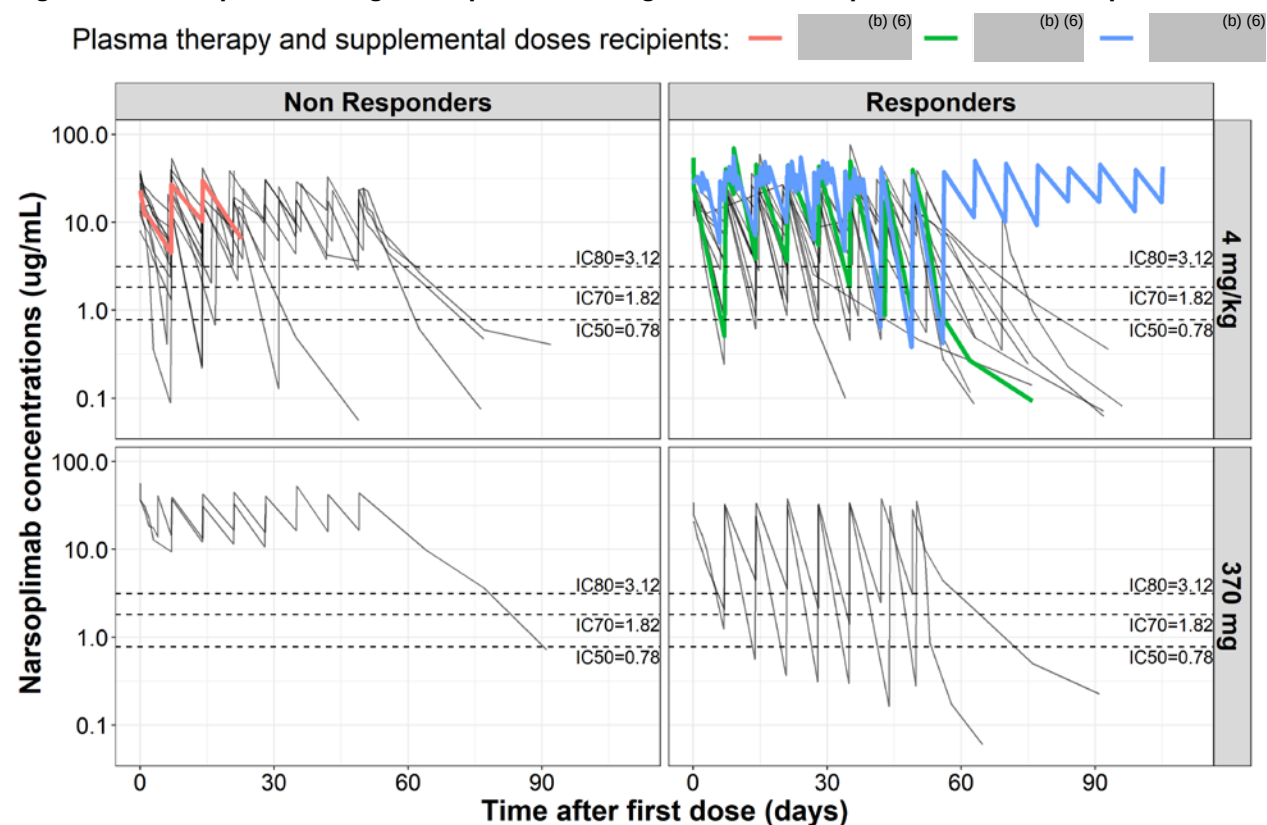
Abbreviation: CV, coefficient of variation; PD, pharmacodynamic; PK, pharmacokinetic; RSE, relative standard error

Association between narsoplimab-wuug concentrations and the level of C4d inhibition during narsoplimab-wuug treatment in patients with HSCT-TMA amongst treatment responders and non-responders

The ex-vivo assay of C4d inhibition was used to justify the selection of 4 mg/kg IV dosing in Phase 2 studies as it was expected to maintain mean lectin pathway inhibition >80% for about 168 hours, the proposed dosing interval. However, C4d inhibition was not used as marker of efficacy or treatment response in the study.

However, no association was observed between narsoplimab-wuug exposure or trough concentrations or the extent of C4d inhibition and the response to narsoplimab-wuug treatment in patients with HSCT-TMA. As depicted from [Figure 34](#), almost all non-responder to narsoplimab-wuug treatment had consistently comparable or higher exposure than treatment responders, with trough narsoplimab-wuug concentrations consistently above IC₈₀ for the majority of non-responders. Conversely, amongst the treatment responders, many patients had their trough narsoplimab-wuug concentrations just above IC₅₀ for C4d inhibition.

Figure 34. Narsoplimab-wuug PK Exposure Among Treatment Responders and Nonresponders



Source: FDA Reviewer

Note: The 3 colored solid lines represent patients with HSCT-TMA who received plasma therapy just before or during narsoplimab-wuug treatment and who received supplemental doses of narsoplimab-wuug during treatment. The horizontal dashed lines represent the average narsoplimab-wuug concentrations responsible for 50%, 70%, and 80% of the maximum C4d inhibition effect (the reported values in $\mu\text{g/mL}$ for IC₅₀, IC70 and IC80 are from the reviewer's assessment of the PK-PD model).

Amongst the patients who responded to narsoplimab-wuug treatment, patient (b) (6) received a single plasma infusion before treatment initiation and one supplemental dose of 2 mg/kg on the

second week of treatment (without justification and regardless of the absence of PLT, [Figure 29](#)). Patient (b) (6) received a single PE before treatment initiation and 21 supplemental doses of 2 mg/kg (until day 42), followed by 9 unscheduled doses of 5 mg/kg between day 56 and day 109 (in addition to weekly 5 mg/kg narsoplimab-wuug doses, [Figure 29](#)). Amongst the patients who did not respond to narsoplimab-wuug treatment, patient (b) (6) received two PE on day 10 and day 11 with one supplemental narsoplimab-wuug dose of 2 mg/kg post-PE.

PK simulations were performed to predict the expected narsoplimab-wuug PK profiles from these 3 patients in the absence of supplemental and unscheduled doses. The PK simulations showed that the PK profiles and narsoplimab-wuug trough concentrations are expected to remain above IC80 during treatment even in the absence of supplemental and unscheduled doses.

14.3.5. Appendix

Information Request Addressed to Applicant on February 23, 2021



Information Request Addressed to Applicant on May 13, 2021

(b) (4)



14.4. Summary of Bioanalytical Method Validation and Performance

Concentrations of narsoplimab-wuug in human serum were determined using a validated ELISA method at the Bioanalytical Laboratory of ^{(b) (4)}. A Nunc 96 well ELISA plate was coated with MASP-2A and incubated overnight at 4 °C. After incubation, the plates were washed and blocked. Diluted narsoplimab-wuug-containing serum samples were transferred to the coated plate and incubated for 2 hours at room temperature. Mouse antihuman IgG4 horseradish peroxidase-conjugated antibodies were added to the wells after washing. The detection substrate TMBred was added after a final wash and detection of TMBox was used to determine narsoplimab-wuug concentrations. The review team has determined that the method validation and sample analysis are acceptable.

Table 111. Bioanalytical Method Validation for Determination of Narsoplimab-wuug in Human Serum

Analyte	Narsoplimab-wuug	
Bioanalytical method validation report name, study number supported	(b) (4) -US-LML-0072 / ORO380EL-142237-A (b) (4) -NL-LML-1549 / ORO503EC-124993-B	OMS721-NHV-001 OMS721-NHV-002 OMS721-TMA-001
Method description	ELISA with mouse antihuman IgG4 HRP conjugated antibodies and TMB detection substrate	
Stability in Human Serum	5 freeze thaw cycles at -20°C and -70°C 188 days at -20°C and 384 days at -70°C 24 hours in serum at room temperature	
Standard calibration curve performance during accuracy and precision runs		
LLOQ	50 ng/mL	
Validated range	50-1000 ng/mL (50, 70, 100, 135, 190, 265, 370, 515, 725, 1000 ng/mL)	
Within run precision (%CV)	≤20%	
Between run precision (%CV)	≤20% (2.5% to 6.5%)	
Accuracy (% Bias)	-2.4% to 3.6%	
Quality control samples performance during accuracy and precision runs		
QC samples	50, 100, 350, 800, 1000 ng/mL	
Within run precision (%CV)	≤20% (1.2% to 3.3%)	
Between run precision (%CV)	≤20% (1.0% to 4.8%)	
Accuracy (% Bias)	3.9% to 7.2%	

Source: FDA Reviewer

Abbreviations: CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase; LLOQ, lower limit of quantification; TMB, 3,3',5,5'-tetramethylbenzidine

15. Trial Design: Additional Information and Assessment

Protocol Amendments

Table 112. Protocol Amendments to Study TMA-001

Amendment	Date	Abbreviated Summary of Change	Patient Enrollment
01	21 Mar 2014	- Added text that if Grade 3 or higher AEs occur in any patient in a cohort, then safety information will be provided to the FDA for review prior to proceeding with dose escalation - Added text on how dose selection will occur for Stage 2 - Added text to provide stopping rules for the study	None
02	31 Mar 2014	- Added text that the safety data will be reviewed by a clinical study monitoring team - Added text that AEs of Grade 3 or higher will be reviewed carefully with respect to number and causality when determining whether dose escalation is appropriate - Added text on how dose selection will occur for Stage 2 - Added text to provide stopping rules for the study	None

Amendment	Date	Abbreviated Summary of Change	Patient Enrollment
03	03 Apr 2014	- Added exclusion criteria of baseline resting heart rate < 45 beats per minute or > 100 beats per minute and baseline QTcF > 470 milliseconds - Added electrocardiogram to safety assessments	None
04	16 Apr 2014	Section 7.4 was amended to remove the limitation on the stopping rule to “treatment-related” AEs and now includes all AEs	Stage 1 Cohorts 1 and 2: 1 TTP and 5 aHUS patients
05	21 Nov 2014	- Inclusion criterion No. 4 was amended to clarify and re-define HSCT-TMA and refractory thrombotic thrombocytopenic criteria - Exclusion criterion No. 5 was amended to change the upper limit of resting heart rate from 100 to 115 beats per minute - Exclusion criterion No. 11 was amended to change the minimum value of abnormal liver function tests from 3 times to 5 times the upper limit of normal - Exclusion criterion No. 14 was added to include hypersensitivity to product constituents - The early termination criterion was amended to remove the requirement to discontinue patients who have received a prohibited concomitant therapy	Stage 1 Cohort 3: 2 HSCT and 1 aHUS patient
06	04 Feb 2015	- Changed refractory TTP to TTP and added biopsy-diagnosed post-renal transplant thrombotic microangiopathy - Removed the time requirement from aHUS screening inclusion criterion - Added TTP inclusion criterion for platelet count and microangiopathic hemolysis - Removed inclusion criterion pertaining to failure to attain a treatment response - Added screening criterion of mycobacterial or significant fungal infection	None
07	26 Mar 2015	- Removed post-renal transplant as a patient population - Added Standard of Care treatment regimen - Increased narsoplimab upper limit half-life range (b) (4)	None

Amendment	Date	Abbreviated Summary of Change	Patient Enrollment
08	20 Jul 2015	- Added third stage to the study, allowing patients with response to therapy to continue on study treatment for an additional 4 weeks or 12 weeks, depending on the disease type - Increased the number of study centers from 35 to 50 - Increased duration of the study from 20 months to 48 months - Increased the number of patients to be enrolled from 29 to 89 - Increased Stage 2 treatment period for aHUS patients from 4 weeks to 12 weeks - Added detection of AEs that occur at an incidence of at least 7.5% in the separate cohorts - Removed text directed to stopping rules and added periodic review by data monitoring committee	Stage 1 Cohort 3: 1 aHUS patient; Stages 2 and 3: 22 HSCT-TMA, 18 aHUS, and 4 TTP patients
09	20 Apr 2017	(b) (4) Note: Amendment 09 was not implemented (changes were carried over into Amendment 10)	None
10	12 Oct 2018	- Closed enrollment to TTP and aHUS patients - Changed the dose to 370 mg IV weekly x 4 for HSCT-TMA patients - Added Amendment Summary of Changes - Updated the nonclinical experience and rationale for selection of dose - Updated patient enrollment numbers for ongoing clinical studies	Stages 2 and 3: 4 HSCT-TMA patients
11	08 May 2020	- Provided for collection of additional data for patients with HSCT-TMA - Changed the primary and secondary objectives to focus on HSCT-TMA - Defined criteria by which to determine clinical response to treatment - Changed all reference to individuals with disease from "subject" to "patient" - Note: Amendment 11 was not implemented (changes were carried over into Amendment 11.1)	None
Amendment	Date	Abbreviated Summary of Change	Patient Enrollment
11.1	01 Jun 2020	- Added language that "As of Amendment 11 of this protocol, enrollment in the study has been completed" - Removed the (b) (4) (b) (4)	None

Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; FDA = Food and Drug Administration; HSCT-TMA = hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV = intravenous; QTcF = corrected QT interval calculated by Fridericia's formula; TTP = thrombotic thrombocytopenic purpura.

Source: Table 2 of Applicant's CSR

Table 113. Enrollment Waivers

Patient ID	Reason for Waiver	Rationale for Waiver Per Applicant	Responder Status(Applicant)
(b) (6)	Creatinine criteria not met	Met other criteria for inclusion, treatment effect could be evaluated based on neurologic dysfunction and transfusions	Responder
	Creatinine criteria not met	Met other criteria for inclusion and had proteinuria	Responder
	Creatinine criteria not met	Met other criteria for inclusion, could be evaluated by other markers and transfusion	Nonresponder
	Creatinine criteria not met	Biopsy proven TMA (GI), could be evaluated by other markers such as neurologic function, transfusions, and GI function	Responder
	Creatinine criteria not met	Patient had persistent TMA despite early improvement in renal function	Responder
	Creatinine criteria not met	Met other criteria for inclusion, could be evaluated by other markers including neurologic findings and transfusions	Nonresponder
	Positive Coombs	Coombs weakly positive at local lab, follow up from central lab was negative	Nonresponder
	Positive Coombs	Coombs weakly positive at local lab, follow up from central lab was negative	Nonresponder
	Positive Coombs Positive Shiga toxin	Coombs weakly positive and local lab and follow up at central lab was negative. Investigator thought Shiga toxin was a false positive	Responder
	Patient was screened 13 instead of 14 days from immunosuppression change	Unlikely to impact response	Nonresponder
	Received mesenchymal stem cells for GVHD 30 days prior to study	Drug is not investigational	Nonresponder

Source: Adapted from Applicant's CSR and Applicant's IR response
Abbreviations: GI, gastrointestinal; GVHD, graft versus host disease; ID, identification

16. Efficacy: Additional Information and Assessment

Patient Narratives from Study TMA-001

Patient (b) (6)

The patient was a 48-year-old Caucasian male who received a matched unrelated donor transplant after failed induction for biphenotypic acute leukemia. He had complicated post-HSCT course. On Day 5 post-HSCT, he developed a productive cough with fever and diarrhea. He was treated empirically with gentamycin and tazocin. Blood cultures were positive for *Streptococcus oralis*. Sputum culture grew *Candida krusei*. On Day 6, his creatinine increased and cyclosporin dose was reduced. On Day 9, he developed hypoxia requiring supplemental oxygen, anti-infectives were changed to meropenem and caspofungin. On Day 11, his creatinine continued to increase, believed to be related to sepsis and intravascular fluid depletion. The mucositis and pneumonia slowly improved allowing pain medications and oxygen to be decreased. Neutrophil engraftment occurred on approximately Day 21.

On day 17, the patient had fever and diarrhea. A diagnosis of liver GVHD was made and the patient was started on methylprednisolone. On day 18, vancomycin was started. The patient improved but developed posterior reversible encephalopathy syndrome (PRES) on day 22 and cyclosporin was stopped. It was at this time the diagnosis of HSCT-TMA was made on day 23. The TMA diagnosis was based on elevated lactate dehydrogenase (LDH), schistocytes, undetectable haptoglobin, and an elevated creatinine. Laboratory markers at the time of study entry and shown in [Table 114](#). On day 33, the patient received his first dose of narsoplimab-wuug, the following day the investigator was informed the patient had *E. coli* 0157. The patient was asymptomatic at that time and therefore no treatment was given. In total, the patient received 8 weekly doses of narsoplimab-wuug. The patient continued to have neutropenia and thrombocytopenia during treatment, this was thought to be secondary to mycophenolate mofetil and valganciclovir, or graft failure. The patient did not engraft platelets and remained platelet and blood transfusion dependent. The patient met a response based on LDH and renal response. Response based on TMA markers was noted 15 days after starting narsoplimab-wuug. The patient ultimately died on day 215 due to neutropenic sepsis.

