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Trial in Progress: An Open-Label, Multi-Center Phase 2 Study Evaluating Efficacy and Safety of the MASP-2 Inhibitor Narsoplimab in Pediatric Patients with High-Risk Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy (HSCT-TMA)

William Pullman, PhD, MBBS[1]; Mary Brough, RN[1]; Carolina Soto, PharmD[1]; Tze-Chiang Meng, MD[1]

[1]Omeros Corporation, Seattle, WA, USA

OBJECTIVE

The purpose of this Phase 2 study is to evaluate the safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of narsoplimab in pediatric-aged patients with TMA following HSCT

CONCLUSIONS

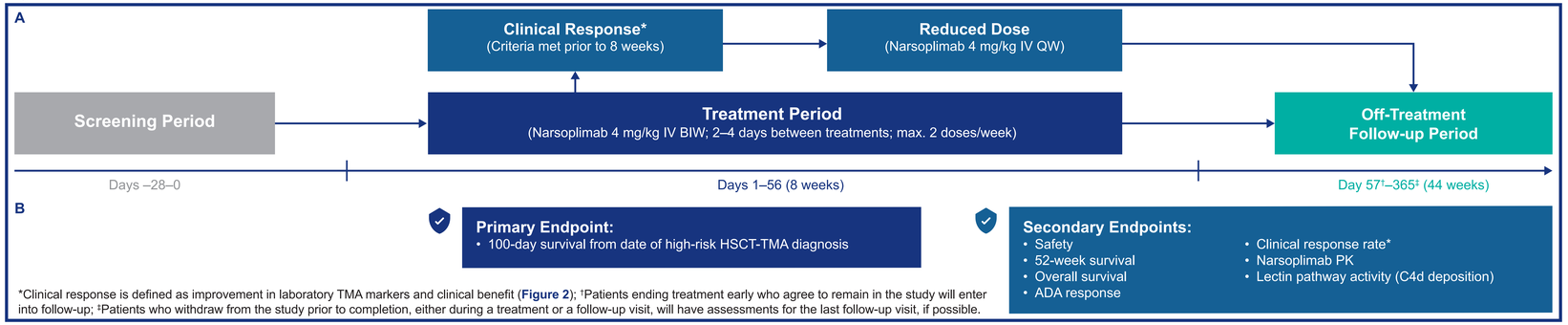
- Following the favorable results obtained in a pivotal Phase 2 study in adults with HSCT-TMA, further evaluation of narsoplimab in pediatric patients with high-risk HSCT-TMA is warranted
- This is the first clinical trial evaluating the efficacy and safety of narsoplimab in pediatric patients with HSCT-TMA

BACKGROUND

- HSCT-TMA (also known as TA-TMA) is a potentially life-threatening complication associated with multi-organ injury and significant morbidity and mortality[1,2]
  - There are currently no approved therapies for HSCT-TMA
- HSCT-TMA incidence rates of up to 39% have been reported in both pediatric and adult alloHSCT recipients[3,4]
- In the HSCT setting, toxic conditioning regimens, infection, and GVHD can cause endothelial injury, which triggers activation of the lectin pathway of complement and in turn the coagulation cascade, together leading to TMA[1]
  - Additionally, genetic predisposition, African American descent, ABO incompatibility, and HLA donor mismatch have been identified as pre-transplant risks[5]
- Narsoplimab (OMS721), a fully human IgG4 mAb, inhibits MASP-2, the effector enzyme of the lectin pathway and an activator of the coagulation cascade[1,6]
- Narsoplimab was previously evaluated for safety and efficacy in adults with high-risk HSCT-TMA in an open-label pivotal trial (NCT02222545)[6]
  - Narsoplimab treatment was well tolerated and resulted in clinical response and favorable overall survival

METHODS

Figure 1. Trial Design



*Clinical response is defined as improvement in laboratory TMA markers and clinical benefit (**Figure 2**); †Patients ending treatment early who agree to remain in the study will enter into follow-up; ‡Patients who withdraw from the study prior to completion, either during a treatment or a follow-up visit, will have assessments for the last follow-up visit, if possible.

Trial Design

- This is an ongoing, open-label, multi-center Phase 2 trial of narsoplimab in pediatric patients being conducted in the USA and European Union. Enrollment is expected to begin in early Q1 2023
- Following screening, patients will receive narsoplimab 4 mg/kg via IV infusion twice weekly during the 8-week treatment period (**Figure 1A**)
  - If a patient meets all clinical response criteria prior to 8 weeks of treatment, dosing may be decreased to 4 mg/kg IV once weekly
- Narsoplimab can be used in conjunction with standard-of-care treatments

Patients

- Eligible patients meeting the key inclusion and exclusion criteria will be enrolled in the trial (**Tables 1–3**)

Trial Endpoints

- The primary and secondary trial endpoints are listed in **Figure 1B**
- Patients' clinical response is defined as improvement in laboratory TMA markers and clinical benefit (**Figure 2**)

Table 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥28 days to <18 years
- alloHSCT recipient (treatment of non-malignant or malignant disease)
  - All donor cell sources permitted:
    - Matched, mismatched, haploidentical
    - Related, unrelated
    - Bone marrow, peripheral blood stem cells, and umbilical cord blood
- High-risk HSCT-TMA diagnosis (**Table 2**)
- Met ≥1 HSCT-TMA high-risk criterion (**Table 3**)

Exclusion Criteria

- Prior treatments with eculizumab, ravulizumab, or defibrotide within 3 months
- STEC-HUS
- ADAMTS13 activity <10%
- Severe, uncontrolled systemic bacterial or fungal infection requiring antimicrobial therapy
- Malignant hypertension
- Abnormal liver function (ALT or AST >5× ULN)

Table 2. High-risk HSCT-TMA Diagnosis Definition

Criteria	Definition
Platelet count	<50,000/μL or a ≥50% decrease in platelet count from the highest value obtained following transplant
and at least one of the following:	
Evidence of microangiopathic hemolysis	• Presence of schistocytes (per high-power field) • Serum LDH (>ULN) • Haptoglobin (<LLN)

Table 3. High-risk HSCT-TMA Criteria

Criteria	Definition
1. HSCT-TMA persistence	≥2 weeks following modification of CNI or sirolimus
or	
2. Evidence of ≥1 one of the following:	• Spot P/C ratio >2 mg/mg • Serum creatinine >1.5× pre-TMA level • Biopsy-proven GI TMA • TMA-related neurological abnormality • Pericardial or pleural effusion* • Pulmonary hypertension* • Grade III or Grade IV GVHD† • Elevated serum C5b-9 >244 ng/mL

*Without alternative explanation; †Or at risk of Grade III or Grade IV GVHD if immunosuppression was to be modified.

Figure 2. Definition of Clinical Response in Pediatric HSCT-TMA Patients

Improvement in TMA Laboratory Markers

LDH		Platelet Count	
<1.5× ULN	+	**Baseline ≤20 × 10^9/L:** Triple baseline and absolute count >30 × 10^9/L and no platelet transfusions for 2 days	**Baseline >20 × 10^9/L:** Increase by ≥50% and absolute count >75 × 10^9/L and no platelet transfusions for 2 days

and

Improvement in Clinical Status in at Least One Organ

Blood	Kidney	Pulmonary	Neurologic	GI
Freedom from transfusions for at least 4 weeks	Reduction of creatinine >40% **or** Creatinine below the upper limit of normal and reduction of creatinine >20% **or** Discontinuation of renal replacement therapy	Extubation and discontinuation of ventilator support **or** Discontinuation of non-invasive mechanical ventilation	Improvement in reversible or stabilization of irreversible neurological conditions	Improvement assessed using GI measures in the MAGIC criteria

Statistical Analysis

- The planned recruitment is at least 18 pediatric patients, distributed across the age range with at least 4 patients from each of the following age groups:
  - 12 to <18 years old
  - 2 to <12 years old
  - 28 days to <2 years old

REFERENCES

1. Gavriilaki E *et al. Exp Hematol Oncol* 2021;10:57.
2. Pagliuca S *et al. Blood Adv* 2019;3:2424–35.
3. Jodele S *et al. Blood* 2014;124:645–53.
4. Postalcioglu M *et al. Biol Blood Marrow Transplant* 2018;24:2344–53.
5. Meri S *et al. Adv Ther* 2022;39:3896–915.
6. Khaled SK *et al. J Clin Oncol* 2022;40:2447–57.

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ABBREVIATIONS

ADA, anti-drug antibody; alloHSCT, allogeneic HSCT; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIW, twice weekly; CNI, calcineurin inhibitor; GI, gastrointestinal; GVHD, graft-versus-host disease; HLA, human leukocyte antigens; HSCT-TMA, hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV, intravenous; LDH, lactate dehydrogenase; LLN, lower limit of normal; MAGIC, Mount Sinai Acute GVHD International Consortium; mAb, monoclonal antibody; MASP-2, mannan-binding lectin-associated serine protease-2; P/C, protein/creatinine; PK, pharmacokinetics; QW, once weekly; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TA-TMA, transplant-associated thrombotic microangiopathy; ULN, upper limit of normal.

DISCLAIMER

- Narsoplimab is an investigational agent and has not been approved by any regulatory agency

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Presenting author: William Pullman (bpullman@omeros.com)