Reviewer comment

This is a complex patient with recent diagnosis of PRES, liver GVHD, and infections in relation to HSCT-TMA. While GVHD and infections are risk factors for HSCT-TMA often, the first step in treatment of HSCT-TMA is to treat the underlying cause and/or withdrawal or reduction of calcineurin inhibitors (CNIs) and sirolimus ([Rosenthal 2016](#); [Khosla et al. 2018](#); [Elemery et al. 2019](#)). Therefore, the impact of treating these risk factors of liver GVHD and infections make it difficult to interpret if the patient's clinical improvement was due to narsoplimab-wuug or treating the underlying cause. The patient also had cyclosporin discontinued at the time of HSCT-TMA diagnosis, 10 days before starting narsoplimab-wuug. The Bone Marrow Transplant Clinical Trials Network Toxicity Committee consensus summary recommended CNI cessation as the first line management ([Ho et al. 2005](#); [Epperla et al. 2020](#)). Although there is debate if

removal of CNIs and sirolimus improves HSCT-TMA, as some recent large cohort. studies have not demonstrated a benefit (Epperla et al. 2020).

The confounders described above make the interpretation of narsoplimab-wuug treatment effect difficult, the clinical reviewer does not consider the patient to be a responder as he did not meet all three components of the predefined response definition. While the reviewer understands the patient never engrafted platelets, this is a critical component of the response definition and therefore response is less compelling. When looking at the patient's TMA markers it is quite apparent that the haptoglobin improved after starting narsoplimab-wuug, this could be a sign of response to narsoplimab-wuug, but this was not included in the primary composite endpoint definition and how this translates to clinical benefit is not clear. While the LDH improved on narsoplimab-wuug, appears to have been down trending prior to narsoplimab-wuug administration, see [Figure 35](#) below. Also, the patient never achieved blood transfusion freedom. Of note, the patient was also reported to have a positive E. coli 0157. The clinical reviewer was not able to confirm this as it was stated in the narrative, but not documented elsewhere. E. coli 0157 can cause typical hemolytic uremic syndrome (HUS), another form of TMA.

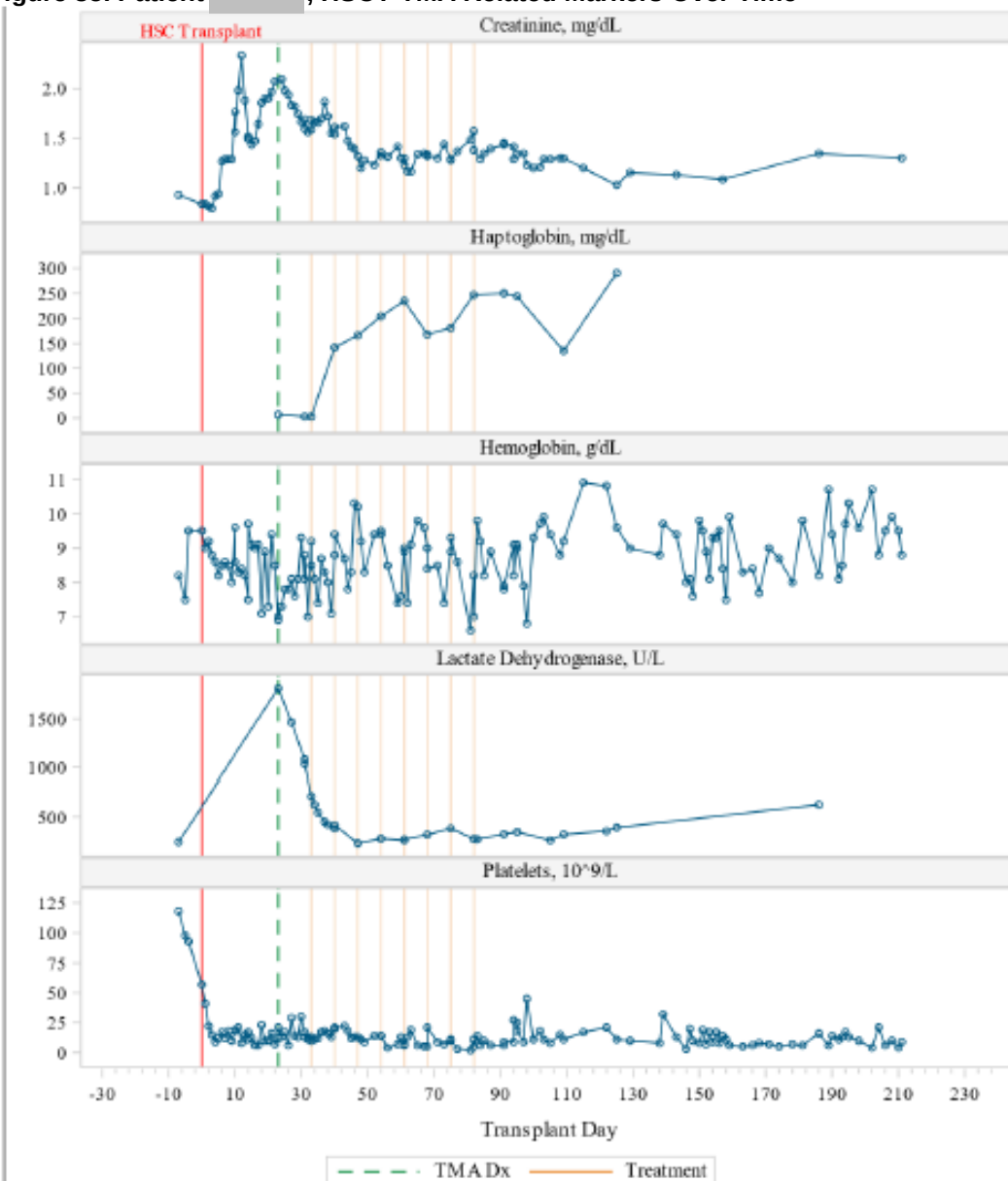
Table 114. Patient ^{(b) (6)} Laboratory Markers at Time of Study Entry, Day 31

Analyte	Platelet Count ^a (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L)	Haptoglobin (mg/dL)	Creatinine (μmol/L)	Hemoglobin ^a (g/dL)
Value	10	712	< 3	148.3	8.5
Normal range	150 – 400	125 – 220	14 – 268	64.0 – 104.0	13.2 – 17.0

Source: Applicant Narrative

^a The patient was receiving transfusion support

Figure 35. Patient (b) (6), HSCT-TMA Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx, diagnosis; HSC, hematopoietic stem cell; TMA, thrombotic microangiopathy

Patient (b) (6)

The patient was a 58-year-old Asian male with a history of myelodysplastic syndrome that evolved into acute myeloid leukemia (AML). After achieving a complete remission, he had a matched related HSCT. Following transplant, the patient developed mucositis requiring total parental nutrition. On day 5, his creatinine increased. He developed possible typhlitis and cefepime and metronidazole was started, with amphotericin B added shortly after. He was requiring both blood and platelet transfusions. On day 12, he required intubation for respiratory distress and was diagnosed with diffuse alveolar hemorrhage (DAH). Vancomycin and steroids

were added to his treatment regimen. Fungal pneumonia was also a concern. He was diagnosed with cytomegalovirus (CMV) reactivation on day 15 and was started on ganciclovir. Neutrophil engraftment occurred on day 15, the patient never engrafted platelets. He developed fluid overload and was started on dialysis. He was extubated on day 19. Tacrolimus and sirolimus was temporarily discontinued from day 15 and day 21, respectively.

The patient was diagnosed with HSCT-TMA on day 21, laboratory makers supporting this diagnosis were schistocytes, thrombocytopenia, and elevated LDH. Laboratory markers at time of study entry on shown in [Table 115](#). The patient received his first dose of narsoplimab-wuug on day 36. He received 8 doses total. Response based on TMA markers was noted 7 days after starting narsoplimab-wuug, the patient met response based on LDH and renal response. He never engrafted platelets.

The patient was discharged home, but subsequently readmitted on day 39 for GI-GVHD and persistent pancytopenia. Tacrolimus, solumedrol, basiliximab, ruxolitinib, and budesonide were added to the patient's treatment plan. On day 48, encephalopathy was noted and tacrolimus was discontinued. On day 54, acyclovir was held for worsening renal function. The patient suffered from encephalopathy, sepsis and additional viral infections. Graft failure was noted on day 96 and the patient died on day 100 due to septic shock.

Reviewers comments

This patient had a complicated post-HSCT course. Around the time of his HSCT-TMA diagnosis the patient was also diagnosed with possible pneumonia, typhlitis and GVHD. The patient was subsequently treated with antibiotics, antivirals and antifungal agents, in addition to steroids for the GVHD. The treatment of these underlying risk factors may impact the interpretability of narsoplimab-wuug.

While the confounders described above make the interpretation of narsoplimab-wuug treatment effect difficult, the clinical reviewer does not consider the patient to be a responder as he did not meet all three components of the predefined response definition. While the reviewer understands the patient never engrafted platelets, this is a critical component of the response definition and therefore response cannot be substantially determined. In addition, the patient was noted to have renal response, but never had a doubling of creatinine from pretransplant level. In fact, at the time of screening, the patient's serum creatinine was 0.76 mg/dL which was down trending (see [Figure 36](#), while the creatinine further decreased on therapy, this magnitude of change is difficult to interpret. The patient did have a reduction in LDH, although the LDH was already down trending prior to narsoplimab-wuug administration (see [Figure 36](#)). Of note, the patient had a low haptoglobin that drastically increased to normal while receiving therapy, this may provide evidence of narsoplimab-wuug effectiveness, but it is unknown how this translates to clinical benefit. It is worth noting that while it is unlikely the patient had TTP, and ADAMTS13 was not documented, this is typically standard to rule out when considering TMA.

Table 115. Patient (b) (6) Laboratory Markers at Time of Study Entry, Day 35

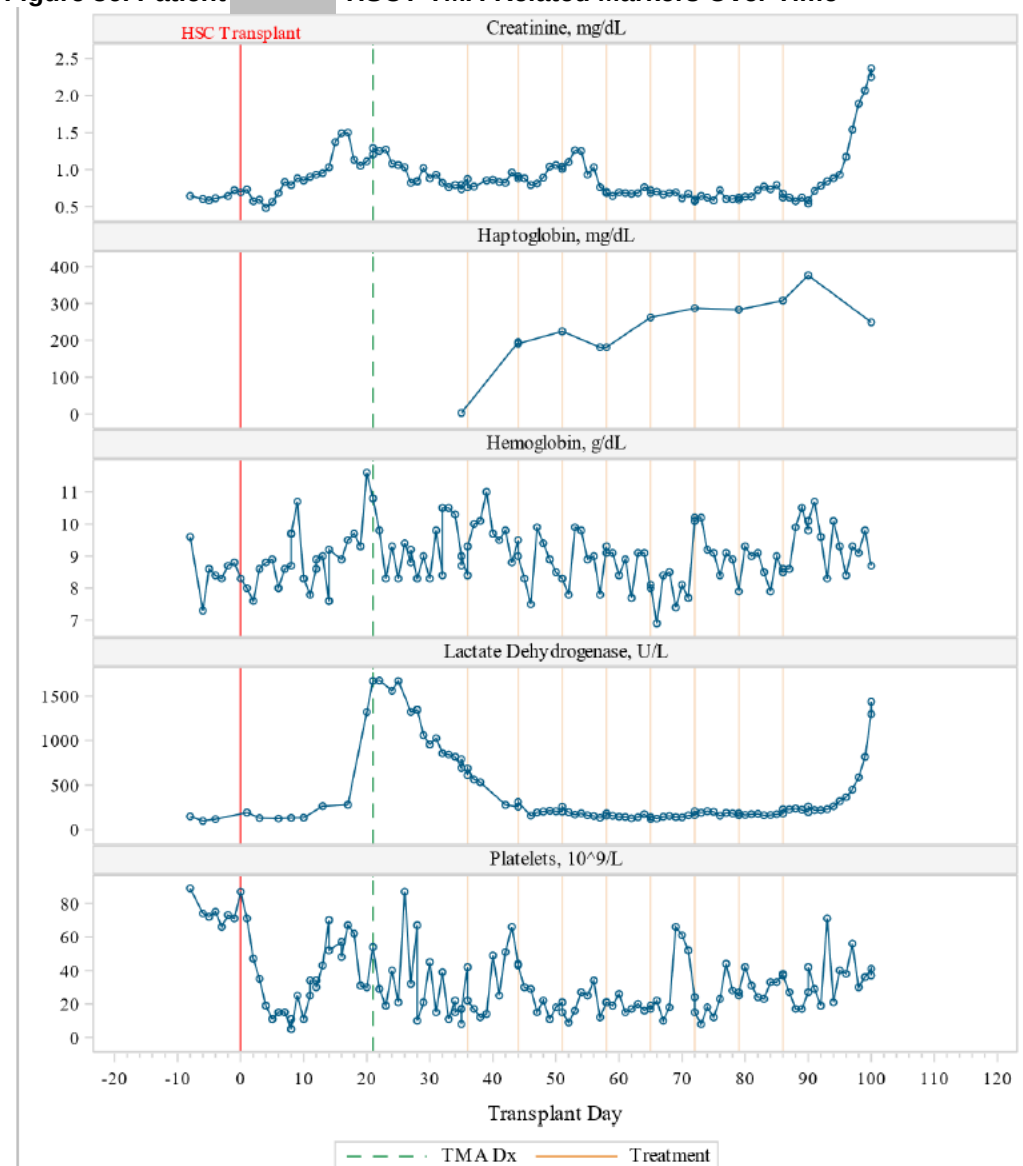
Analyte	Platelet Count (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L) ^b	Haptoglobin (g/L)	Creatinine (mg/dL)	Hemoglobin ^a (g/dL)
Value	17	792	< 3	0.73	8.7
Normal range	130 – 400	125 – 220	14 – 268	0.72 – 1.18	13.2 – 17.0

Source: Applicant Narrative

^a Transfusion supported

^b Day 64

Figure 36. Patient (b) (6) HSCT-TMA-Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx, diagnosis; HSC, hematopoietic stem cell; TMA, thrombotic microangiopathy

Patient (b) (6)

The patient was a 22-year-old Hispanic female with a history of relapsed B-acute lymphoblastic leukemia (ALL) who received a matched sibling HSCT. On day 18, she developed a persistent fever, she was treated with micafungin, cefepime and vancomycin. Her blood cultures were positive for *Haemophilus influenzae*. On day 20, she was diagnosed with GI-GVHD and was treated with solumedrol, basiliximab, and budesonide. Day 24 bronchoscopy was significant for aspergillus and amphotericin B was initiated. On day 32, she had a GI bleed likely related to GVHD and blood counts were decreasing. Schistocytes were noted on day 36. On day 40, she had CMV reactivation and ganciclovir was added. Ruxolitinib was also added for GVHD. At this time her creatinine was increased, thought to be secondary to medications. She continued to have multiple episodes of bacteremia for which gentamicin was added. For her GVHD she also received photopheresis and infliximab. On day 69, she was transferred to the intensive care unit (ICU) for increased abdominal pain and GI bleeding. Echocardiography showed pulmonary arterial hypertension. On day 92 liver GVHD was suspected. She developed *Klebsiella pneumoniae* on day 95. She had a colonoscopy on day 113 which showed mild GVHD and HSCT-TMA.

Her diagnosis of HSCT-TMA was based on colonoscopy results, in addition to thrombocytopenia, anemia, schistocytes, increased creatine and elevated LDH, [Table 116](#) shows the patients screening labs. Tacrolimus was discontinued on day 121 and the patient started narsoplimab-wuug that same day. The patient received 8 weekly doses of narsoplimab-wuug, and initial response based on TMA makers occurred approximately 11 days after starting therapy. Response was based on LDH and renal response, as the patient never engrafted platelets and remained blood transfusion dependent.

Shortly after starting narsoplimab-wuug, the patient developed fever, she was found to have CMV reactivation, in addition to positive blood cultures for fungal and subsequently bacterial infections. She was treated with various antibiotics and antifungals. On day 166 her kidney injury improved. Unfortunately, the patient continued to have a complicated course including viral infections, possible pneumonia, GI-GVHD, transfusion dependence, renal dysfunction, catheter related thrombosis and sepsis. The investigator noted on day 220 there were no signs of HSCT-TMA. The patient ultimately died on day 291 due to GVHD, respiratory failure and sepsis.

Clinical reviewer comment:

This patient had very complicated transplant course, most notable for steroid refractory GVHD and recurrent infections for which she was treated with a variety of medications. Tacrolimus was discontinued the same day of narsoplimab-wuug treatment. The treatment of these underlying risk factors may impact the interpretability of narsoplimab-wuug. While not mentioned in the patient narrative, the Applicant was able to confirm the patient did receive a plasma exchange while receiving narsoplimab-wuug therapy. Plasma exchange is not standard of care for HSCT-TMA and response rates have been reported to be 27-80%, but in select patients it may be of benefit ([Rosenthal 2016](#); [Jodele 2018](#); [Khosla et al. 2018](#)). Of note, the patient did not have an ADAMTS13 reported.

The confounders described above make the interpretation of narsoplimab-wuug treatment effect difficult. In addition, the clinical reviewer does not consider the patient to be a responder as she did not meet all three components of the predefined response definition. While the reviewer understands the patient never engrafted platelet this is a critical component of the response definition and therefore response cannot be substantially determined. Of note, the renal function acutely worsened on therapy, but then significantly down trended as shown in [Figure 37](#). LDH improved on therapy. As for other TMA markers, blood transfusions were continued but this could have been due to poor graft function. Haptoglobin was never decreased.

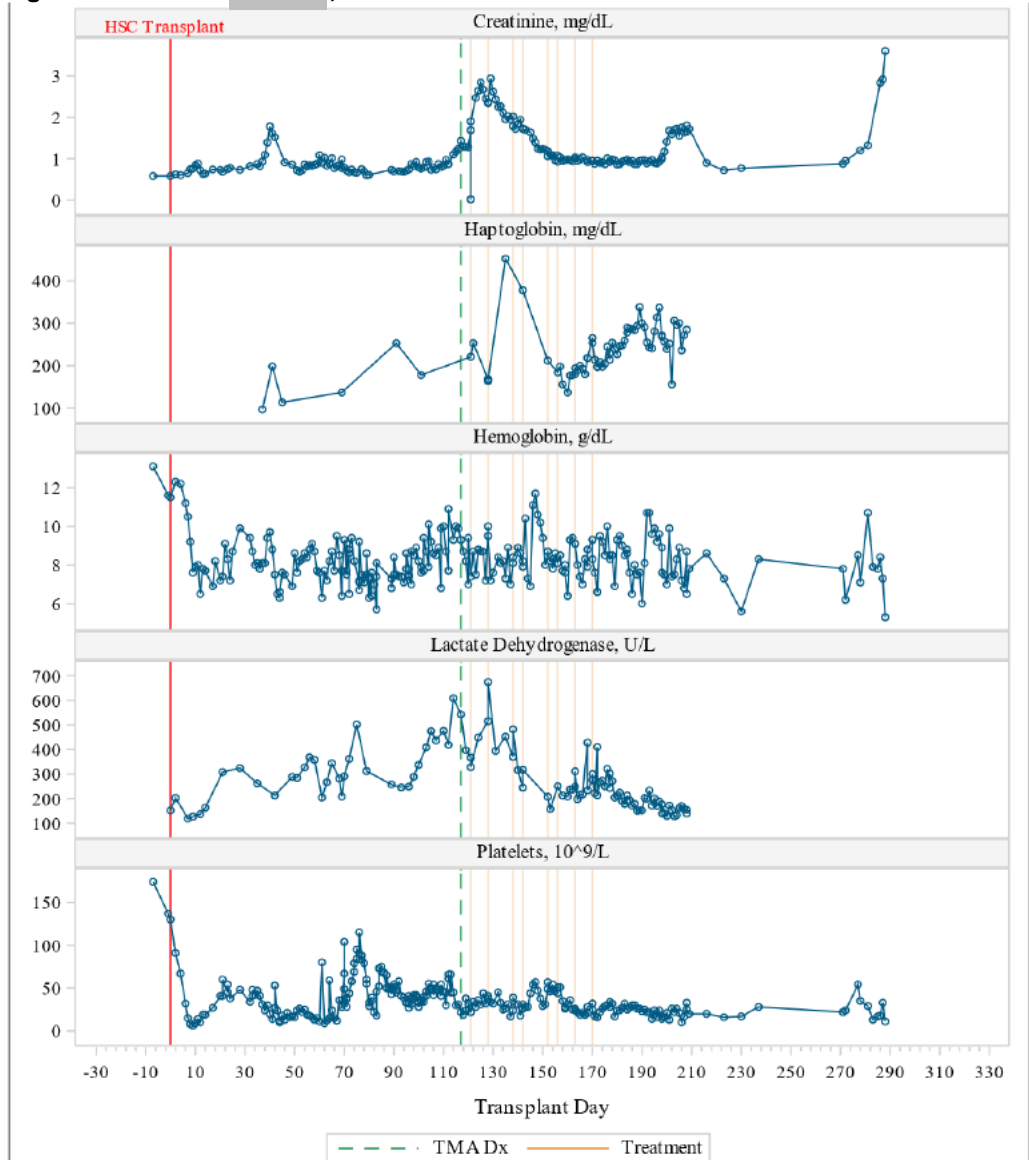
Table 116. Patient (b) (6) Laboratory Markers at Time of Study Entry, Day 121

Analyte	Platelet Count ^a (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L)	Haptoglobin (mg/dL)	Creatinine (mg/dL)	Hemoglobin ^a (g/dL)
Value	22	328	221	1.90	7.4
Normal range	130 – 400	125 – 220	35 – 273	0.55 – 1.02	13.2 – 17.0

Source: Applicant Narrative

^a Transfusion supported

Figure 37. Patient (b) (6), HSCT-TMA-Related Markers Over Time



Source: Applicant Narrative
Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis
Abbreviations: Dx, diagnosis; HSC, hematopoietic stem cell; TMA, thrombotic microangiopathy

Patient (b) (6)

The patient was a 34-year-old male with a past medical history significant for ALL that was refractory to treatment. He received a matched sibling donor transplant. The patient had a complicated post-transplant course. On day 3, he developed a fungal rash for which micafungin was started and on day 6 he developed neutropenic sepsis (blood culture was positive for coagulase negative Staphylococcus). Platelet engraftment was noted on day 9 and neutrophil engraftment occurred on day 12. The patient had persistent fevers for which meropenem was added. Engraftment syndrome was diagnosed on day 13 and steroids were started. Cefepime and vancomycin were replaced with linezolid. Upper and lower endoscopy showed esophageal

candidiasis, GVHD, and CMV colitis. On day 30 he developed acute kidney injury suspected to be from dehydration. He was treated with a variety of antibiotics for fevers.

On day 35 he had thrombocytopenia, anemia and elevated LDH concerning for microangiopathic hemolytic anemia. Cyclosporin was discontinued on day 40 and tacrolimus was started. The patient was screened for Study TMA-001 on day 49 but had a positive direct antiglobulin test (DAT) therefore, he was not eligible. He was treated with a reduction in tacrolimus dose and intravenous immunoglobulin (IVIG). The patient was re-admitted on day 71 for weakness, elevated creatinine, and mild jaundice. The patient received plasma exchange 12 times without resolution of the TMA and additional IVIG.

On day 91 he was screened again for enrollment and the DAT was negative. His diagnosis of HSCT-TMA was based on thrombocytopenia, anemia, LDH, and schistocytes, his screening labs are shown in [Table 117](#). On day 107 he had acute kidney injury due to poor oral intake. On day 117 he received his first dose of narsoplimab-wuug. He received 8 doses total. Response based on LDH and platelets occurred 228 days after starting narsoplimab-wuug. There were no clinical components of the response definition for which he was evaluable.

The remainder of his post-transplant course was significant for herpes ophthalmicus, chronic GVHD of the skin, and pneumonia.

Clinical reviewer comment:

This patient was diagnosed with HSCT-TMA on day 35 following transplant but, was unable to enroll in Study TMA-001 due to a persistently positive DAT (a key exclusion criteria). The patient received IVIG and plasma exchange but the TMA did not improve. He was ultimately started therapy approximately 80 days after diagnosis. It is unusually to have a positive DAT and HSCT-TMA as this is not immune related process. A positive DAT could indicate an autoimmune hemolytic anemia or Evan's syndrome (Dvorak 2019). Although, at the time of rescreening the investigator did note the patient had schistocytes, which does suggest a microangiopathic hemolytic anemia process. In addition, DAT can become positive with recurrent blood transfusions. The positive DAT certainly complicates the patient's diagnosis.

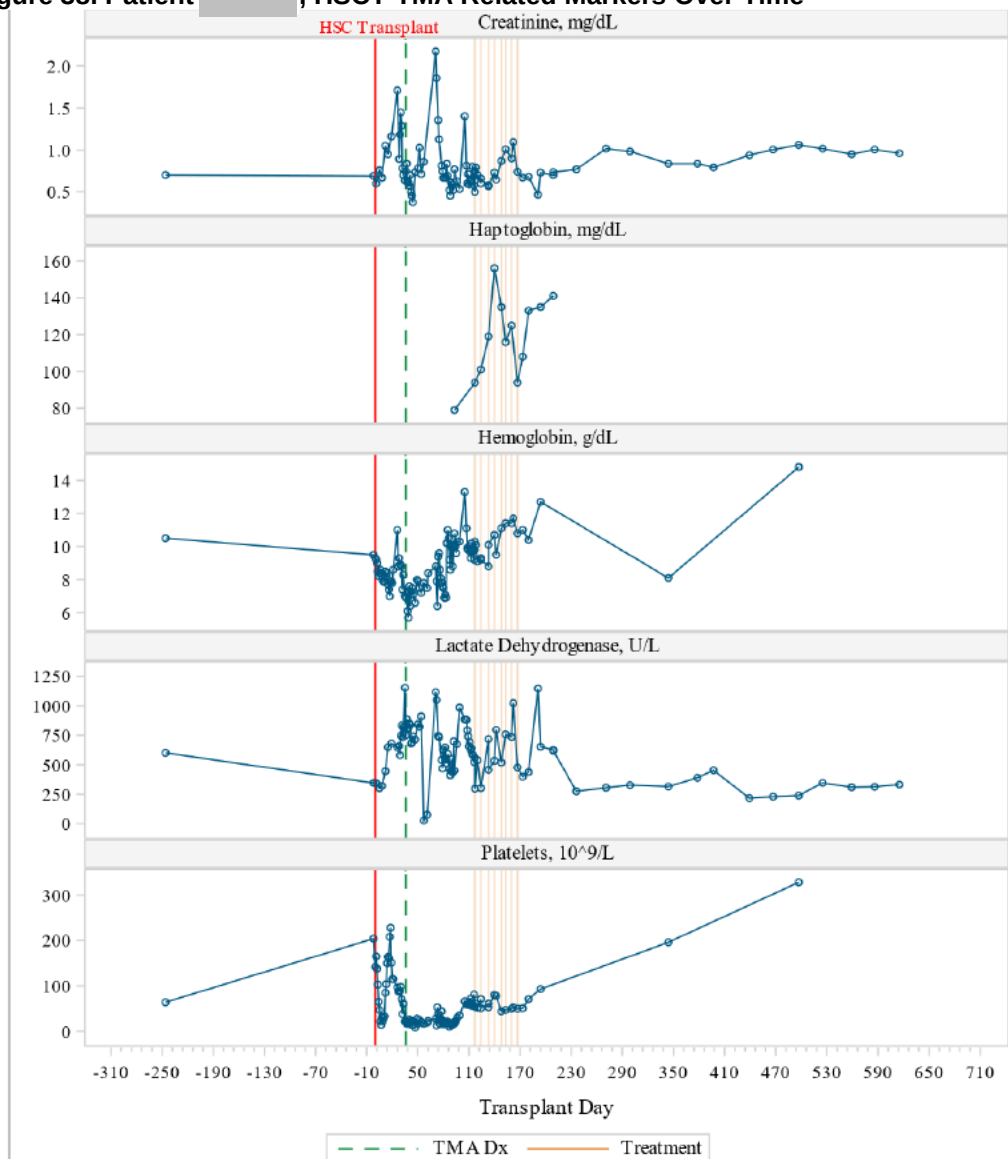
The clinical reviewer does not consider the patient to be a responder as he did not meet all three components of the predefined response definition. His response was based on platelets and LDH alone. The patient was never evaluated for clinical improvement as these components were not evaluable, in addition he had a normal creatinine. The Applicant's rationale for including him as a responder was due to an increase in hemoglobin, but this was not a component of the primary endpoint and it's not clear if the magnitude of hemoglobin response is significant with a baseline hemoglobin around 10 g/dL. The other concern was response based on TMA markers (LDH and platelets) was not documented until 228 after starting narsoplimab-wuug. This was discussed with clinical pharmacology colleagues who agreed that based on the half-life of narsoplimab-wuug its too difficult to determine if this response was related to narsoplimab-wuug. The Applicant states the delay of response was secondary to an incurrent infection but, most patients in Study TMA-001 had infection without a delayed response. Of note, the patient did not meet the inclusion criteria of doubling of creatinine.

Table 117. Patient (b) (6) Laboratory Markers at Time of Study Entry, Day 90

Analyte	Platelet Count (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L)	Creatinine (μmol/L)	Hemoglobin (g/dL)
Value	14	550	52	10.1
Normal range	142 – 350	240 – 480	62.0 – 106.0	13.5 – 17.4

Source: Applicant Narrative

Figure 38. Patient (b) (6), HSCT-TMA Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx, diagnosis, HSC, hematopoietic stem cell, TMA, thrombotic microangiopathy

Patient (b) (6)

The patient was a 57-year-old male with history of relapsed mantle cell lymphoma who underwent a double cord blood transplant. The patient developed veno-occlusive disease on day

4. He achieved neutrophil engraftment on day 17. After having intermittent diarrhea, he was diagnosed with GI-GVHD based on sigmoidoscopy. He was treated with solumedrol and budesonide, with improvement. He developed CMV reactivation and was treated with ganciclovir initially which was subsequently changed to foscarnet for increasing viral load. On day 58 he had loss of consciousness and possible seizure, weakness and hallucinations. He was diagnosed with skin GVHD on day 103 and was treated with prednisone and basiliximab. On day 124 he was admitted for weakness and altered mental status. His skin GVHD was ongoing.

On day 126 he was diagnosed with HSCT-TMA based on thrombocytopenia, decreased haptoglobin, and elevated LDH. Tacrolimus was discontinued. He was also diagnosed with Guillain Barré syndrome (GBS) and was treated with IVIG. CMV reactivation also occurred on that day. Platelet and red blood cell transfusions were started. On day 134 Evan's syndrome was suspected and the patient was treated with rituximab and IVIG. Of note a DAT was checked on day 155 and was negative. On day 144 schistocytes and LDH were increased. The patient entered the study on day 160 (see [Table 118](#) for screening labs) and received his first dose of narsoplimab-wuug on day 167. He received 4 total doses. TMA markers improved approximately 35 days after starting narsoplimab-wuug, and transfusions were discontinued.

The remainder of his transplant course was notable for liver GVHD for which he was treated with steroids and GBS for which he received IVIG. He also developed a positive DAT and was treated with IVIG and rituximab. On day 295 he was started on eltrombopag for pancytopenia.

Clinical reviewer comment

Around the time of HSCT-TMA diagnosis the patient also had a diagnosis of acute and chronic GVHD, Evan's syndrome, CMV reactivation, and GBS. The patient was actively treated for Evan's syndrome which has overlapping characteristics of HSCT-TMA, such as thrombocytopenia, anemia, and elevated LDH. The clinical reviewer is not convinced that the patient had a diagnosis of Evan's syndrome given the DAT was negative and schistocytes were presents, this is consistent with microangiopathic hemolysis. The patient did receive rituximab for Evan's syndrome shortly before narsoplimab-wuug, there have been a few small studies and case reports suggesting that rituximab may be an effective treatment for HSCT-TMA ([Kim et al. 2015](#)). With that being said, timing of response does favor narsoplimab-wuug. Overall, the concurrent disease diagnosis and treatments obscure the treatment effect of narsoplimab-wuug, although favors that this patient responded to narsoplimab-wuug.

The patient was noted to have a renal response (this was not required to meet the responder definition), but the patient did not meet the renal inclusion criteria of doubling of serum creatinine. With a baseline creatinine of 0.94 mg/dL (screening creatinine was 0.61 mg/dL) and without doubling of the pretransplant creatinine, the significance of the magnitude of reduction is unclear.

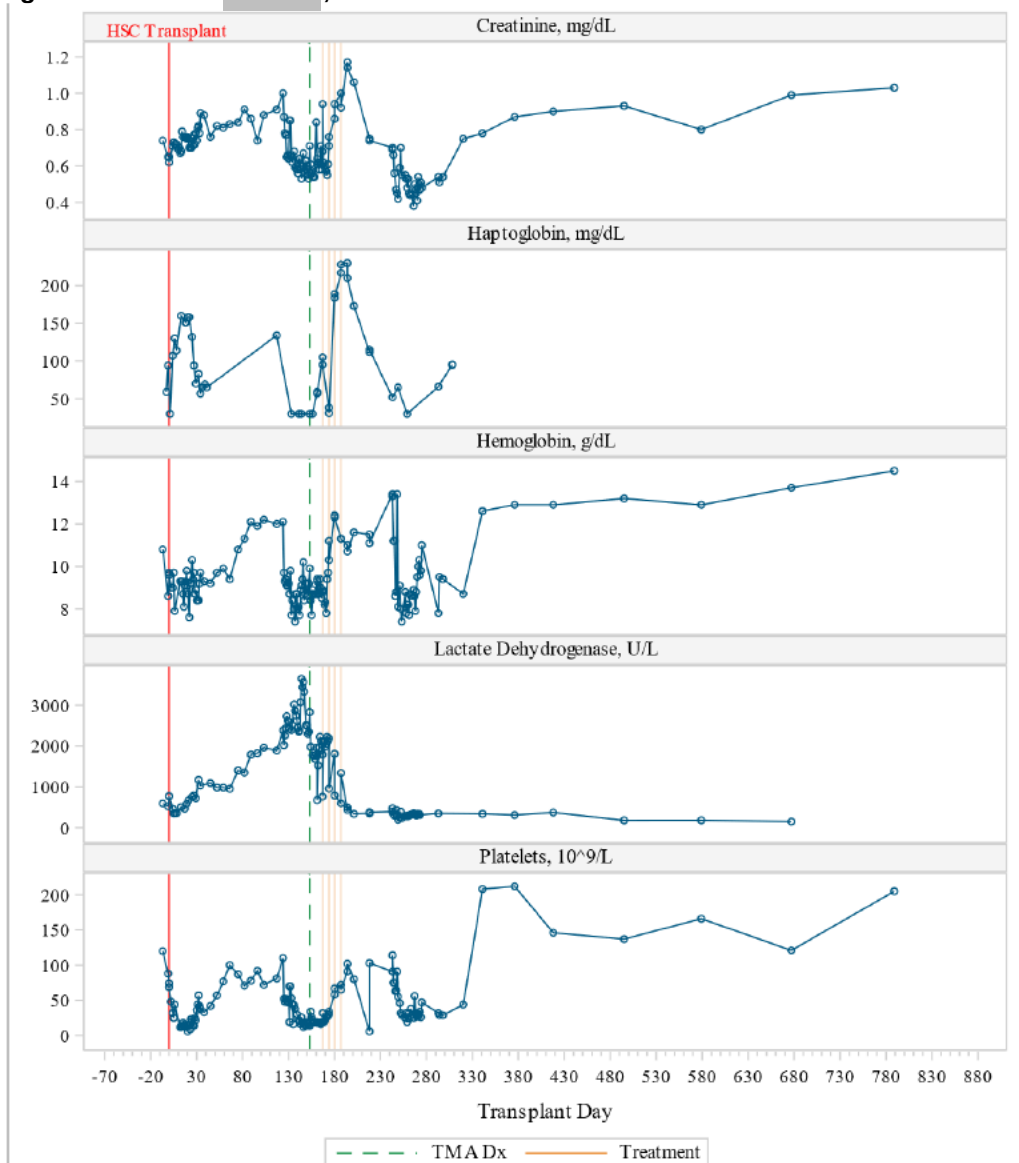
Table 118. Patient (b) (6), Laboratory Markers at Time of Study Entry, Day 160

Analyte	Platelet Count ^a (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L)	Haptoglobin (g/L)	Creatinine (mg/dL)	Hemoglobin ^a (g/dL)
Value	18	678	57	0.61	9.3
Normal range	130 – 400	120 – 246	40 – 240	0.7 – 1.3	13.0 – 17.5

Source: Applicant Narrative

^a Transfusion supported

Figure 39. Patient (b) (6), HSCT-TMA Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx, diagnosis; HSC, hematopoietic stem cell; TMA, thrombotic microangiopathy

Patient (b) (6)

The patient was a 32-year-old male with a history of high-risk ALL who underwent a matched related donor transplant. Day 1 post-transplant, he developed mucositis requiring parental nutrition and opioid management. On day 6, he developed bacteremia (blood culture was positive for staphylococcal aureus), he was treated initially with meropenem. The patient achieved neutrophil and platelet engraftment on day 18 and 22, respectively. On day 88, he was diagnosed with oral GVHD. His cyclosporine was discontinued on day 145. On day 159, he had elevated liver function tests, liver biopsy demonstrated severe panlobular hepatitis with hepatocyte necrosis, concerning for aGVHD. The patient was treated with prednisone. He also had CMV reactivation. Around day 178, he was diagnosed with acute skin and liver GVHD, in addition to chronic GVHD of the eye.

On day 194 he was diagnosed with HSCT-TMA, based on thrombocytopenia, elevated LDH, elevated creatinine and anemia. The patient had been restarted on cyclosporin two weeks prior but this was discontinued once HSCT-TMA was diagnosed. At this time, he was also diagnosed with PRES. With blood pressure control the patient recovered. He also had a low-grade fever. He received his first dose of narsoplimab-wuug on day 201, screening labs are shown in [Table 119](#). He received 8 total doses. Response occurred 153 days after starting narsoplimab-wuug and was based on improvement in LDH, platelets, neurologic dysfunction and transfusions. See TMA marker changes in [Figure 40](#). Following initiation of narsoplimab-wuug he had recurrent episodes of delirium and confusion, this was thought to be secondary to steroids, and/or self-discontinuation of lorazepam and haloperidol. He was last seen on day 297 in outpatient clinic.

Clinical reviewer comment

The patient was diagnosed and treated for CMV reactivation, fever and GVHD around the same time as his HSCT-TMA diagnosis and starting narsoplimab-wuug. In addition, the patient was diagnosed with PRES at the same time as HSCT-TMA. Neurologic deficits have been reported in up to half of patients with HSCT-TMA and can include confusion, headaches, hallucinations and seizures ([Jodele et al. 2015](#)). The most common of CNS injury is likely due to uncontrolled TMA associated hypertension, including PRES ([Jodele et al. 2015](#)). While the reviewer acknowledges that PRES can be a manifestation of HSCT-TMA it is difficult to tell if improvement was based on hypertension control or narsoplimab-wuug. The timing of PRES improvement is not clear. In addition, the patient had delirium and confusion, but this occurred after the patient had already been started on narsoplimab-wuug. Treatment of concurrent disease diagnosis make it difficult to interpret the treatment effect of narsoplimab-wuug.

The patient did not meet the responder definition until 153 days after starting narsoplimab-wuug. It is difficult to determine if a response this far out from treatment can be attributed to narsoplimab-wuug. The clinical pharmacology team also agreed it is difficult to determine given the half-life of narsoplimab-wuug.

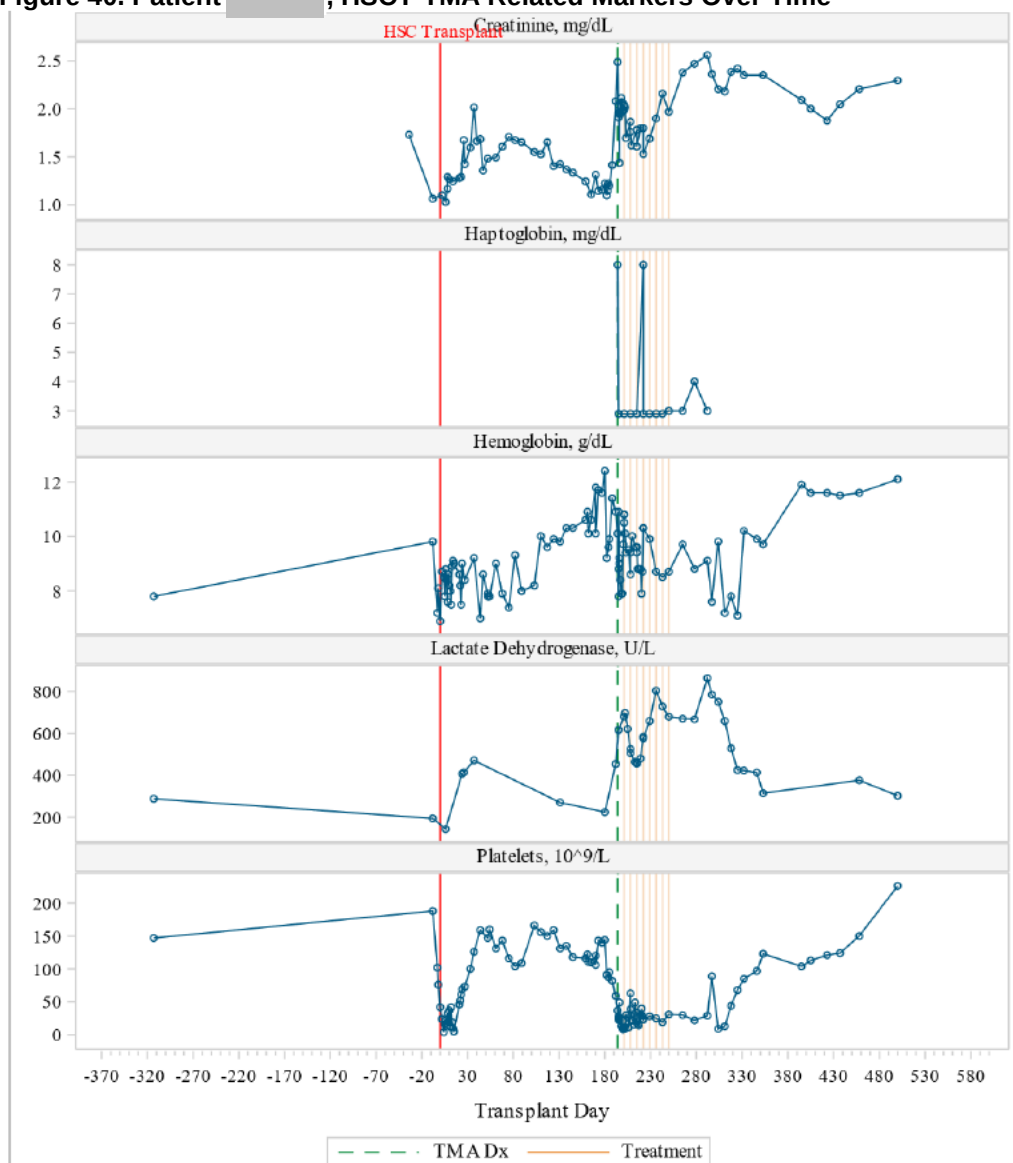
Of note, the patient also did not meet inclusion/exclusion criteria. The patient had a weakly positive Coombs test (although the repeat central laboratory test was negative) and a positive shiga toxin. Most likely, these tests were false positives given repeat Coombs test was negative and the patient did not have diarrhea.

Table 119. Patient (b) (6), Laboratory Markers at Time of Study Entry, Day 194

Analyte	Platelet Count (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L)	Creatinine (mg/dL)	Hemoglobin (g/dL)
Value	28	616	172.2	8.8
Normal range	150 – 400	125 – 220	64.0 – 104.0	13.2 – 17.0

Source: Applicant Narrative

Figure 40. Patient (b) (6), HSCT-TMA Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx, diagnosis, HSC; hematopoietic stem cell; TMA, thrombotic microangiopathy

Patient (b) (6)

The patient is a 34-year-old African American male who had a history of S/β° thalassemia and underwent a matched sibling HSCT, but experienced late graft failure. He then developed myelodysplastic syndrome and underwent a second matched sibling HSCT. On day 10 post-transplant, he had a fever and was treated with antibiotics. On day 14, he had increasing blood pressure and CT of the chest consistent with an atypical infection. Neutrophil engraftment occurred on day 20. On day 23, he developed hematuria and was BK virus positive. He was subsequently diagnosed with CMV reactivation and repeat chest CT showed multifocal infection. He was treated with vancomycin. Platelet engraftment was achieved on day 36. His course was further complicated by head CT showing a subdural hematoma on day 43.

On day 66 he was diagnosed with HSCT-TMA, supporting his diagnosis was thrombocytopenia, elevated creatinine, increased LDH, anemia, and schistocytes. See screening labs in [Table 120](#). He received his first dose of narsoplimab-wuug on day 85. Tacrolimus was discontinued on day 89. He received 4 doses per protocol. His response based on TMA markers occurred 28 days after starting narsoplimab-wuug. Response was based on improvement in creatinine, platelets and LDH (see [Figure 41](#)).

Following response to narsoplimab-wuug the patient's course was complicated by GVHD.

Clinical reviewer comment

The patient had tacrolimus discontinued at the time of narsoplimab-wuug treatment. The impact of tacrolimus on this patient's response appears less likely as the patient did not meet the response definition until 28 days after starting narsoplimab-wuug. Therefore, it appears narsoplimab-wuug most likely caused an improvement in TMA markers and serum creatinine.

The patient's LDH was just above the upper limit of normal at the time of HSCT-TMA diagnosis at 221 U/L (normal range: 100-200U/L). The highest the LDH increased was to 278 U/L and the baseline LDH level was 237 U/L. Therefore, while the LDH may have decreased further on narsoplimab-wuug, it is difficult to determine the significance of magnitude of change. To meet the LDH component of response the patient had to have and LDH <1.5x upper limit of normal (ULN), but this patient never had an LDH >1.5x ULN. The clinical reviewer remains convinced that this patient responded to narsoplimab-wuug given improvement in platelet count and serum creatinine. This is further supported by an increase in hemoglobin (while not receiving transfusions) and improvement in haptoglobin.

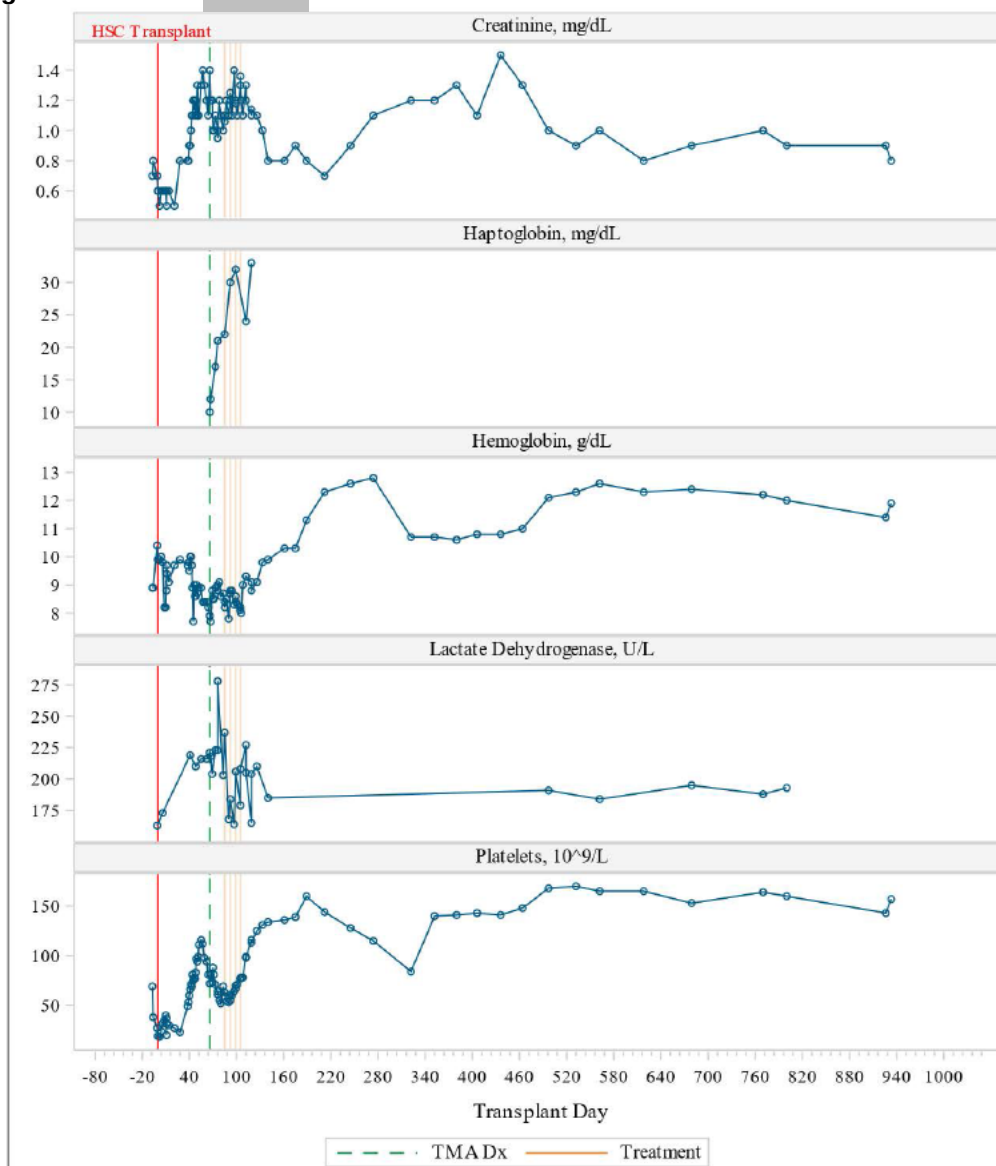
Table 120. Patient (b) (6), Laboratory Markers at Time of Study Entry, Day 76

Analyte	Platelet Count ^a (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L)	Creatinine (mg/dL)	Hemoglobin ^a (g/dL)
Value	64	278	0.95	9.0
Normal range	150 – 400	125 – 220	0.72–1.18	13.2 – 17.0

Source: Applicant Narrative

^a Transfusion supported

Figure 41. Patient (b) (6) HSCT-TMA Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx. Diagnosis; HSC. hematopoietic stem cell; TMA. thrombotic microangiopathy

Patient (b) (6)

The patient was a 46-year-old Caucasian male with a history of relapsed T-ALL, who underwent an unrelated 9/10 matched HSCT. The patient engrafted neutrophils and platelets on day 21. He did well following transplant until day 121 when he developed steroid refractory GI-GVHD. He was treated with pentostatin and mesenchymal stem cells with resolution. He experienced CMV reactivation on day 144 and campylobacter diarrhea on day 186. On day 210, he had a GI biopsy for GI bleeding which demonstrated both GI-GVHD and HSCT-TMA. On day 228, he developed polyneuropathy restricting him to bed which was confirmed on electromyogram. On day 236, HHV6 infection was identified.

On day 242 HSCT-TMA was diagnosed based on colonic biopsy, platelet reduction and elevated LDH. The patient also became transfusion dependent. [Table 121](#) shows laboratory markers at time of study entry. The patient received his first dose of narsoplimab-wuug on day 263. The patient received 8 weekly doses. Response was based on improvement in LDH, platelets, neurologic dysfunction (polyneuropathy improved on day 290) and GI dysfunction (melena resolved on day 275). Response based on TMA markers occurred 43 days after starting narsoplimab-wuug. See TMA marker changes in [Figure 42](#). Cyclosporin dose was decreased during narsoplimab-wuug treatment.

Following completion of the clinical trial the patient developed GI and skin GVHD on day 442. He developed Epstein-Barr virus (EBV) reactivation, GI candida infection, and E. coli sepsis that led to his death on day 515.

Clinical reviewer comment

While the patient should still be considered a responder, the issues outlined below make the interpretation of the treatment effect of narsoplimab-wuug difficult.

The patient was determined by the Applicant to have a GI response. The improvement in melena does seem to correlate temporarily to narsoplimab-wuug administration, but this is confounded by the fact the patient also had GI-GVHD and was being treated with steroids during that time. It does not appear that the steroid treatment could account for the GI response alone as the dose had not significantly changed and the patient was on a low dose of prednisone (25 mg). Therefore, it is likely narsoplimab-wuug was responsible for GI improvement.

The patient was also determined to have a neurologic response based on improvement in polyneuropathy per the Applicant. Polyneuropathy during transplant can be multifactorial including medications. It is difficult to confidently determine if the patient's polyneuropathy is related to HSCT-TMA and if improvement was due to narsoplimab-wuug.

The patient's response was also confounded by a decreasing cyclosporin dose during narsoplimab-wuug treatment. Of note, the cyclosporin was already at a low dose when it was reduced.

Based on [Figure 42](#), the patient did have a significant reduction in LDH, and improvement in platelets and haptoglobin.

Of note, the patient did not meet renal inclusion criteria for study entry, although the renal component of response was not needed to meet the response definition.

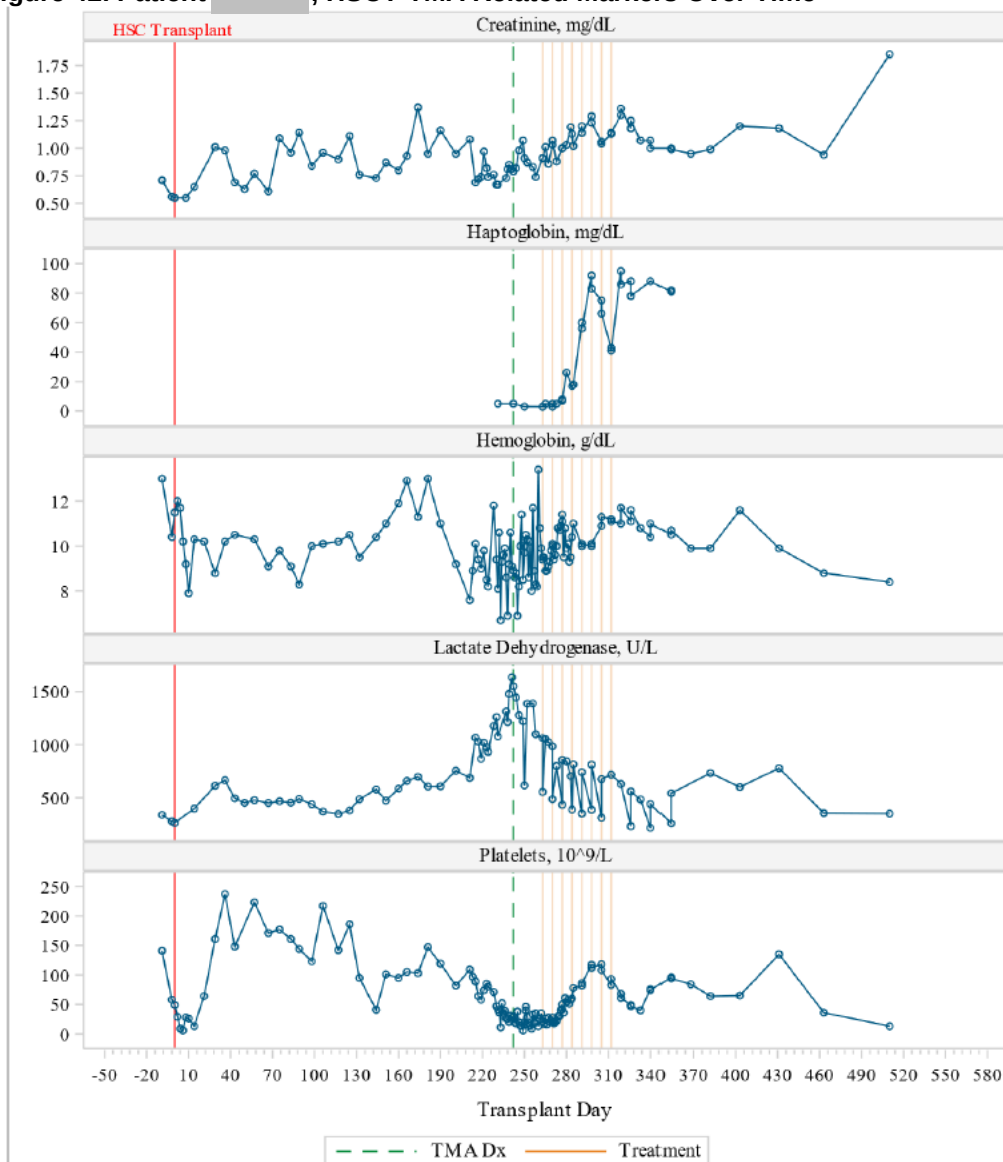
Table 121. Patient ^{(b) (6)} Laboratory Markers at Time of Study Entry, Day 250

Analyte	Platelet Count ^a (x 10 ⁹ /L)	Lactate Dehydrogenase (U/L)	Haptoglobin (mg/dL)	Creatinine (mg/dL)	Hemoglobin ^a (g/dL)
Value	20	617	3	0.91	10.0
Normal range	150 – 400	125 – 220	14 – 268	0.72 – 1.18	13.2 – 17.0

Source: Applicant Narrative

^a Transfusion supported

Figure 42. Patient (b) (6), HSCT-TMA Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx, diagnosis; HSC, hematopoietic stem cell; TMA, thrombotic microangiopathy

Patient (b) (6)

The patient is a 23-year-old Asian male with a history of chronic myeloid leukemia who received a 9/10 matched related HSCT. Neutrophil engraftment occurred on day 20 and platelet engraftment on day 23. The patient received anti-infective agents, including antibacterial, antifungal, and antiparasitic early after transplant, but no infection was noted in the case report form. On Day 6, the patient developed asymptomatic BK virus cystitis. On Day 26, the patient developed acute kidney injury. CMV reactivation occurred on day 36.

The patient developed HSCT-TMA on day 76, diagnosis was supported by thrombocytopenia, elevated creatinine and decreased hemoglobin, see [Table 122](#) for labs at study entry. He received

8 weekly doses of narsoplimab-wuug. The first dose was on day 82. He responded based on LDH, platelets and creatinine 15 days after his first dose of narsoplimab-wuug. TMA marker changes can be found in [Figure 43](#). The patient had cyclosporin reductions during narsoplimab-wuug treatment. The patient's last follow up was on day 302.

Clinical reviewer comment

Ok. The patient had a reduction and discontinuation of cyclosporin during narsoplimab-wuug treatment, therefore the treatment impact of narsoplimab-wuug is difficult to interpret.

In addition, the patient responded to narsoplimab-wuug based on creatinine reduction and improvement in platelets. Response based on the LDH component is less clear. While the patient did have a reduction of LDH during treatment, the baseline LDH was 261U/L (normal: 125-220 U/L) as this is just above the ULN, the magnitude of this reduction is unclear. As meeting the response definition is a reduction in LDH $<1.5 \times$ ULN the patient already met response prior to initiating narsoplimab-wuug. The clinical reviewer still thinks the patient is a responder given response based on the platelet and renal components of the response definition. This was further supported by an improvement in hemoglobin and haptoglobin.

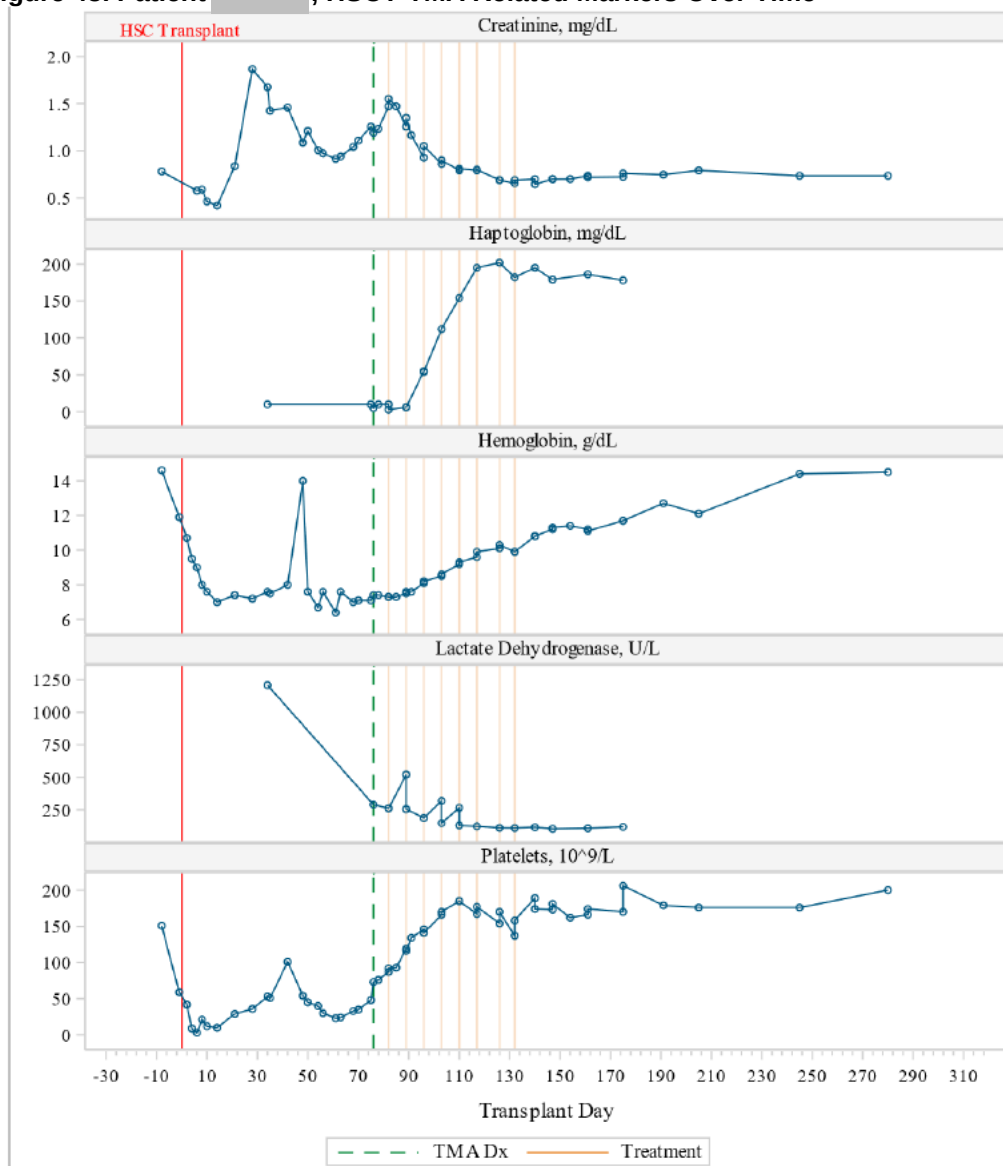
Table 122. Patient (b) (6) Laboratory Markers at Time of Study Entry, Day 76

Analyte	Platelet Count ($\times 10^9/L$)	Lactate Dehydrogenase ^a (U/L)	Creatinine (mg/dL)	Hemoglobin (g/dL)
Value	48	–	111	7.1
Normal range	140 – 440	125 – 220	54 – 101	14 – 18

Source: Applicant Narrative

^a Not done

Figure 43. Patient (b) (6), HSCT-TMA Related Markers Over Time



Source: Applicant Narrative

Note: Orange lines represents days of narsoplimab-wuug treatment, the red line represents the day of HSCT, and the dashed green line represents the time of TMA diagnosis

Abbreviations: Dx, diagnosis; HSC, hematopoietic stem cell; TMA, thrombotic microangiopathy

Compassionate Use Patient Narratives

- Patient (b) (6): The patient is a (b) (6) with a history of Diamond-Blackfan anemia who received an unrelated 9/10 matched allogeneic HSCT. (b) (6) transplant course was complicated by mucositis, veno-occlusive disease, pulmonary and nasal aspergillosis requiring antifungal treatment and nasal debridement, renal insufficiency, and viral infections. On day 138, (b) (6) developed pleural and pericardial effusions and ascites. The patient developed varicella zoster virus reactivation and HSCT-TMA on day 167 post-transplant, diagnosis was supported by thrombocytopenia, elevated LDH, schistocytes, negative Coomb's test, proteinuria, and anemia. (b) (6) was not receiving

a CNI inhibitor at the time of (b) (6) HSCT-TMA diagnosis. Around the time of HSCT-TMA diagnosis the patient had infections including sepsis, chronic kidney disease requiring dialysis, seizures, and DAH. The patient failed plasma exchange, defibrotide, and eculizumab. On day 400 post-transplant the patient initiated narsoplimab-wuug 4 mg/kg IV three times weekly. Following treatment (b) (6) TMA markers improved and (b) (6) was able to discontinue dialysis, respiratory support and transfusions. The patient's HSCT-TMA recurred during narsoplimab-wuug treatment taper in the setting of a respiratory syncytial virus infection. (b) (6) improved with increasing narsoplimab-wuug treatment to the initial frequency. (b) (6) received her last narsoplimab-wuug dose on Day 896 and was still alive on Day 1495.

- Patient (b) (6): The patient is a (b) (6) Caucasian male with a significant past medical history for autoimmune nephrosis and myeloproliferative neoplasm, for which he underwent an unrelated 10/10 matched HSCT. On day 41 post-transplant, he developed thrombocytopenia, elevated LDH, decreased hemoglobin, and decreased haptoglobin. These findings supported a diagnosis of HSCT-TMA. The cyclosporin dose was tapered but continued through his transplant course. He received his first dose of narsoplimab-wuug on day 62 and received 16 twice weekly 4 mg/kg doses. The patient was considered a responder to narsoplimab-wuug due to improvement in TMA laboratory markers (platelet count, LDH, and haptoglobin) and achieving transfusion independence.
- Patient (b) (6): The patient is a 20-year-old Caucasian female who underwent a related matched HSCT for B-cell ALL. Her transplant course was complicated by gastroenteritis, febrile neutropenia, and micronodular liver lesions. She developed skin and GI-GVHD and day 118. She was diagnosed with HSCT-TMA on day 184 post-transplant, demonstrating thrombocytopenia, elevated LDH, decreased hemoglobin and blood transfusions. The patient had GVHD at the time of HSCT-TMA diagnosis. She received narsoplimab-wuug on day 196 and received 18 once weekly 4 mg/kg IV dosing initially. Later the frequency of narsoplimab-wuug was increased to twice weekly dosing based on an initial poor response. The patient was considered a responder due to decreased LDH, and discontinuation of blood and platelet transfusion support. She was alive at their last site contact on day 568.
- Patient (b) (6): The patient was a 48 years old Caucasian male with a history of human immunodeficiency virus-1 (HIV-1), latent tuberculosis, renal failure, chemotherapy induced cardiotoxicity and chronic obstructive pulmonary disease, who underwent an unrelated mismatched HSCT for Hodgkin's disease with nodular sclerosis in CR3. The patient developed HSCT-TMA on day 0, demonstrating thrombocytopenia, elevated LDH, elevated creatinine, and decreased hemoglobin. His transplant course was complicated by multiple infections, hemodialysis and transfusions. The patient received the first narsoplimab-wuug dose on Day 6 and received 8 twice weekly doses of 4 mg/kg. The patient did not respond to narsoplimab-wuug and died of a cardiac arrest on day 31.
- Patient (b) (6): The patient is a 31-year-old Asian female who underwent a matched unrelated donor transplant for aplastic anemia. The patient developed HSCT-TMA on day 11 post-transplant, demonstrating thrombocytopenia, elevated LDH, elevated creatinine, and decreased hemoglobin. Cyclosporin was stopped at that time. The patient received 3 doses of narsoplimab-wuug (4 mg/kg) on days 20 through 27. She received 12 plasma

exchanges and 4 plasma infusions. The patient continued to required transfusions and no improvement was observed in TMA markers. In addition, she required dialysis through treatment. The patient experienced a left temporal hemorrhagic cerebral infarction on day 28 and died on day 31.

Clinical reviewer comment

In total, the Applicant states 3 out of 5 compassionate use patients responded to narsoplimab-wuug therapy. Compassionate use patients did not use the same response criteria, although based on the narrative descriptions, narsoplimab-wuug did seem to have a positive clinical impact. It is also important to note that compassionate use patients did not receive the same dosing frequency as patients in Study TMA-001. In fact, all patients received more frequent dosing than once weekly. Data collected from the compassionate use patients is limited and the sample size is small (n=5) therefore it is difficult to make conclusions based on the compassionate use program. The compassionate use program will not be included in the United States Prescribing Information (USPI) as efficacy will be determined from Study TMA-001.

17. Clinical Safety: Additional Information and Assessment

Duration of Exposure in Supportive Safety Population

Table 123. Duration of Exposure, Supportive Safety Population, Trial ISS

	OMS721- TMA-001 (aHUS and TTP) Total IV N=30 n (%)	OMS721- GNP-001 Total IV N=21 n (%)	OMS721- GNP-001 Placebo IV N=8 n (%)	OMS721- HUS-002 370 mg IV Followed by 150 mg SC N=6 n (%)	OMS721- NHV-001 ≤2.0 mg/kg IV N=13 n (%)	OMS721- NHV-001 Placebo IV N=5 n (%)	OMS721- NHV-001 ≤2.0 mg/kg SC N=15 n (%)	OMS721- NHV-001 Placebo SC N=8 n (%)	OMS721- NHV-002 Total IV N=12 n (%)	OMS721- NHV-002 Placebo IV N=4 n (%)	OMS721- NHV-002 Total SC N=58 n (%)	OMS721- NHV-002 Placebo SC N=16 n (%)
Duration of treatment (weeks)												
Mean (SD)	17.7 (17.1)	37.4 (40.7)	53.5 (35.5)	47.9 (26.6)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	6.0	6.0	4.9 (1.6)	5.1 (1.4)
Median (min, max)	11.0 (3.0, 52.4)	12.3 (3.1, 145.1)	51.4 (12.0, 104.1)	58.6 (6.3, 70.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	6.0 (6.0, 6.0)	6.0 (6.0, 6.0)	6.0 (1.0, 6.0)	6.0 (3.0, 6.0)
Subjects treated, by duration, n (%)												
≥1 to <4 weeks	3 (10.0)	1 (4.8)	0	0	0	0	0	0	0	0	19 (32.8)	5 (31.2)
≥4 to <8 weeks	8 (26.7)	0	0	1 (16.7)	0	0	0	0	12 (100.0)	4 (100.0)	39 (67.2)	11 (68.8)
≥8 weeks	19 (63.3)	20 (95.2)	8 (100.0)	5 (83.3)	0	0	0	0	0	0	0	0

Source: Clinical data analyst, adex.xpt; Software: Python

Abbreviations: aHUS, atypical hemolytic uremic syndrome; ISS, integrated summary of safety; IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with at least one event; SC, subcutaneous; SD, standard deviation; TTP, thrombotic thrombocytopenic purpura

Overview of Adverse Events in the Supportive Safety Population

Table 124. Overview of Adverse Events (n (%)), Supportive Safety Population, Trial ISS

Event Category	OMS721- TMA-001 (aHUS and TTP) Total IV N=30	OMS721- GNP-001 Total IV N=21	OMS721- GNP-001 Placebo IV N=8	OMS721- HUS-002 370 mg IV Followed by 150 mg SC N=6	OMS721-NHV- 001≤2.0 mg/kg IV N=13	OMS721- NHV-001 Placebo IV N=5	OMS721-NHV- 001≤2.0 mg/kg SC N=15	OMS721- NHV-001 Placebo SC N=8	OMS721- NHV-002 Total IV N=12	OMS721- NHV-002 Placebo IV N=4	OMS721- NHV-002 Total SC N=58	OMS721- NHV-002 Placebo SC N=16
Any AE	25 (83.3)	20 (95.2)	8 (100.0)	6 (100.0)	9 (69.2)	2 (40.0)	10 (66.7)	2 (25.0)	5 (41.7)	3 (75.0)	41 (70.7)	7 (43.8)
Grade 3-5	20 (66.7)	5 (23.8)	4 (50.0)	5 (83.3)	0	0	0	0	0	0	1 (1.7)	0
Any SAE	16 (53.3)	2 (9.5)	2 (25.0)	5 (83.3)	0	0	0	0	0	0	0	0
SAE with fatal outcome	3 (10.0)	0	0	1 (16.7)	0	0	0	0	0	0	0	0
AE leading to discontinuation of study drug	4 (13.3)	0	0	1 (16.7)	0	0	0	0	0	0	1 (1.7)	0
AE leading to dose modification of study drug	8 (26.7)	2 (9.5)	2 (25.0)	2 (33.3)	0	0	0	0	0	0	0	0
AE leading to interruption of study drug	8 (26.7)	2 (9.5)	2 (25.0)	2 (33.3)	0	0	0	0	0	0	0	0
AE leading to reduction of study drug	0	0	0	0	0	0	0	0	0	0	0	0
AE leading to delay of study drug	0	0	0	0	0	0	0	0	0	0	0	0

Source: Clinical data analyst; adae.xpt; Software: Python

Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

Grading scale used was National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Abbreviations: AE, adverse event; aHUS, atypical hemolytic uremic syndrome; HUS, hemolytic uremic syndrome; ISS, integrated summary of safety; IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; SC, subcutaneous; TTP, thrombotic thrombocytopenic purpura

Deaths

Primary Safety Population

Table 125. List of Deaths, Primary HSCT-TMA Safety Population, Study TMA-001

Study Arm	Subject ID	Age	Sex	Cause of Death	Study Day of Death	Duration of Exposure (Days)
OMS721 370 mg IV weekly x 4	(b) (6)	34	M	Septic shock	32	29
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	58	M	Neutropenic sepsis	65	51
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	22	F	Cardio-pulmonary arrest	172	50
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	58	F	Hsct related cause	40	8
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	53	M	Pneumonia	826	48
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	46	M	Escherichia sepsis; gastrointestinal candidiasis	253	50
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	48	M	Unknown	92	29
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	54	F	General physical health deterioration	63	23
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	48	M	Pseudomonal sepsis	183	50
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	48	M	Acute myeloid leukemia	14	8
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	63	F	Neutropenic sepsis	92	50
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	28	M	Pneumonia	345	109
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	39	F	Unknown	99	22
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	48	M	Disease progression	76	15
OMS721 4.0 mg/kg IV weekly x 4	(b) (6)	61	M	Graft versus host disease in gastrointestinal tract; thrombotic microangiopathy	70	50

Source: Clinical data analyst, adsl.xpt; Software: Python
Abbreviations: ID, identification; IV, intravenous(ly)

Narratives of Patients Who Died of Treatment-Emergent Deaths During the AE Evaluation Period

- Patient** (b) (6) died of neutropenic sepsis 14 days after the last dose of narsoplimab-wuug. The patient was a 58-year-old male with a complicated past medical history including AML, type 2 diabetes mellitus, coronary artery disease, hypertension, hepatitis B and peripheral neuropathy. On (b) (6) the patient received an allogeneic HSCT from a matched related donor for his diagnosis of AML. He received nonmyeloablative conditioning with fludarabine and melphalan. His immunosuppression consisted of tacrolimus and sirolimus. Transplant course was complicated including mucositis, possible typhlitis, diffuse alveolar hemorrhage, possible fungal pneumonia, CMV reactivation, and fluid overload requiring dialysis. He was subsequently diagnosed with HSCT-TMA on day 21 post-transplant. On (b) (6) he was started on weekly narsoplimab-wuug 4 mg/kg IV and received 8 weekly doses. On (b) (6) the patient developed

diarrhea, nausea, and abdominal cramps. He was hospitalized and found to be pancytopenic. Shortly thereafter, he developed bloody diarrhea requiring platelet transfusions and antibiotics. A colonoscopy on (b) (6) revealed diffuse inflammation and erythema. Treatment for GI-GVHD was initiated with tacrolimus, sirolimus, CellCept, Solu-medrol, basiliximab, and later with ruxolinitib. Tacrolimus was discontinued due to encephalopathy. The patient also developed HHV6 reactivation and coagulase-negative staphylococcal bacteremia. By (b) (6) the patient was diagnosed with graft failure versus leukemia recurrence. During this time, he developed respiratory distress and hypotension, and required vasopressor support and mechanical ventilation. On (b) (6) the patient died. Sepsis was specified as the most likely cause of death.

- **Patient** (b) (6) died of septic shock 3 days following the last dose of narsoplimab-wuug. The patient was a 24-year-old male with a history of relapsed Hodgkin's lymphoma and autologous transplant with subsequent progression of disease. When he was "close to remission" he underwent a matched unrelated donor allogeneic HSCT on (b) (6). He received myeloablative conditioning with fludarabine, total body irradiation, and thymoglobulin. His immunosuppression prophylaxis consisted of cyclosporin and methotrexate. Transplant course was complicated by mucositis, nephrotoxicity, CMV reactivation, renal failure, GI infections, bilateral pneumonia, elevated blood pressure and septic shock. On day 279 post-transplant (b) (6) HSCT-TMA was suspected. On (b) (6) the patient started narsoplimab-wuug 370 mg IV once a week. On (b) (6) he was diagnosed with bilateral pneumonia and was treated with antibiotics, antifungal and antiviral therapies. His condition worsened over the next two days and he was subsequently intubated for respiratory failure. He improved and was extubated, with a resolution of the event on (b) (6). On (b) (6), the patient developed septic shock, blood and urine cultures were positive for *Pseudomonas aeruginosa*. Despite antibiotics and vasopressors he developed multi-organ dysfunction and died shortly after.
- **Patient** (b) (6) died of graft-versus-host-disease (GVHD) and HSCT-TMA 20 days following the last narsoplimab-wuug dose. The patient was a 61-year-old male with a history of ALL. He underwent a mismatched unrelated donor allogeneic HSCT on (b) (6). He received myeloablative conditioning with busulfan and fludarabine. Immunosuppression consisted of cyclosporin. His transplant course was complicated by *E. coli* sepsis, mucositis, fever, cytomegalovirus (CMV) reactivation, Coombs-positive autoimmune hemolytic anemia (AIHA), EBV reactivation, fungal pneumonia, GVHD, influenza and respiratory syncytial virus pneumonia. He was diagnosed with HSCT-TMA on day 124 (b) (6). On (b) (6) he started narsoplimab-wuug 4 mg/kg IV once a week. On (b) (6) he developed fever and diarrhea. Colonoscopy on (b) (6) was diagnostic for GI-GVHD. The GVHD was resistant to steroids, pentostatin, and mesenchymal cells. The patient also developed pneumonia and influenza during this time. Seven days following his last narsoplimab-wuug dose, HSCT-TMA was noted to worsen. On (b) (6) the patient died of multiorgan failure secondary to pneumonia, viral and fungal infections, GI-GVHD and TMA.
- **Patient** (b) (6) died of progressive AML 6 days following the last narsoplimab-wuug dose. The patient was a 48-year-old male with a history of AML in his second complete remission. He underwent a matched related donor allogeneic transplant on (b) (6) and received reduced intensity conditioning. Immunosuppression consisted of cyclosporin and mycophenolate mofetil. His transplant course was complicated by septic shock, sinusitis, choledocholithiasis requiring endoscopic retrograde cholangiopancreatography, GI hemorrhage, and nephrolithiasis. He was diagnosed with HSCT-TMA 31 days following transplant (b) (6). Starting (b) (6) he received 2

doses of narsoplimab-wuug at 4 mg/kg IV once weekly. The patient's HSCT failed, and he died on (b) (6). The investigator determined this was secondary to his underlying leukemia.

Clinical reviewer comment

There were 4 patient deaths in the adverse event (AE) evaluation period. Of those deaths, 2 were related to infections and considered possibly related to narsoplimab-wuug. The other two deaths during the AE evaluation period were unlikely related to narsoplimab-wuug, and more likely related to the underlying disease process such as HSCT-TMA, GVHD, or leukemia. Ultimately, more than half of patients treated on TMA-001 died. This is not unexpected given the patient population consisted of complex, critically ill patients on immunosuppressive therapies, and concurrent disease processes thus increasing their risk for death. In addition, HSCT-TMA has a high mortality rate.

Supportive Safety Population

In patients with aHUS and TTP, 3 of 30 patients (10%) in Study TMA-001 and 1 of 6 patients (16.7%) in Study OMS-HUS-002 died during the study ([Table 126](#)). The most common cause were infections, including Escherichia sepsis and pneumonia. There were two deaths in compassionate use patients. Narratives are described below.

There were no deaths in the NHV studies, OMS721-GNP-001 or OMS721-IGA-001.

Patient Narratives

- **Patient** (b) (6): The patient was a 54-year-old female in Study TMA-001, with aHUS, asthma, heart failure, and arterial hypertension who died due to the treatment-emergent adverse event (TEAE) of pneumonia. The patient had received 7 doses of 4 mg/kg IV narsoplimab-wuug when she developed grade 4 pneumonia supported by a bronchoscopy which demonstrated suppurative pneumonia. Respiratory cultures were positive for *Burkholderia cepacia* and she was treated with antibiotics. During this time narsoplimab-wuug was continued. Shortly after the patient developed respiratory failure with cardiac arrest and died. The patient's death occurred 64 days from the first dose of narsoplimab-wuug.
- **Patient** (b) (6): The patient was a 43-year-old female in Study TMA-001, with aHUS, hypertension, and gastritis, who died of a TEAE of sepsis. The patient received 5 scheduled doses of narsoplimab-wuug, in addition to supplemental doses while receiving plasma exchange therapy. During hospitalization the patient hallucinated and experienced convulsions. A CT scan was negative, and the patient was started on valproic acid and haloperidol. Following the initiation of valproic acid the patient developed pancytopenia, but this resolved after discontinuation. A little over two weeks after recovery from the pancytopenia the patient developed an infection, blood cultures grew *Escherichia coli* and *Klebsiella pneumonia*. Despite treatment with IV antibiotics and immunoglobins the patient deteriorated and died.

- **Patient** (b) (6): The patient was a 73-year-old male in Study TMA-001, with aHUS, chronic parenchymal liver disease, and hyperammonemia, who died of a TEAE of sudden death. After 5 doses of narsoplimab-wuug 4 mg/kg IV the patient was admitted to the hospital for hematemesis. An endoscopy showed esophageal varices and portal hypertensive gastropathy. He continued on dialysis for his end-stage renal disease. Approximately 2.5 months later the patient developed massive ascites. The patient recovered from the event. Approximately 10 days after recovery and discharge from the hospital the patient had lost consciousness at home and was pronounced dead at the hospital. At the time of death, the patient had received 19 doses of narsoplimab-wuug. Cause of death was not determined.
- **Patient** (b) (6): The patient was a 40-year-old male in Study OMS721-HUS-002, with aHUS, epilepsy, arterial hypertension, renal failure, type 2 diabetes mellitus, mediastinal abscesses, and pancreatitis, who died due to TEAEs of *Escherichia coli* and intracerebral hematoma. Prior to starting narsoplimab-wuug the patient was hospitalized for seizures. A CT scan showed a new left subdural hematoma and bilateral hygroma. Approximately a week later a repeat CT showed bilateral chronic subdural hematomas with active bleeding with mass effect. The patient had neurologic deterioration. Shortly after this event narsoplimab-wuug was initiated. Approximately 14 days after starting narsoplimab-wuug the patient became unresponsive. Head CT showed numerous hypodense foci in the white matter of both hemispheres, followed by a repeat CT which showed evolution of the subdural hematomas. In addition, the patient developed GI bleeding and blood culture was positive for *E. coli*. Despite antibiotic therapy the patient died of sepsis and intracerebral hematoma. It was also noted the patient had grade 4 thrombocytopenia which likely contributed to the bleeding events.
- **Patient** (b) (6): The patient was a 48-year-old male with HSCT-TMA treated on compassionate use. The patient had a complicated medical history consisting of HIV-1, latent tuberculosis, Hodgkin's lymphoma with nodular sclerosis, renal failure, chronic obstructive pulmonary disease and cardiotoxicity. He received an unrelated mismatched donor allogeneic transplant. The conditioning regimen included, cyclophosphamide, fludarabine, busulfan, and thymoglobulin, and cell source was umbilical cord. Tacrolimus was started prior to transplant, the patient developed HSCT-TMA on day 0 (same day as HSCT). He started narsoplimab-wuug on day 6. Post-transplant course was complicated by cocaine and heroin abstinence syndrome, human papillomavirus, *E. faecalis* bacteremia, and CMV viremia on day 15. Shortly after he developed febrile neutropenia and severe esophagitis. Bronchoalveolar lavage was positive for aspergillus. He died of cardiac arrest on day 31. He received 8 twice weekly narsoplimab-wuug doses of 4 mg/kg from day 6 to day 31.
- **Patient** (b) (6): The patient was a 31-year-old female with HSCT-TMA treated on compassionate use. The patient had a history of severe aplastic anemia. She received a matched unrelated donor allogeneic transplant. She received reduced intensity conditioning with fludarabine, cyclophosphamide, antithymocyte globulin, and total body irradiation. She was diagnosed with HSCT-TMA on day 11. She received 3 doses of narsoplimab-wuug on day 20 to 27 and plasma infusions. She required blood and platelet transfusions, in addition to hemodialysis. She experienced a left temporal hemorrhagic cerebral infarction on day 28 and died on day 31. Cause of death was listed as HSCT-TMA, acute GVHD, and postallogeneic stem cell transplant aplastic anemia.

Table 126. Deaths, Supportive Safety Population, Trial ISS

	OMS721-TMA-001 (aHUS and TTP) N=30	OMS721-HUS-002 (aHUS) N=6
Preferred Term	n (%)	n (%)
Any AE leading to death	3 (10.0)	1 (16.7)
Escherichia sepsis	1 (3.3)	1 (16.7)
Pneumonia	1 (3.3)	0
Sudden death	1 (3.3)	0
Cerebral hematoma	0	1 (16.7)

Source: Clinical data analyst [adae.xpt; Software: Python]

Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

Abbreviations: AE, adverse event; aHUS, atypical hemolytic uremic syndrome; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; TTP, thrombotic thrombocytopenic purpura

Discontinuations

Table 127. Adverse Events Leading to Discontinuation, Safety Population, Trial ISS

	OMS721-TMA-001 (aHUS and TTP) Total IV N=30	OMS721-HUS-002 370 mg IV Followed by 150 mg SC N=6	OMS721-NHV-002 Total SC N=58
Preferred Term	n (%)	n (%)	n (%)
Any AE leading to discontinuation	4 (13.3)	1 (16.7)	1 (1.7)
Escherichia sepsis	1 (3.3)	0	0
Granuloma Orchitis	1 (3.3)	0	0
Pancytopenia	1 (3.3)	0	0
Renal graft infection	1 (3.3)	0	0
Hepatic failure	0	1 (16.7)	0
Urinary tract infection	0	1 (16.7)	0
Supraventricular tachycardia	0	0	1 (1.7)

Source: Clinical data analyst, adae.xpt; Software: Python

Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

Abbreviations: AE, adverse event; aHUS, atypical hemolytic uremic syndrome; ISS, integrated summary of safety; IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous; TTP, thrombotic thrombocytopenic purpura

Patient Narrative

- **Patient** (b) (6): Patient is a 20 year old male, healthy volunteer, on study OMS721-NHV-002 who discontinued narsoplimab-wuug for a TEAE of supraventricular tachycardia. On Day 1, he received narsoplimab-wuug 6.0 mg/kg subcutaneously. On Day 8, he received a second

dose of narsoplimab-wuug 6.0 mg/kg IV after which he reported no TEAEs. On Day 9, supraventricular tachycardia was reported which resolved approximately 6:30 hours later on the same day after treatment with adenosine (6 mg IV, twice and 12 mg IV once) and 500 mL sodium chloride 0.9%, IV. No further information was provided.

- **Patient** (b) (6): Patient is a 28-year-old woman on study OMS721-HUS-002, with aHUS, poorly controlled hypertension, kidney hematoma, obesity and hemodialysis dependent end stage renal disease. The patient discontinued narsoplimab-wuug due to TEAEs of grade 3 urinary tract infection and grade 4 liver insufficiency. The patient started narsoplimab-wuug with the protocol-defined induction regimen on (b) (6). While receiving narsoplimab-wuug on (b) (6) the patient was admitted to hospital with fever following a seafood meal. The patient's partner had gastroenteritis following the seafood meal. The patient had signs of liver insufficiency, hypotension, and hypoxia. Urinalysis was consistent with a urinary tract infection. Imaging demonstrated an enlarged liver with signs of steatosis and a persistent left kidney hematoma. Viral serologies for hepatitis and cytomegalovirus (CMV) were negative. Herpes simplex virus and EBV were also negative. The patient denied alcohol, acetaminophen, herbal supplements, and over-the-counter products. The etiology of the patient's fever was subsequently determined to be due to a urinary tract infection and she was treated with broad spectrum antibiotics. Shortly thereafter (b) (6) the patient was diagnosed with liver insufficiency which met Hy's Law criteria. Narsoplimab-wuug was discontinued (37 days after the first dose). Laboratory results showed gradual decrease in aminotransferase levels and simultaneous increase in total (275 µmol/L), direct bilirubin (156 µmol/L) and ammonia (239.6 µg/L). Coagulation abnormalities were also observed. Follow-up scans revealed a liver of normal size, granular echogenicity, and a rim of fluid in the area of the gallbladder. The patient had hemodialysis and plasmapheresis for an exacerbation of aHUS. She recovered from her liver insufficiency and was discharged home on (b) (6).
- **Patient** (b) (6): The patient is a 40-year-old male in Study TMA-001, with aHUS, IgA nephropathy, end stage renal disease and renal transplant. The patient had a history of Mycobacterium haemophilum over a three-year period, approximately 5 years prior to receiving narsoplimab-wuug. The patient discontinued narsoplimab-wuug due to a TEAE of granulomatous orchitis. The patient received 0.675 mg/kg IV narsoplimab-wuug, after receiving 3 doses of narsoplimab-wuug he reported right testicular swelling. Testicular biopsy demonstrated granulomatous disease and no malignant cells. Cultures were negative, including for Mycobacterium. The event resolved approximately one month later. Narsoplimab-wuug was discontinued.

Adverse Events by SOC

Table 128. Adverse Events by System Organ Class, Primary HSCT-TMA Safety Population, Study TMA-001

	Narsoplimab-wuug 4.0 mg/kg IV N=24 n (%)	Narsoplimab-wuug 370 mg IV N=4 n (%)	Narsoplimab-wuug Total IV N=28 n (%)
System Organ Class			
Infections and infestations	18 (75.0)	2 (50.0)	20 (71.4)
Gastrointestinal disorders	17 (70.8)	1 (25.0)	18 (64.3)
General disorders and administration site conditions	16 (66.7)	2 (50.0)	18 (64.3)
Metabolism and nutrition disorders	14 (58.3)	2 (50.0)	16 (57.1)
Blood and lymphatic system disorders	12 (50.0)	1 (25.0)	13 (46.4)
Respiratory, thoracic and mediastinal disorders	11 (45.8)	2 (50.0)	13 (46.4)
Musculoskeletal and connective tissue disorders	11 (45.8)	1 (25.0)	12 (42.9)
Immune system disorders	10 (41.7)	0	10 (35.7)
Investigations	10 (41.7)	0	10 (35.7)
Nervous system disorders	10 (41.7)	0	10 (35.7)
Skin and subcutaneous tissue disorders	10 (41.7)	0	10 (35.7)
Vascular disorders	8 (33.3)	0	8 (28.6)
Cardiac disorders	7 (29.2)	0	7 (25.0)
Injury, poisoning and procedural complications	6 (25.0)	0	6 (21.4)
Renal and urinary disorders	6 (25.0)	0	6 (21.4)
Psychiatric disorders	5 (20.8)	1 (25.0)	6 (21.4)
Hepatobiliary disorders	3 (12.5)	0	3 (10.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (12.5)	0	3 (10.7)
Eye disorders	2 (8.3)	1 (25.0)	3 (10.7)
Endocrine disorders	1 (4.2)	1 (25.0)	2 (7.1)

Source: Clinical data analyst, adae.xpt; Software: Python

Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment.

For specific preferred terms, see the table "Adverse Events by System Organ Class and Preferred Term..."

Abbreviations: IV, intravenous(ly); N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy

AESI Infections

Table 129. FDA MedDRA Queries, Infections, Adverse Events of Special Interest, Entire TMA Safety Population Excluding HSCT-TMA

	TMA-001 aHUS N=25 n (%)	TMA-001 TTP N=5 n (%)	HUS-002 aHUS N=6 n (%)	Total N=36 N (%)
FDA MedDRA Queries				
Infection, all	17 (68%)	1 (20%)	5 (83.3%)	23 (63.8%)
Infection, bacterial*	4 (16%)	0	3 (50%)	7 (19.4%)
Pneumonia*	6 (24%)	0	0	6 (16.7%)
Urinary tract infection*	2 (8%)	1 (20%)	2 (33.3%)	5 (13.9%)
Upper respiratory tract infection	5 (20%)	0	0	5 (13.9%)
Infection, fungal*	3 (12%)	0	0	3 (8.3%)
Nasopharyngitis*	3 (12%)	0	0	3 (8.3%)
Infection, viral*	2 (8%)	0	1 (16.7%)	3 (8.3%)
Sepsis	1 (4%)	0	1 (16.7%)	2 (5.6%)
Bronchitis	1 (4%)	0	0	1 (3.3%)
Influenza	1 (4%)	0	0	1 (3.3%)

Source: Clinical Reviewer, ADAE.xpt

* The following preferred terms were combined:

Infection, bacterial: clostridium difficile colitis, clostridium difficile infection, staphylococcal infections, Escherichia sepsis, pneumonia bacteria, urinary tract infection bacterial, urea plasma infection, urinary tract infection enterococcal

Infection, fungal: oral fungal infection, pneumocystis jirovecii pneumonia, pneumonia fungal, tinea versicolor

Infection, viral: cytomegalovirus infection, pneumonia cytomegaloviral, molluscum contagiosum

Nasopharyngitis: nasopharyngitis, pharyngitis

Pneumonia: pneumonia, bacterial pneumonia, pneumocystis jirovecii pneumonia, cytomegaloviral pneumonia, fungal pneumonia

Urinary tract infection: urinary tract infection, urinary tract infection bacteria, urinary tract infection enterococcal

Abbreviations: HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; HUS, hemolytic uremic syndrome; MedDRA, Medical Dictionary for Regulatory Activities; TTP, thrombotic thrombocytopenia purpura

Table 130. Serious Infection Adverse Events by System Organ Class and Preferred Term, Entire TMA Safety Population (Excluding HSCT-TMA)

System Organ Class Preferred Term	TMA-001 aHUS and TTP N=30 n (%)	HUS-002 aHUS N=6 n (%)	Total TMA N=36 n (%)
Infections and infestations (SOC)	8 (26.7)	4 (66.7)	12 (33.3)
Pneumonia	2 (6.7)	0	2 (5.6)
Staphylococcal infection	2 (6.7)	0	2 (5.6)
Clostridium difficile colitis	1 (3.3)	0	1 (2.8)
Epstein-Barr virus test positive	1 (3.3)	0	1 (2.8)
Escherichia sepsis	1 (3.3)	1 (16.7)	2 (5.6)
Orchitis	1 (3.3)	0	1 (2.8)
<i>Pneumocystis jirovecii</i> pneumonia	1 (3.3)	0	1 (2.8)
Pneumonia bacterial	1 (3.3)	0	1 (2.8)
Renal graft infection	1 (3.3)	2 (33.3)	3 (8.3)
Urinary tract infection bacterial	1 (3.3)	0	1 (2.8)
Urinary tract infection	0	2 (33.3)	2 (5.6)

Source: Clinical data analyst, adae.xpt; Software: Python

Treatment-emergent adverse events defined as those occurred or worsened in intensity after the start of study treatment

Abbreviations: aHUS, atypical hemolytic uremic syndrome; FMQ, FDA Medical Dictionary for Regulatory Activities query; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; TTP, thrombotic thrombocytopenic purpura

90-Day Safety Update

The 90-Day Safety Update presents additional safety data collected from the 2 ongoing clinical trials from December 21, 2019 to August 31, 2020 (Studies OMS721-HUS-002 and OMS721-IGA-001) and safety data from compassionate use patients with HSCT-TMA from December 21, 2019, to October 31, 2020. Deaths, study drug discontinuations and serious adverse events (SAEs) were reviewed. Overall, there was no change in the risk/benefit assessment based on the 90-day safety update. There were four deaths described in the 90-day safety update. This included one sudden death in study OMS721-IgA-001 and three deaths in compassionate use patients. The narratives are described below.

- Patient (b) (6):** The patient was a 55 year old M with IgA nephropathy, with a past medical history of coronary artery disease and acute myocardial infarction, who was on blinded study treatment once weekly IV narsoplimab-wuug per protocol and completed the extended study therapy on (b) (6). On (b) (6) the patient died suddenly due to a pulmonary embolism. No further information was provided.
- Patient (b) (6):** The patient was a 72 year old female with HSCT-TMA, treated on compassionate use, who died due to an event of respiratory failure. On (b) (6) (prior to starting narsoplimab-wuug) the patient developed dyspnea and was hospitalized

with bilateral pleural effusions and leukopenia. The patient was subsequently intubated due to respiratory failure. On (b) (6) the patient improved and was transferred out of the ICU. On (b) (6), she started treatment with narsoplimab-wuug, 370 mg IV twice a week. On (b) (6) the patient developed acute respiratory failure and was transferred to the ICU for BiPAP therapy. She had a bronchoscopy and thoracentesis. Additional findings revealed pneumonia, pulmonary edema, acute respiratory distress syndrome, acute kidney injury, pressure ulcer, septic shock and empyema of the chest. The patient received her last dose of narsoplimab-wuug on (b) (6) with no reported dose interruptions. The patient died on (b) (6) due to respiratory failure.

- **Patient** (b) (6): The patient was a 16-year-old male, in the compassionate use program, with lymphoproliferative disease and HSCT-TMA, who discontinued treatment after receiving 3 doses of 370 mg IV narsoplimab-wuug due to deterioration. The patient was diagnosed with HSCT-TMA on (b) (6). Treatment was initiated with eculizumab and therapeutic plasma exchange. Eculizumab was discontinued, but subsequently restarted due to a relapse of HSCT-TMA on (b) (6). His course was complicated by further progression of TMA markers, renal replacement therapy and worsening hypertension. The patients developed PRES and septic shock which resolved. On (b) (6), the patient discontinued eculizumab and a few weeks later began narsoplimab-wuug per the compassionate use program at 370 mg IV, 2 times per week. After receiving three doses the patient had a general deterioration and discontinued narsoplimab-wuug. The patient was discharged home with hospice care and died at home. Cause of death was reported as renal failure.
- **Patient** (b) (6): The patient was a (b) (6) female, in the compassionate use program, with Diamond Blackfan Anemia had a bone marrow transplant was suspected to have HSCT-TMA 14 days following transplant. She was started on eculizumab. On day 79 (date not included) she continued to have HSCT-TMA and a pericardial effusion. On (b) (6), narsoplimab-wuug was started. She received two doses before the drug was interrupted for concern of sepsis. She switched to plasmapheresis, and decompensated requiring mechanical ventilation with cardiac support. The patient died on (b) (6).

There were two study drug discontinuations described in the 90-day safety update. Both patients were on blinded treatment in study OMS721-IGA-001 ([Table 131](#)).

Table 131. Adverse Events Leading to Discontinuations, 90-Day Safety Update

Protocol	Site-Subject	Treatment	Age	Sex	Race	AE Start Date	AE End Date	System Organ Class Preferred Term Verbatim	Investigator Causality	Serious?
OMS 721-IGA-001	(b) (6)	Blinded	46	Male	White	(b) (6)	Ongoing	Neoplasms benign, malignant, and unspecified (incl cysts and polyps) Nasopharyngeal cancer Nasopharyngeal cancer	Not related	Yes
OMS 721-IGA-001	(b) (6)	Blinded	39	Male	White	(b) (6)	(b) (6)	Renal and urinary disorders Chronic kidney disease Exacerbating chronic kidney disease	Not related	Yes

Adverse events between 21 Dec2019 and 31 Aug 2020.

Abbreviations: AE = adverse event; incl = including.

Source: 90-day safety update provided by Applicant

18. Mechanism of Action / Drug Resistance: Additional Information and Assessment

Narsoplimab-wuug is a monoclonal antibody that binds to and blocks MASP-2, the effector enzyme of the lectin pathway of complement. Further review of the mechanism of action of narsoplimab-wuug was undertaken by the clinical team.

An information request was sent to the Applicant to further evaluate the mechanism of action in terms of the HSCT-TMA. The Applicant provided an additional document pertaining to the mechanism of action (MOA) of narsoplimab-wuug for the treatment of HSCT-TMA on March 19, 2021. The Applicant also submitted responses to additional information requests (IRs) on August 4, 2021, August 6, 2021 and August 12, 2021 which were also reviewed.

The Applicant states that there are several different lines of evidence that provide confirmatory support of the mechanism of action of the drug to include in vitro models of HSCT-TMA that demonstrate that narsoplimab-wuug inhibits complement deposition, endothelial cell injury, and apoptosis. In addition, the Applicant provided data that the lectin pathway involvement in HSCT-TMA is demonstrated by immunohistochemistry findings of deposition of lectin pathway components in affected tissue of patients with HSCT-TMA.

The Applicant cites that separate studies of ongoing immunohistochemical analyses from skin biopsies of patients with persistent HSCT-TMA show positive staining for MASP-2, the effector enzyme of the lectin pathway of complement in 6 of 7 patients ([Gavrilaki et al. 2017](#)). In patients who did not develop TMA, there was no MASP-2 staining in the biopsies suggesting that TMA-related complement activation involves the lectin pathway. The Applicant states that by blocking MASP-2, narsoplimab-wuug blocks activation and complement activation.

In plasma samples from patients with acute TMA arising from a variety of clinical settings to include aHUS, HSCT-TMA, narsoplimab-wuug showed evidence of blocking microvascular endothelial cell apoptosis. In this model of microvascular injury, primary human microvascular endothelial cells grown in tissue culture media were exposed to control plasma or plasma from individual patients with active HSCT-TMA, in the presence of narsoplimab-wuug or isotype-matched control. Endothelial injury was evaluated by quantification of caspase 8 activity.

Caspase 8 activation was observed in 14 out of the 22 TMA patient's plasma. Blockade of MASP-2 by narsoplimab-wuug led to a decrease in caspase 8 activity for all 14 patient plasma suggesting that narsoplimab-wuug suppressed TMA plasma-mediated caspase 8 activation in microvascular endothelial cells. This suggests that there is a role in for narsoplimab-wuug to block MASP-2 however it is not known how much of this blockade impacts the downstream signaling of the complement cascade.

The Applicant also provided data from an ex-vivo assay using HSCT-TMA patient serum and the effect of narsoplimab-wuug. Serum from patients with acute HSCT-TMA had higher complement (C5b-9) deposition on human microvascular endothelial cells and this response was suppressed by addition of narsoplimab-wuug ([Galbusera M et al. 2021](#)). However, this is ex-vivo data and it is unclear how much of suppressive response narsoplimab-wuug induces.

The Applicant provided data indicating that host responses to COVID-19 share aspects of HSCT-TMA pathophysiology which can be improved upon with the use of narsoplimab-wuug. According to the Applicant, COVID-19 and HSCT-TMA share a similar pathophysiology and are endothelial injury syndromes. MASP-2 has been described in lung injury in patients with coronavirus infection with MASP-2 and mannan-binding lectin staining in immunohistochemical analysis of lung tissues from patients who died of COVID-19 ([Magro et al. 2020](#)). In addition, microvascular deposits of MASP-2, C4d, C3d, and C5b-9 in some organ systems have been described ([Magro et al. 2020](#)). The Applicant provided data from an initial cohort of 9 patients with COVID-19 treated with narsoplimab-wuug under a compassionate use program. According to the Applicant, patients had elevated circulating endothelial cells counts at baseline, which decreased after the first week of narsoplimab-wuug. An additional cohort of 10 patients was treated with narsoplimab-wuug under compassionate use. Eight of 10 patients recovered and survived and were discharged following 5-8 doses of narsoplimab-wuug. The D-dimer levels rapidly normalized following administration of narsoplimab-wuug and correspond with clinical status/recovery. The Applicant states that severe COVID-19 is pathogenetically similar to HSCT-TMA. Narsoplimab-wuug shows effects on TMA-associated pathophysiological processes and clinical outcomes in critically ill patients with COVID-19.

Brief Summary of Nonclinical Data (Taken From Summary by Pharmacology-Toxicology Review Team)

TMA Study in Mice

In vivo efficacy of OMS721 was assessed in a mouse model of TMA in which localized thrombosis was induced by photo-activation of fluorescein isothiocyanate-labeled dextran in the microvasculature of the cremaster muscle of C57Bl/6 mice.

Administering OMS721 one hour before induction of thrombosis delayed the initiation of thrombus formation and the time to complete vessel occlusion, demonstrating a contribution of the lectin complement pathway to the thrombotic response to injury. However, over time, thrombus formation still occurred in a similar percentage of mice regardless of treatment, suggesting that pathways in addition to lectin complement activation contribute to and eventually result in microvascular thrombosis.

Human aHUS Study

Serum was taken from healthy people or from aHUS patients and incubated with endothelial cells in culture. MAC (C5b-9) deposition and platelet adherence to the EC were subsequently measured.

- Serum from aHUS patients robustly caused MAC deposition and platelet adherence to ECs.
- Narsoplimab partially prevented MAC deposition and platelet adhesion, indicating some contribution of lectin, but also showing contribution by other C-activation pathways.

Narsoplimab is specific for MASP-2 and selectively blocks lectin-initiated complement activation. The lectin pathway contributes to C-activation and thrombus formation in defined models of endothelial injury, which presumably reflect a key element of TMA. Narsoplimab inhibited this contribution. However, other C-activation pathways are also contributory; thus, vascular occlusion appeared delayed, but occlusion still occurred.

There is insufficient mechanistic evidence to provide confirmatory evidence for this application. There does appear to be sufficient literature to document the presence of MASP-2 and lectin components in TMA and HSCT-TMA. However, the Applicant has not provided mechanistic data to demonstrate a beneficial clinical outcome in TMA by blocking MASP-2. Although there appears to be partial mitigation of C-activation and a delay in thrombotic onset by narsoplimab-wuug in animal and in vitro models, the Applicant has not shown sufficient evidence that this translates into a measurable clinical benefit, either directly or indirectly. It is possible that narsoplimab-wuug's inhibition of the lectin pathway is not sufficient to alter the outcome in HSCT-TMA in a sufficient magnitude to demonstrate clinical benefit.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The Division requested that Office of Scientific Investigations inspect a clinical study clinical investigator site, and the Applicant were inspected in support of BLA 761152. Based on these inspections the conduct of the Study TMA-001 appears to be adequate. The study data derived from the clinical investigator's site and the Applicant are considered reliable.

For the clinical investigator site, 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.

Subject (b) (6) had three adverse events that were not recorded to an electronic data capture 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.

The response from the clinical site to FDA Form 483, dated January 12, 2021, appeared adequate. Although the above findings are regulatory violations, these adverse events were included in the submission and these findings do not appear to have significant impact on the safety assessment of the study.

In terms of the Applicant site audit, no regulatory deficiencies were observed during the inspection and no Form FDA-483, Inspectional Observations were issued.

21. Labeling Summary of Considerations and Key Additional Information

The following provides a summary of the labeling recommendations however as the recommended action is a complete response, no additional labeling discussions occurred.

Table 132. Labeling Recommendations

Section Name	Change Recommended
Universal Changes	Replaced proposed suffix (b) (4) with wuug throughout.
Highlights of Prescribing Information	Product Title revised per guidance (b) (4) to "for intravenous use." Indication revised to reflect age of population; added "adult." Dosage and Admin: Revised for clarity and removed text (b) (4) Dosage Forms and Strengths: Deleted (b) (4) per guidance. Adverse Reactions: Removed exculpatory text (b) (4)
Table of Contents	Updated based upon changes to FPI.
Full Prescribing Information	
Indications and Usage	Added "adult" to provided indicated ages.
Dosage and Administration	Moved (b) (4). Removed text (b) (4) (b) (4). Deleted text (b) (4) Added route of administration as required by regulations. Added more detailed storage information.
Dosage Forms and Strengths	Removed (b) (4) and added the total concentration of the vial (370 mg/2 mL).
Contraindications	No changes.

Section Name	Change Recommended
Warnings and Precautions	5.1 Revised title (b) (4) to "Serious Infections because we incorporated some localized infections. Updated to provide rates of AE. Added introductory statement to describe class risk. Added final paragraph which describes mitigating strategies.
Adverse Reactions	1.1 Revised title to make "Trial" plural per PLR template. This entire section revised based upon our current approach to NMEs to provide standardized data presentation. We revised the AR table format to provide columns for "all grades" and "Grade ≥3." (b) (4) (b) (4) (b) (4) grouped terms are now defined below the table (per AR guidance). 1.2 Revised text to be consistent with text recommended in the Biosimilar labeling guidance (also pertinent to all biological product labeling).
Drug Interactions	Deleted proposed text which did not provide clinically meaningful information (b) (4) (b) (4) per Drug Interactions Guidance.
Use in Specific Populations	8.1 Pregnancy: Revised significantly to be consistent with PLLR Guidance. Revised (b) (4) to use non-proprietary name when discussing nonclinical studies. 8.2 Lactation: Revised this section to be consistent with PLLR Guidance. 8.3 Females and Males of Reproductive Potential: Deleted this section per PLLR Guidance (b) (4) (b) (4). 8.4 Deleted text (b) (4) and added standard text for product without pediatric indication. 8.5 Geriatric Use: Revised to be consistent with September 2020 Geriatric Use Guidance.
Overdosage	Revised to remove text that provides no useful information (b) (4) (b) (4) Removed text (b) (4) (b) (4) (not allowed per regulations).
Description	Revised to add pH adjusters and inactive ingredients.
Clinical Pharmacology	Asked Applicant to add introductory paragraph to 12.3 describing the clinically significant PK properties. Distribution and Eliminations: Updated values to reflect the geometric mean from 'all patients' population based upon individual parameters from popPK. Inserted metabolism and excretion subheadings, per Clinical Pharmacology Labeling Guidance.
Nonclinical Pharmacology	Revised text to describe the dose administered, route of administration, and exposure multiple.

Section Name	Change Recommended
Clinical Studies	Revised to describe patient population studied, removed text (b) (4) (b) (4). Revised the trial population for the efficacy results (b) (4) to “full analysis.” Deleted (b) (4) and described efficacy results in text. (b) (4) deleted.
How Supplied / Storage and Handling	Revised for clarity and to use correct package term (single-dose vials). Deleted (b) (4) as it is not specific to their product. That is a general pharmacy practice.
Patient Counseling Information	Added required introductory statement: “Advise patients of the possible risks of YARTEMLEA therapy” ... Asked Applicant to add the manufactured by information and US License number (or placement holder for same).
Patient Labeling (MedGuide, IFU)	There is no MedGuide or IFU for this product.

Source: FDA Reviewer

Abbreviations: AE, adverse event; AR, adverse reaction; FPI, full prescribing information; IFU, instructions for use; NME, new molecular entity; PK, pharmacokinetic; PLLR, pregnancy and lactation labeling rule; PLR, physician labeling rule; popPK, population pharmacokinetics

22. Postmarketing Requirements and Commitments

The recommended regulatory actions is a complete response and any postmarketing requirements and commitments will be addressed in a future review cycle.

23. Financial Disclosure

The Applicant provided certification on FDA Form 3454 to indicate that there were no financial arrangements between the Applicant and Investigators that could be affected by the outcome of Study TMA-001. The Applicant did not provide the number of investigators and an IR was sent to the Applicant in which the Applicant stated that the total number of investigators identified was 163. They also stated that two of the 163 investigators received payments that reached a cumulative monetary value that exceeded \$25,000 and that this occurred in 2021. The value did not exceed \$35,000. Per 21 CFR 54.2 significant payments of other sorts includes cumulative monetary value that exceeds \$25,000. The Applicant provided Form FDA 3455 for each investigator that included the disclosable financial interest/arrangements and a description of the steps taken to minimize potential bias.

Table 133. Covered Clinical Studies: [OMS721 TMA-001]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 163		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Two of the 163 investigators received payments that reached a cumulative monetary value that exceeds \$25,000. The cumulative values are \$35,0000 or less. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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25. Review Team

Table 134. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Courtney Hamilton
Nonclinical Reviewer	Pedro Del Valle, Geeta Negi, Bo Lee
Nonclinical Team Leader	Pedro Del Valle / Todd Bourcier
Office of Clinical Pharmacology Reviewer(s)	LaiMing Lee
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan
Clinical Reviewer	Carrie Diamond
Clinical Team Leader	Tanya Wroblewski
Statistical Reviewer	Sarabdeep Singh
Statistical Team Leader	Yeh-Fong Chen
Cross-Disciplinary Team Leader	Tanya Wroblewski
Division Director (pharm/tox)	Todd Bourcier
Division Director (OCP)	Shirley Seo
Division Director (OB)	Thomas Gwise
Division Director (clinical)	Albert Deisseroth
Office Director (or designated signatory authority)	Lisa Yanoff

OCP = Office of Clinical Pharmacology

OB = Office of Biostatistics

Table 135. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
Microbiology	
OPDP	
OSI	
OSE/DEPI	
OSE/DMEPA	
OSE/DRISK	
Other	

OPQ = Office of Pharmaceutical Quality

OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

OSE = Office of Surveillance and Epidemiology

DEPI = Division of Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DRISK = Division of Risk Management

Table 139 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Carrie Diamond	OND/DNH	2.1, 3, 4, 6, 7, 15, 16, 17, 24 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Carrie E. Diamond -S Digitally signed by Carrie E. Diamond -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002351268, cn=Carrie E. Diamond -S Date: 2021.10.12 12:26:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Tanya Wroblewski, MD	OND/DNH	1, 2, 3, 4, 6, 7, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 ☒ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	Signature: Tanya M. Wroblewski - S3 Digitally signed by Tanya M. Wroblewski -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011605845, cn=Tanya M. Wroblewski -S3 Date: 2021.10.13 13:07:26 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Albert Deisseroth, MD, PhD	OND/DNH	All sections ☐ Authored ☐ Contributed ☒ Approved
Deputy Director	Signature: Albert B. Deisseroth -S Digitally signed by Albert B. Deisseroth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000589069, cn=Albert B. Deisseroth -S Date: 2021.10.14 08:36:31 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Bo Lee, PhD	OND/DPTCHEN	13 ☐ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Bo Yeon Lee -S Digitally signed by Bo Yeon Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bo Yeon Lee -S, 0.9.2342.19200300.100.1.1=2002269725 Date: 2021.10.12 08:21:39 -04'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Geeta Negi, PhD	OND/DPTCHEN	5 and 13 ☒ Authored Sections ☐ Contributed ☐ Approved
Reviewer	Signature: Pedro L. Del Valle -A Digitally signed by Pedro L. Del Valle -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001000884, cn=Pedro L. Del Valle -A Date: 2021.10.12 08:28:33 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Pedro Del Valle, PhD, FATS	OND/DPTCHEN	5, 7.1, 8, and 13 ☒ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Pedro L. Del Valle -A Digitally signed by Pedro L. Del Valle -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001000884, cn=Pedro L. Del Valle -A Date: 2021.10.12 08:31:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Todd Bourcier, PhD	OND/DPTCHEN	5, 7.1, 8, 13, and 18 ☒ Authored ☒ Contributed ☒ Approved
Division Director	Signature: Todd M. Bourcier -S Digitally signed by Todd M. Bourcier -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235462, cn=Todd M. Bourcier -S Date: 2021.10.12 17:19:18 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	LaiMing Lee, PhD	OTS/OCP/DCEP	Section: 5, 6.1, 8.1, 8.2, 14.1, 14.2, and 14.4 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Lai M. Lee -S Digitally signed by Lai M. Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lai M. Lee -S, 0.9.2342.19200300.100.1.1=1300366890 Date: 2021.10.08 14:25:34 -04'00'		

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Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 139. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Elyes Dahmane, PhD	OTS/OCP/DPM	Section: 6.1, 8.1, 8.2 and 14.3 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Elyes Dahmane -S Digitally signed by Elyes Dahmane -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Elyes Dahmane -S, 0.9.2342.19200300.100.1.1=2003183231 Date: 2021.10.08 13:27:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Sudharshan Hariharan, PhD	OTS/OCP/DCEP	5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3 and 14.4 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Sudharshan Hariharan -S Digitally signed by Sudharshan Hariharan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000394743, cn=Sudharshan Hariharan -S Date: 2021.10.08 15:59:50 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Justin Earp, PhD	OTS/OCP/DPM	Section: 6.1, 8.1, 8.2 and 14.3 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	Signature: Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2021.10.08 12:08:54 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Doanh Tran, PhD	OTS/OCP/DCEP	5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3 and 14.4 ☐ Authored ☐ Contributed ☒ Approved
Deputy Director	Signature: Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2021.10.08 16:14:08 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Sarabdeep Singh, PhD	OTS/OB/DBIX	6.2 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	Signature: Yeh Fong Chen -S Digitally signed by Yeh Fong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yeh Fong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2021.10.07 15:34:41 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Yeh-Fong Chen, PhD	OTS/OB/DBIX	Section: 1 & 6 ☒ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Yeh Fong Chen -S Digitally signed by Yeh Fong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yeh Fong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2021.10.07 15:35:15 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Thomas Gwise, PhD	OTS/OB/DBIX	Section: 1 & 6 ☐ Authored ☐ Contributed ☒ Approved
Division Director	Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2021.10.07 16:01:45 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Courtney Hamilton	ORO/DROCHEN	Appendix 3 section 12 ☒ Authored ☐ Contributed ☐ Approved
Regulatory Project Manager	Signature: Courtney Hamilton Digitally signed by Courtney Hamilton DN: cn=Courtney Hamilton, o, ou, email=Courtney.Hamilton@fda.hhs.gov, c=US Date: 2021.10.07 14:53:01 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Charlene Wheeler	ORO/DROCHEN	Appendix 3 section 12 ☐ Authored ☒ Contributed ☒ Approved
Chief, Project Management	Signature: Charlene N. Wheeler -S Digitally signed by Charlene N. Wheeler -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000621384, cn=Charlene N. Wheeler -S Date: 2021.10.07 13:51:45 -04'00'		

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/s/

COURTNEY V HAMILTON
10/15/2021 11:51:43 AM

LISA B YANOFF
10/15/2021 11:53:53 AM
I agree with the conclusions presented in this review.